PRINT ISSN 1119-8362
Electronic ISSN 2659-1499

Full-Text Available Online At
https://www.ajol.info/index.php/jasem
https://www.bioline.org.br/ja

J. Appl. Sci. Environ. Manage.
Vol. 28 (11B Supplementary) 3823-3832 Nov. 2024

Evaluating the Relationship between Plasma Chloride, Calcium and Interleukin-18 in Essential Hypertensive Subjects

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ABSTRACT: The mechanism underlying a persistent blood pressure elevation and its sequelae on the inflammatory cascades and electrolyte imbalance have not been fully elucidated. The objective of this study was to assess the relationship between plasma chloride (Cl), calcium (Ca) and interleukin-18 (IL-18) in essential hypertensive subjects in Ado-Ekiti, Ekiti state, Nigeria. The electrolytes, Ca, and IL-18 were determined using various standard method. Data obtained for BMI, blood pressure, IL-18 and electrolyte levels in treated and untreated essential hypertensive subjects were BMI (Kg/m^2) 24.53±3.62; 26.76 ± 2.07; SBP (mmHg) 152.12±10.06; 156.54 ± 4.37; DBP (mmHg) 94.99 ± 4.81; 102.33 ± 6.21; IL-18 (pg/ml); 350.63 ± 82.17; 641.73 ± 69.66; Na (mmol/L); 139.75± 3.23; 150.15 ± 5.09; K (mmol/L) 3.97± 0.27; 3.34±0.31; Ca (mg/dl) 9.34± 0.62; 8.59 ± 0.33; and Cl (mmol/L) 113.62± 1.77; 104.22 ± 2.44 respectively. The BMI, SBP, DBP, IL-18 and Na were significantly higher ($p<0.05$), while K, Ca and Cl were significantly ($p<0.05$) lower in treated and untreated hypertensives compared with control. BMI was non-significantly lower, while blood pressure (SBP and DBP) and IL-18 were significantly lower in treated hypertensive subjects compared to untreated hypertensive subjects ($p<0.05$). Na was significantly higher ($p<0.05$) while K, Cl and Ca were significantly lower ($p<0.05$) in treated hypertensives compared to control. In conclusion, electrolyte disturbance and inflammation are associated with essential hypertension which can be reversed through lifestyle and diet modifications and antihypertensive drugs. Measurement of plasma chloride is a more independent marker of treatment efficacy in treated hypertensives.

DOI: https://dx.doi.org/10.4314/jasem.v28i11.41

Cite this Article as: ODEWUSI, O. O; AKINDELE, O. A; OMON, E. A; [3]OBADIRE, S. O; ADESIYAN, A. A; EKUNDAYO, O. A; SULEIMAN, K. D (2024). Relationship between Plasma Chloride, Calcium and Interleukin-18 in Essential Hypertensive Subjects. *J. Appl. Sci. Environ. Manage.* 28 (11B Supplementary) 3823-3832

Dates: Received: 21 September 2024; Revised: 27 October 2024; Accepted: 04 November 2024 Published: 30 November 2024

Keywords: Essential hypertension; electrolytes; interleukins; anti-inflammatory; pro-inflammatory

Hypertension, also known as high blood pressure, is a long-term medical condition in which the blood pressure in the arteries is persistently elevated (Humphrey, 2021). Hypertension defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg is a global problem that affects approximately 15-20% of all adults (Mills and Stefanescu, 2020). High blood pressure usually does not cause symptoms. It is,

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however, a major risk factor for stroke, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia (Princewel *et al*., 2019). Hypertension is a major cause of premature death worldwide (Kario *et al.,* 2024). High blood pressure is classified as primary (essential) hypertension or secondary hypertension. About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors (Zhou *et al*., 2021). Lifestyle factors that increase the risk include excess salt in the diet, excess body weight, smoking, physical inactivity and alcohol use (Humphrey, 2021). The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to a clearly identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills (Tackling and Borhade, 2023). Lifestyle changes and medications can lower blood pressure and decrease the risk of health complications. Lifestyle changes include weight loss, physical exercise, decreased salt intake, reducing alcohol intake, and a healthy diet. If lifestyle changes are not sufficient, then blood pressure medications are used (Humphrey, 2021).

Interleukin 18 belongs to the IL-1 family of cytokines, which is a group comprising 11 member cytokines that promote the activity of the innate immune system (Detry *et al.,* 2022). IL-18 stimulates both the innate immune and acquired immune responses. The activity of IL-18 in both the innate and adaptive immune response implicates it in several inflammatory and autoimmune conditions (Hirooka and Nozaki, 2021). IL-18 promotes the production of interferon gamma (IFN-γ) and strongly induces a Th1 response. IL-18 drives the same myeloid differentiation factor 88 (MyD88)/nuclear factor kappa B (NF-κB) signaling pathway as IL-1β (Wang *et al.,* 2023). In physiological conditions, IL-18 is regulated by the endogenous inhibitor IL-18 binding protein (IL-18BP), and the activity of IL-18 is balanced (Detry *et al.,* 2022). It is reported that in several inflammatory diseases, the IL-18 activity is unbalanced, and IL-18 neutralization by IL-18BP is insufficient. IL-18 acts synergistically with IL-12 to induce the production of IFN-γ as a Th1 cytokine, and IL-18 acts alone to induce the production of Th2 cytokines such as IL-4 and IL-13 (Ihim *et al.,* 2022). Experimental research has shown that interleukin 18 enhances atherosclerosis through release of interferon gamma and induces expression of inflammatory cytokine IL-6 in the vascular endothelial and smooth muscle cells (Tsioufis *et al.,* 2022).

Electrolytes are essential for basic life functioning, such as maintaining electrical neutrality in cells and generating and conducting action potentials in the nerves and muscles (Shrimanker and Bhattarai, 2023). Sodium (Na^+), Potassium (K^+), and Chloride (Cl^-) are the primary electrolytes (ions) in the body. Changes in electrolyte concentration and or ratio of anions and cations will cause changes in cell activity that can endanger life. Na^+ is the primary electrolyte of extracellular fluid, which in the case of hyponatremia or hypernatrium, the Na^+ concentration is regulated by the kidneys (Ambati *et al.,* 2023). K^+ is the central intracellular cation and plays a vital role in cell metabolism. Changes in plasma potassium levels (hyperkalemia or hypokalemia) can affect neuromuscular and heart function. Clinical features of potassium disorder can be the most life-threatening disorder compared to others (Fauziah *et al.,* 2021). Chloride is the primary extracellular anion in humans. It is essential to maintain serum neutrality, acid-base balance, homeostasis of body fluids, osmotic pressure, production of hydrochloric acid (HCl) in the gastrointestinal tract, kidney function, and electrical activity in muscular activity (Kataoka, 2021). If not managed properly, changes in fluid and electrolyte concentration can cause serious problems. Calcium has a significant physiological role in the body. It is involved in skeletal mineralization, contraction of muscles, the transmission of nerve impulses, blood clotting, and secretion of hormones. The diet is the predominant source of calcium. Calcium is a predominately extracellular cation (Ambati and Kho, 2023). Calcium absorption in the intestine is primarily controlled by the hormonally active form of vitamin D, which is 1, 25-dihydroxy vitamin D3. Parathyroid hormone also regulates calcium secretion in the distal tubule of the kidneys. Calcitonin acts on bone cells to decrease calcium levels in the blood (Shrimanker *et al.,* 2023). Since hypertension has been described to be a manifestation of immunological and other factors, hence, the objective of this research was to evaluate the relationship between plasma chloride, calcium and interleukin-18 in essential hypertensive subjects carried out in Ado-Ekiti and its immediate environs, Ekiti State, Southwestern Nigeria.

MATERIALS AND METHODS

Study Design: A cross-sectional design using a stratified random sampling method was used. Stratification was by age and therapy.

Study Area: The study was carried out in Ado-Ekiti and its immediate environs. Ado-Ekiti is the capital of Ekiti State in Southwestern Nigeria. The state is

mainly highland area about 50 meters above sea level. Its coordinates are 70 40'N 50 15'E.

Sample Size: The minimum sample size (N) was calculated to be 308 by single proportion formula based on a prevalence of 29.9%.

$$N = \frac{Z^2 p(1-p)}{w^2}$$

Where Z = confidence level at 95%, N=Minimum sample size, w= allowance for error=0.05, P = estimated prevalence of hypertension in Ado-Ekiti

q=1-p=1-0.299=0.701
$N=1.96^2$ x 0.299 x $0.701/0.05^2$=322.1
Therefore to make up for possible drop outs and outliers, a total of three hundred and thirty four (334) subjects were investigated.

Inclusion and Exclusion Criteria: Men and women who are hypertensive whether on therapy or not were included in this study. Inclusion was based on the cutoff of at least 140mmHg systolic and or 90mmHg diastolic Blood pressure, while Subjects below the age of 18 years, pregnant women, nursing mothers, diabetes mellitus subject, chronic kidney disease, and sufferers of other disease conditions were excluded.

Grouping: Treated hypertensives are those that have been diagnosed of Hypertension and have been on treatment for at least 3months. Treatment being the administration of antihypertensive drugs alongside DASH diets and lifestyle modifications. Untreated hypertensives are those that have just been newly diagnosed of having essential hypertension or a known hypertensive that have not been on treatment for at least 3 months.

Ethical Approval: Ethical approval for this study was sought for, from the Health Research Ethics and Review Committee, Afe Babalola University Multi-System Hospital, Ado-Ekiti, Ekiti state. Informed consent were obtained from each participant who participated in the study.

Sample Collection: Venous blood sample of about 5ml was collected from the cubital fossa using a 22G needle and syringe and dispensed into a plain bottle (non-anticoagulant bottle). The blood was allowed to clot and centrifuged at 12,000rpm for 5 minutes to separate the serum from cells. The serum samples were stored at temperature of -20 degree Celsius.

Anthropometric analysis

Blood Pressure: Blood pressure was determined with digital sphygmomanometer.
Height and weight were obtained using a meter gauge and a bathroom scale respectively.

Body Mass Index (BMI): BMI was derived from the height and weight using the formula:

$$BMI = \frac{weight\ (m)}{height\ (m^2)}$$

Sample analysis: Plasma monovalent metals (Sodium and Potassium) and Calcium levels were estimated using flame emission spectrophotometry and atomic absorption spectrophotometry respectively.

Plasma Chloride level was estimated by colorimetry.

Interleukin 18 was estimated using ELISA based ABCAM® patented kits according to manufacturer's instructions.

Statistical analysis: Results obtained were subjected to statistical analysis using SPSS (version 23.0 software, SPSS Inc. Chicago, Illinois, USA). Values of all parameters were expressed as mean ± SD. Student's t-test and ANOVA were the tool of choice in comparing the means. Significant difference was pegged at $p<0.05$.

RESULTS AND DISCUSSION

Table 1 showed the Body mass index (BMI), Systolic and Diastolic blood pressure (SBP and DBP), Interleukin 18 (IL-18), Calcium and Electrolytes (Na, K and Cl) in treated and untreated hypertensives compared with control. The results obtained showed that BMI, blood pressures (SBP and DBP), IL-18 and Na were significantly higher, while K, Ca and Cl were significantly lower in treated and untreated hypertensives compared with control. BMI was non-significantly lower, while blood pressure (SBP and DBP) and IL-18 were significantly lower in treated hypertensives compared with untreated hypertensives. Na was significantly higher ($p<0.05$) while K, Cl and Ca were significantly lower ($p<0.05$) in treated hypertensives compared with control.

Figure 1 shows the SBP and DBP in response to treatment with antihypertensive drugs in treated hypertensives. From the results obtained, treatment with diuretics was the most effective in bringing blood pressure under check, while ACE inhibitor was the least effective, the intermediates being angiotensin receptor blockers followed by calcium channel blockers. Both DBP and SBP in all treatment

plans was seen to be significantly lower ($p<0.001$) than that seen in untreated hypertensives but also significantly higher ($p<0.001$) than that seen in control subjects. Blood pressure in all treatment plans can thus be said to be far removed from that seen in untreated hypertension but not close enough to that seen in control. Figure 2 shows the BMI in response to treatment with antihypertensive drugs in treated hypertensives. Treatment with angiotensin receptor blockers was the most effective while diuretics was the least effective. The intermediates being calcium channel blockers followed by ACE inhibitors. All treatment plans except angiotensin receptor blockers showed a significantly lowered BMI compared to control. Except for angiotensin receptor blockers which showed a significantly reduced BMI ($p<0.05$) compared to untreated hypertensives, all other treatment plans showed insignificantly lower BMI.

Figure 3 shows the plasma Na and Cl levels in response to treatment with antihypertensive drugs in treated hypertensives. All drugs appear to have a similar effect on plasma Na and Cl levels. All treatment plans resulted in a significantly higher Na but lower chloride levels compared to control ($p<0.001$) respectively. There was also a significant lower Na but higher chloride ($p<0.001$) respectively when compared with untreated hypertensives. Figure 4 and 5 shows the plasma Ca and serum IL-18 levels in treated hypertensives in response to treatment with antihypertensive drugs. There was significant variation in plasma calcium when all antihypertensive treatment plans were compared with both control and untreated hypertensives ($p<0.05$). Calcium was however lowest in those treated with diuretics. All antihypertensive treatment plans resulted in a significant lower Interleukin 18 levels when compared with untreated hypertensives ($p< 0.001$), but were significantly higher when compared with control. Treatment with diuretics resulted in the lowest IL-18 levels.

Table 1: BMI, blood pressure, IL-18 and electrolyte levels in treated and untreated essential hypertensive subjects compared with control

Variables	Hypertensives on treatment (n=116) (mean ± SD)	Untreated hypertensives (n= 113) (mean ± SD)	Control (n=105) (mean ± SD)
BMI (Kg/m^2)	24.53±3.62	26.76 ± 2.07[a]	23.96 ± 3.09
SBP (mmHg)	152.12±10.06[a]	156.54 ± 4.37[a]	113.12± 6.71
DBP (mmHg)	94.99 ± 4.81[ac]	102.33 ± 6.21[a]	76.15 ± 2.77
IL-18 (pg/ml)	350.63 ± 82.17[ab]	641.73 ± 69.66[a]	78.26 ± 33.03
Na (mmol/L)	139.75± 3.23[ac]	150.15 ± 5.09[a]	134.24± 2.62
K (mmol/L)	3.97± 0.27[dc]	3.34 ± 0.31[a]	4.21± 0.18
Ca (mg/dl)	9.34± 0.62[ac]	8.59 ± 0.33[a]	9.81± 0.46
Cl (mmol/L)	113.62± 1.77[ac]	104.22 ± 2.44[a]	115.25± 1.34

[a]= statistically significant relative to control at P< 0.001
[b]= statistically significant relative to untreated hypertensive patients at P< 0.05
[c]= statistically significant relative to untreated hypertensive patients at P< 0.001

Essential hypertension, the persistent elevated blood pressure to which no specific cause can be adduced, results from a complex interplay between multiple regulatory systems that are themselves influenced by a multitude of genetic and environmental factors (Ahn and Gupta, 2018). As hypertension has been described as a manifestation of electrolyte, toxicological and immunological dimensions, this study was primarily designed to assess body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), plasma electrolytes (Sodium[Na], Potassium[K], Chloride[Cl] and Calcium[Ca]) and interleukin 18 (IL-18) of hypertensive subjects. The mean systolic and diastolic blood pressures were found to be significantly higher in both treated and untreated hypertensives than in control. In treated hypertensives, there was also a significantly lower SBP and DBP compared to untreated hypertensives. These findings are in line with previous studies (Diego *et al*., 2017; Norbert *et al.*, 2017; Odewusi and Osadolor, 2019; Odewusi *et al.*, 2023) where SBP and DBP in hypertensives with or without treatment was significantly higher compared to controls.

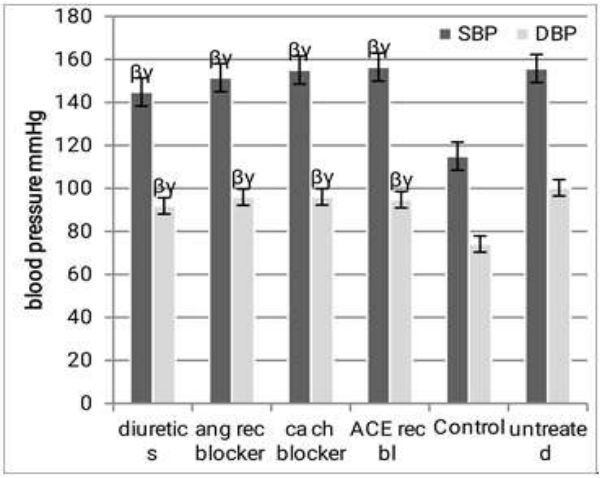

Fig 1: SBP and DBP in response to treatment with antihypertensive drugs in treated hypertensives

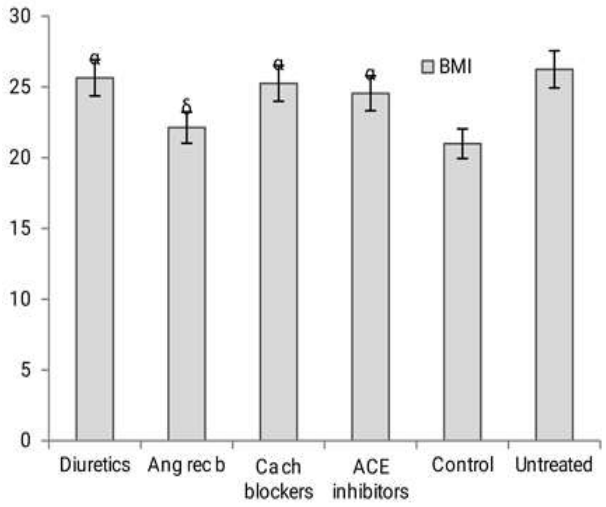

Fig 2: BMI in response to treatment with antihypertensive drugs in treated hypertensives

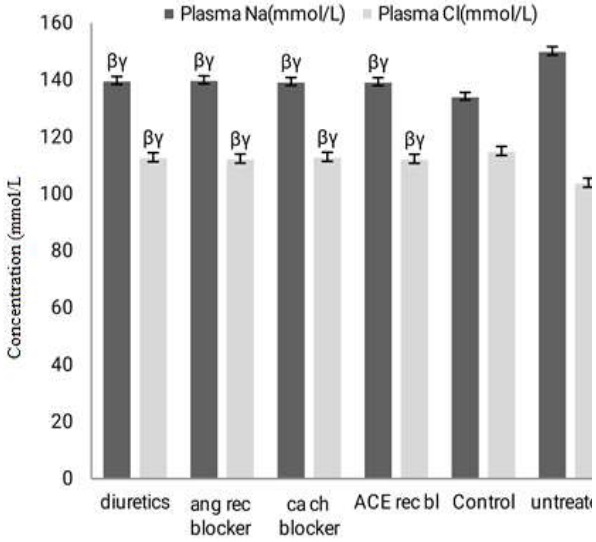

Fig 3: Plasma Na and Cl levels in response to treatment with antihypertensive drugs in treated hypertensives

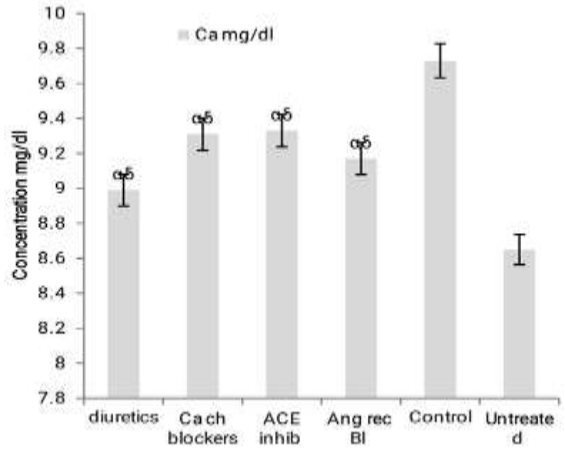

Fig 4: Plasma Ca levels in treated hypertensives in response to treatment with antihypertensive drugs

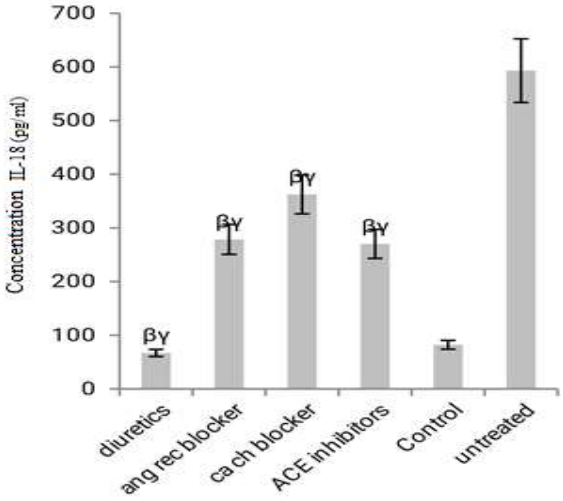

Fig 5: Plasma serum IL-18 levels in treated hypertensives in response to treatment with antihypertensive drugs

The essence of therapy is to close the gap in the levels of parameters seen in hypertensives and bring it to that observed in controls, in which case essential hypertensives would fare better and be less prone to complications if treatment is effective. In this study, the use of diuretics gave the best result in keeping both DBP and SBP under check. There was no gender disparity with reference to SBP and DBP in untreated hypertensives but it was observed that response to treatment fairly reduces with advancement in age. Age can thus be said to be a factor that determines how fast an essential hypertensive responds to treatment. Treatment in the form of drug therapy, DASH diets and adherence to appropriate lifestyles has beneficial effects on essential hypertensives as regards blood pressure (Xiao *et al.*, 2020).

In this study, the BMI was non-significantly higher in treated hypertensives and significantly higher in untreated hypertensives when both were compared to that observed in control. However, there was no significant variation in the BMI seen in untreated hypertensives compared with hypertensives on treatment. This result is consistent with the findings by Vrettos *et al.* (2020) and Odewusi *et al.* (2023) who reported that BMI of treated hypertensive patients had a nearly normal BMI with control. Additionally, this study supported El-Meouchy *et al.* (2022) findings that hypertension people had significantly higher body mass indices than control subjects, whether they were receiving treatment or not. In this study, treatment with angiotensin receptor blockers was more effective in reducing BMI of hypertensive subjects. Increased BMI among hypertensive patients like other lifestyle characteristics is an amendable health risk factor for

the prevention of hypertension. Moreover, for therapeutic purposes, weight loss reduces blood pressure in most hypertensive subjects (El-Meouchy *et al.,* 2022). Nevertheless, the overall results of lifestyle modification to reduce obesity are poor and in most long-term trials of weight reduction, it was found that in most cases weight returns to baseline levels after several years (Vrettos *et al.,* 2020). BMI was significantly higher in male untreated hypertensives. Its pattern of increase is also fairly consistent with advancement in age in untreated hypertensives but among treated hypertensives, there was no definite pattern. A high BMI can thus be said to be associated with the severity of essential hypertension.

Serum interleukin 18, an indicator of the activation of the inflammation cascades was seen to be significantly higher in both treated and untreated hypertensives compared to control. In addition, untreated hypertensives also had their IL-18 levels significantly higher compared to treated hypertensives. This is in line with previous studies (Odewusi and Osadolor, 2019; Hao *et al.,* 2019; Thomas *et al.,* 2021; Ihim *et al*., 2022) which reported significant increase in serum interleukin-18 in essential hypertension. The activity of IL-18 in both the innate and adaptive immune response implicates it in several inflammatory and autoimmune conditions (Ihim *et al*., 2022). Elevated circulating IL-18 levels have been linked to vascular changes in the carotid artery, including increased carotid intima-media thickness, which, in turn, is a predictor of cardiovascular events in patients with established coronary disease (Higashi, 2022). IL-18, either directly or through oxidative stress pathways and matrix metalloproteins, can alter endothelial function or induce vascular smooth muscle cell migration and/or proliferation to produce the vascular changes that occur with hypertension (Ma *et al.,* 2023). The pattern of increase in IL-18 in this study is fairly consistent with age progression and interleukin 18 levels were found to be significantly higher in females compared with their male counterpart.

We reported significantly higher plasma Na^+ levels in both treated and untreated hypertensives compared with control. This finding supports previous studies which reported that hypertension is associated with a significant increase in plasma Na^+ level (Grillo *et al.,* 2019; Bosch *et al.,* 2021; Graudal *et al.,* 2023). A rise in plasma sodium may affect blood pressure by a direct effect on the brain and the blood vessels, and it may also enhance the activity of the renin-angiotensin system (Bosch *et al.,* 2021). Increased salt consumption may provoke water retention, thus leading to a condition of high flow in arterial vessels. The mechanism of pressure natriuresis has been proposed as a physiologic phenomenon where an increase in BP in the renal arteries causes increased salt and water excretion (Grillo *et al.,* 2019). This hemodynamic load may lead to an adverse microvascular remodeling by the effects of increased BP levels (Graudal *et al.,* 2023). Furthermore, plasma Na^+ levels was significantly higher in untreated hypertensives compared with treated group, which implies that treatment was effective enough to bring about a marked significant reduction in the level of this most abundant osmotic cation in plasma, hence a reduced blood volume and pressor effect (Graudal *et al.,* 2023). Most treatment types of essential hypertension are aimed at reducing the levels of Na in plasma- by way of reduced dietary NaCl, increased sodium excretion or by arresting the renin angiotensin aldosterone system (Fountain *et al.,* 2023). Treatment with diuretics gave the best result in bringing the plasma Na levels towards the reference values.

In this research, there was a significant decrease in the plasma K of treated and untreated hypertensives compared to control. This finding is consistent with previous studies (Burnier *et al.,* 2019; Krogager *et al.,* 2020; Flack *et al*., 2024), which reported reduced plasma potassium levels in both treated and untreated hypertensives compared with control. The most common cause of hypokalemia in a hypertensive patient is diuretic use. By enhancing urinary flow and sodium delivery through the collecting tubule, both thiazide and loop diuretics promote renal potassium secretion. Potassium secretion is further enhanced in the setting of diuretic-induced intravascular volume depletion and secondary aldosterone stimulation (Krogager *et al.,* 2020). Since potassium functions in maintaining cardiac and vascular integrity, it is advisable to place hypertensives on diuretics on an appropriate supplementation of potassium as many in this class of antihypertensives are non-potassium sparing (Burnier *et al.,* 2019), this will give better results and prevent the development of vascular complications. High intake of salt is well known to induce hypertension and cardiovascular damage, but supplementation with dietary potassium counters these harmful effects by lowering BP in hypertensives (Mills and Stefanescu, 2020). Therefore, potassium's protective effect would manifest with excess salt compared to salt depletion. Treatment with angiotensin converting enzyme inhibitors (ACE inhibitors) resulted in the best plasma K level seen in treated hypertensives. In this research, plasma Cl^- levels was significantly

increased in both treated and untreated hypertensives compared with control, giving an indication that hypertension was associated with a change in plasma chloride level. When the plasma chloride levels of untreated hypertensives was compared with that of treated hypertensives, a significant reduction was observed thus partially agreeing with other epidemiologic studies which curiously show that lower circulating levels of Cl^- are associated with higher cardiovascular and all-cause mortality (Kataoka, 2021; Koulouridis and Koulouridis, 2023). Among the environmental factors affecting blood pressure, the most studied was dietary sodium along with chloride, and there is general consensus that increased intake of sodium chloride increases blood pressure (Kim *et al*., 2024). However, there is a pile of evidence that chloride can play a role in regulating blood pressure, which may be even more important than NaCl (Kataoka, 2021; Koulouridis and Koulouridis, 2023). Although more than 85% of Cl^- is consumed as chloride of sodium, there is evidence that Na^+ and Cl^- concentrations do not necessarily go hand in hand as they may originate from different sources, therefore, clarifying the role of Cl− as an independent blood pressure regulator will have positive clinical and public health implications in addition to advancing our present understanding of electrolyte/acid-based blood pressure mediation regulation. Chloride anion is one of the most important elements in the human body and its role is not only to neutralize the extracellular and intracellular cations. It actually contributes significantly to the osmolality of extracellular and intracellular compartments, thereby participating in the regulation of volume homeostasis (Kataoka, 2021). In the context of cell volume regulation, chloride anion serves as a crucial rescue osmole, particularly in regulatory volume decrease (RVD). It functions as the main osmole extruded outside the cell via volume-regulated anion channels (VRAC), rapidly reducing intracellular osmolality and restoring cell volume to normal. Chloride involvement in cell volume regulation and its impact on various renal processes highlight its integral role in maintaining homeostasis (Koulouridis and Koulouridis, 2023). Therefore, investigation and management of hypertension according to the dynamics of serum chloride is rational considering that chloride is an established key electrolyte for tubulo-glomerular feedback in the kidney and a possible regulatory electrolyte for body fluid distribution. A significantly lower Calcium (Ca) level in both treated and untreated hypertensives compared with control, which indicates that hypertension was associated with plasma Ca level change. We also observed significant lower plasma Ca levels in untreated hypertensives compared with the treated group, which agrees with previous studies that show that lower circulating Ca levels are associated with hypertension (Villa-Etchegoyen *et al.,* 2019; Hua *et al.,* 2021; Rastogi *et al*., 2021). Low calcium intake produces a rise of parathyroid gland activity. The parathyroid hormone increases intracellular calcium in vascular smooth muscles resulting in vasoconstriction. Low calcium intake also increases the synthesis of calcitriol in a direct manner or mediated by parathyroid hormone (PTH). Calcitriol increases intracellular calcium in vascular smooth muscle cells. Both low calcium intake and PTH may stimulate renin release and consequently angiotensin II and aldosterone synthesis (Villa-Etchegoyen *et al.,* 2019). Renin release stimulated low extracellular calcium and PTH, activates the renin–angiotensin–aldosterone system (RAAS). In addition, PTH increases angiotensin II and aldosterone synthesis, which also leads to vasoconstriction and increases renal water reabsorption, increasing blood pressure (Zheng *et al.,* 2020). It has also been shown that restoring increased plasma calcium by vitamin D supplements reduced blood pressure with existing vitamin D deficiency in hypertensive individuals (Chen *et al.,* 2015). Previous research showed a correlation between chronically low levels of vitamin D and plasma calcium with an increased likelihood of becoming hypertensive (Villa-Etchegoyen *et al.,* 2019). Researchers in this study believe that the significant discrepancy between the treated and untreated hypertensives in plasma Ca levels shows the effectiveness of treatment in the form of the administration of antihypertensive drugs alongside DASH diets. However, plasma calcium was lowest in diuretics treated hypertensives while the highest was noticed in those treated with calcium channel blockers. To minimize the likelihood of muscle, cardiac and vascular dysfunction, this would mean that patients undergoing diuretic therapy should be placed on a higher calcium supplementation.

Conclusion: In conclusion, electrolyte disturbance and inflammation are associated with essential hypertension which can be reversed, first through lifestyle and diet modifications, then hypertensive drugs. Chloride anions seem to be a marker of response to treatment of hypertension. Hence, mmeasurement of plasma chloride is a more independent marker of treatment efficacy in treated hypertensives. Diuretics appears to be the most effective class of drugs in lowering blood pressure in this research, hence it should be recommended for hypertensives in this area. If combined with mineral supplementation, physical activity, life style modifications, regular blood pressure monitoring and

DASH diets, the treatment of essential hypertension will result in better clinical outcomes.

Declaration of Conflict of Interest: The authors declare no conflict of interest.

Data Availability Statement: Data are available upon request from the first author or corresponding author or any of the other authors.

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