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Effects of the Captopril- Calcium Combination in the Management of Dexamethasone-Induced Hypertension in Adult Male Wistar Rats; Its Effect on the Kidney Function and Thyroid Gland

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Abstract: Background: Hypertension is a major cause of clinical and preclinical damage to the kidneys, heart, and other body organs. Damage to these organs manifests as cardiovascular diseases, impaired renal disease, heart failure, stroke, etc. Cardiovascular diseases are the primary cause of death in the world. Objective: This study evaluated the antihypertensive effect of the co-administration of calcium and captopril on dexamethasone-induced hypertension in adult male Wistar rats on Systolic blood pressure, Histology of the kidney, Oxidative stress level in the kidney; Catalase (CAT), Glutathione (GSH) and Superoxide dismutase (SOD), Lipid peroxidation level in the kidney (malondialdehyde (MDA), Thyroid gland histology and Renal function: urea and creatinine. Methods: Twenty-five male Wistar rats weighing 160g-200g were randomly grouped into 5 groups of 5 rats each; control group A(distilled water only), test group B (0.5 mg/kg dexamethasone injection), test group C (0.5 mg/kg dexamethasone injection and 150mg/kg calcium), test group D (0.5 mg/kg dexamethasone injection and 40mg/kg captopril tablet), test group E (0.5 mg/kg dexamethasone injection, 40mg/kg captopril tablet and 150 mg/kg of calcium after thirty minutes). Results: The combination of calcium and captopril resulted in the restoration of the kidney function loss as seen in the histology of the kidney and thyroid gland. While the administration of captopril only showed more effectiveness in the treatment of systolic blood pressure. Conclusion: These results showed that the combination of Calcium and Captopril may be used in the treatment of organ damaged by hypertension while Captopril is a potent antihypertensive.

Keywords: Hypertension, Calcium, Captopril, Systolic Blood Pressure, Renal Function, Antioxidant Enzymes

1. Introduction

Systemic arterial hypertension, also known as hypertension, is characterized by consistently elevated blood pressure in the arteries of the body's systemic circulation [1]. The ratio of the systolic blood pressure to the diastolic blood pressure is a common way to express blood pressure. Hypertension is the most common preventable risk factor for cardiovascular disease (including coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, and peripheral artery disease), chronic kidney disease (CKD), and cognitive impairment, and is the main cause of all-cause death and disability in the globe [2]. The relationship between blood pressure and the increased risk of cardiovascular disease is graded and continuous, starting as low as 115/75 mmHg, well within what is considered to be the normotensive range. Reduced disease load and increased longevity among the global population are largely dependent on effective hypertension prevention and treatment [3].

Combination therapy is more advantageous than monotherapy for the treatment of hypertension due to the complementary effects of the antihypertensive mechanisms, the superposition of efficacy, and the eventual reduction of the disease's unfavorable consequences [4].

Successful treatment of hypertension is possible with limited side effects given the availability of multiple antihypertensive drug classes [5]. Captopril, which is an angiotensin-converting enzyme inhibitor, is widely used in experiments dealing with the treatment of cardiovascular diseases like hypertension. Additionally, it is used to treat heart failure, safeguard the kidneys from diabetes-related damage, and increase survival rates following a heart attack. Captopril is an ACE inhibitor that eases blood vessel tension to facilitate easier blood flow. Several studies

have documented the favorable and cardioprotective effects of captopril treatment [6]. Captopril blocks the conversion of angiotensin I to angiotensin II and prevents the degradation of vasodilatory prostaglandins, thereby inhibiting vasoconstriction and promoting systemic vasodilation [7].

Calcium is the fifth most abundant element in the human body. As a macronutrient with a daily requirement of more than 1000 mg, calcium is a vital mineral for human growth and development [8]. Since calcium is a mineral that is frequently found in human diets, it is important to research how it affects bodily functions and human health. This study will evaluate the effect of the combination of calcium and captopril on blood pressure, selected body organ histology, and biochemical indices in male Wistar rats.

2. Materials and Methodology

2.1 Animal care and grouping

Twenty-five healthy male Wistar rats weighing about 160g – 200g were used for this experiment. The rats were bred in plastic and wire gauze cages in the animal house of the Obafemi Awolowo College of Health Science, Sagamu campus, Olabisi Onabanjo University, Ago-Iwoye, Ogun State, Nigeria. The rats were allowed to acclimatize for a period of two weeks; they were fed with a standardized pellet diet and allowed free access to water. The care and handling of the animals were by the internationally accepted standard guidelines for animals' use by the National Research Council (2011).

They were given access to distilled water and pelletized rat chow. The animals were weighed and randomly assigned to groups as shown in the table 1 below.

2.2 Preparation and administration of Captopril

50 mg captopril tablet was crushed and dissolved in 6.3 ml of distilled water. 40 mg dose of captopril was obtained from the stock solution according to the method described by [9].

2.3 Induction of hypertension

Hypertension was induced according to the methods described by Zhang et al., (2004) [10] and Ong et al., (2007) [11]. In the test groups, dexamethasone (0.5 mg/kg), was administered by subcutaneous injection every evening for seven days.

2.4 Measurement of blood pressure

The systolic blood pressure and diastolic blood pressure were measured by the noninvasive tail-cuff method weekly in conscious restrained rats. The animals were restrained in a rat restrainer. Rats were trained with blood pressure measuring equipment for one week before initiation of the experiment. Blood pressure was recorded at least three times for each rat and averaged to obtain a mean systolic blood pressure.

2.5 Preparation and administration of calcium

300 mg calcium tablet was crushed and dissolved in 20 ml of distilled water. 150 mg dose of captopril was obtained from the stock solution according to the method described by Erhirhie et al., (2014) [9].

Table 1. Animal grouping and treatment administered

Group	Treatment	Number of rats per group
A: normal control	Distilled water only	5
B: hypertensive control	0.5 mg/kg of dexamethansone injection (S. C)	5
C: calcium treatment group	0.5 mg/kg of dexamethansone injection (S.C) and 150 mg/kg of calcium (P.O)	5
D: captopril treatment group	0.5 mg/kg of dexamethansone injection (S.C) and 40 mg/kg of captopril tablet (P.O)	5
E: combined treatment group	0.5 mg/kg of dexamethasone injection (SC), 40 mg/kg of captopril tablet (P.O), and 150 mg/kg of calcium (P.O) after thirty minutes	5

S.C: subcutaneous, P.O: oral route of administration.

2.6 Procedure for blood collection

Blood was collected from the orbital venous sinus, the rat was restrained, the neck gently scruffed and the eye made to bulge. A capillary tube was inserted dorsally into the eye and blood was allowed to flow by capillary action through the capillary tube into the lithium heparin sample bottle.

2.7 Urea level determination

Urea was assayed according to the method described in Randox urea kits. 2.50 ml of reagents 1, 2, and 3 were added to 10 micro litter of plasma sample and were mixed immediately and incubated at 37°C for 10 minutes. The absorbance of the plasma sample and standard were measured against the blank at 546 nm.

2.8 Creatinine level determination

Creatinine was assayed according to the method described in Randox kits. 2.0 ml of working reagent was added to 0.2 ml of plasma. This was measured against the blank containing the standard solution. It was mixed and after 30 seconds, the absorbance of A1 of the standard and plasma were read at 492 nm. Exactly 2 minutes later, the absorbance of A2 of standard and plasma was read at 492 nm.

2.9 Procedure for determination of antioxidant enzymes

The kidney tissues to be assessed for oxidative studies were homogenized in phosphate buffer in a ratio of four to one. Superoxide dismutase (SOD) activities, glutathione reductase (GSH) activities, catalase (CAT) activities and malondialdehyde (a marker of lipid peroxidation (MDA) were determined. Superoxide dismutase activities were determined according to the method of Valerino and McCormack (1971) [12]. Increased absorbance was monitored with a UV spectrophotometer at 480 nm every 60 seconds for 180 seconds. One unit of SOD activity was given as the amount of SOD necessary to cause 50% inhibition of the oxidation of adrenaline to adrenochrome during one minute. The activity of SOD was expressed as µg/mg protein. Reduced glutathione was determined using the methods of Sedlak and Lindsay (1968) [13]. The absorbance of the yellow color formed upon the addition of Ellman's reagent was read within 5 minutes at 412 nm with a UV spectrophotometer. A plot of absorbance versus concentration of reduced GSH was then obtained from a serial dilution of the stock GSH prepared by adding 1.5 mL of phosphate buffer and 1.5 mL of Ellman's reagent. The amount of GSH was expressed as µg/mg protein [14]. Catalase activity was determined with the method described by Sinha (1972) [15]. Proper dilution of the serum samples was done at a ratio of one to ten dilution in series. Catalase was expressed as mmoles of H_2O_2 consumed per minute per mg protein. It used the principle that dichromate in acetic acid is an unstable intermediate. The chromic acetate produced was measured colorimetrically at 570nm. Malondialdehyde (MDA) was determined spectrophotometrically from the pink color product of thiobarbituric acid (TBA) reactive substances complex. 0.1 mL of the test sample was mixed with 0.5 mL of 10% TCA and 0.5 mL of 75% TBA was added to it. The mixture was then placed in a water bath at 80^{o}C for 45 minutes. The resulting pink solution's absorbance was measured against a reference blank of distilled water at 532 nm. The test sample was calibrated using the MDA as a standard and the result was expressed as the amount of free MDA produced. The MDA level was calculated according to Adam-Vizi and Sergi (1982) [16]. The Lipid peroxidation was expressed as µg/mg Protein.

2.10 Histological examination

After, harvesting the heart and thyroid tissue, it was fixed in a 10% neutral buffered formalin, it was later embedded in paraffin and 5µm thick sections were prepared and stained with hematoxylin and eosin using standard procedures. The slides were viewed under a light microscope and photomicrographs were taken (200×).

2.11 Statistical Analysis

All analysis was done using SPSS- VIS statistical software package and student's T-test. Data were expressed as Mean ± SEM with $P<0.05$ considered statistically significant.

3. Results and Discussion

3.1 Effect of calcium-captopril combination on systolic blood pressure changes in dexamethasone-induced hypertension in male Wistar rats

Table 2 below shows the effect of calcium-captopril interaction on systolic blood pressure changes in dexamethasone-induced hypertension in male Wistar rats, in rats administered with 0.5 mg/kg of dexamethasone injection (S.C) there was a significant increase in the systolic blood pressure after induction and at week one of treatment (165.33±16.50 and 162.67±16.5) respectively. In groups administered with 0.5 mg/kg of dexamethasone injection (S.C) and 150 mg/kg of calcium (P.O), there was a significant increase in the systolic blood pressure when compared to the control group (186.00±8.89) after induction, while at week two of treatment there was a significant increase when compared to test group A and decrease

when compared to test group B (120.67±1.15). In groups administered with 0.5 mg/kg of dexamethasone injection (S.C) and 40 mg/kg of captopril tablet (P.O) there was a significant increase in the systolic blood pressure after induction and at week two when compared to the control group (157.33±14.29, 107.33±15.63), when compared to test group B, there was significant decrease at week one and two (103.33±30.02 107.33±15.63), also there was a significant decrease in the systolic blood pressure after induction when compared to test group C (157.33±14.29). In groups administered with 0.5 mg/kg of dexamethasone injection (SC) and 40 mg/kg of captopril tablet (P.O) and 150 mg/kg of calcium (P.O) after thirty minutes, there was a significant increase in the systolic blood pressure after induction and at week two when compared to the control group A (153.33±12.58, 115.67±9.2), also there was significant decrease at week two in the systolic blood pressure when compared to test group B (115.67±9.2)

Systolic hypertension in most cases develops as a result of the reduced elasticity of the arterial system as seen in our study rats administered with 0.5 mg/kg of dexamethasone injection which showed an increase in the systolic blood pressure which indicated that dexamethasone can reduce vascular pressor responsiveness thereby causing structural impairment in the blood vessel which will result in reduced compliance of the arterial vessels, decreased lumen-to-wall ratio, and increased thickening and fibrotic remodeling of the vascular intima and media. As a result, these stiffened conduit arteries lead to an increase in pulse pressure and pulse wave velocity, causing an elevation in systolic blood pressure [17]. According to Table 2, calcium in the co-administration group and captopril-treated rats, all showed positive changes in the systolic blood pressure with the captopril-treated group showing the highest positive changes at the end of week two, captopril function in reducing hypertension by attenuation of angiotensin II–induced facilitation of peripheral sympathetic neurotransmission or by lowering of the increased activity of brain RAS that drives the enhanced sympathetic outflow, also captopril eliminates the angiotensin II–induced decrease of norepinephrine reuptake to nerve endings leading to enhanced sympathetic vasoconstriction and therefore leading to vasodilation of the blood vessels resulting in a decrease in systolic blood pressure [18], [19].

3.2 Effect of calcium- captopril combination on antioxidant enzyme activity and lipid peroxidation level in male Wistar rats

Table 3 shows the effect of calcium-captopril interaction on antioxidant enzyme activity and lipid peroxidation level in male Wistar rats. Group B, which received only dexamethasone injection, had significantly lower levels of GSH, SOD, and CAT, but higher levels of MDA compared to Group A, which received only distilled water. Group C, which received dexamethasone injection and calcium, showed significant improvement in GSH, SOD, and CAT levels, but not in MDA levels compared to Group B. Group D, which received dexamethasone injection and captopril, showed significant improvement in GSH and SOD levels, but not in CAT and MDA levels compared to Group B. Group E, which received dexamethasone injection, captopril, and calcium, showed significant improvement in GSH, SOD, MDA and CAT levels.

In our study, there was an increase in the MDA level in the hypertensive group, it was proven that essential hypertension has lower nitric oxide levels (NO) and elevated MDA levels caused by excessive oxidative stress, compared with normotensive individuals [20].

Table 2. Effect of calcium-captopril combination on systolic blood pressure changes in dexamethasone-induced hypertension in male Wistar rats

Groups	Pre- Systolic (mmHg)	After induction systolic (mmHg)	Week one systolic (mmHg)	Week two systolic (mmHg)
A	120.67±16.01	108.00±6.56	107.00±13.86	82.00±8.54
B	112.67±25.33	165.33±16.50A	162.67±16.5A	164.00±14.93
C	109.00±12.77	186.00±8.89A	131.33±22.50	120.67±1.15A,B
D	102.33±22.23	157.33±14.29A,C	103.33±30.02B	107.33±15.63A,B
E	112.33±10.79	153.33±12.58A	135.67±34.85	115.67±9.29A,B

Each value is an expression of mean ± SEM. (P <0.05)

a - Values were significant when compared to group A, b-Values were significant when compared to group B, c-Values were significant when compared to group C, d- Values were significant when compared to group D

Table 3. Effect of calcium- captopril combination on antioxidant enzyme activity and lipid peroxidation level in male Wistar rats

Groups	GSH (µmol/ml)	SOD (µmol/ml/min/mg/pro)	CAT (µmol/ml/min/mg/pro)	MDA (µmol/ml)
A	45.985±2.57	11.665±1.15	14.57±3.07	3.2±0.014
B	8.395±0.23^{A}	0.34±0.25^{A}	1.65±0.66^{A}	15.43±0.72^{A}
C	33.98±4.29 $^{A, B}$	3.16±0.25 $^{A, B}$	9.68±0.16^{B}	4.68±3.46 ^{B}
D	25.64±7.47 $^{A, B}$	2.81±0.16 $^{A, B}$	7.79±0.48$^{B, C}$	7.15±2.53^{B}
E	86.6±29.67^{B}	3.19±0.23^{A,B}	10.05±0.49$^{B, D}$	3.25±0.30^{B}

Each value is an expression of mean ± SEM. (P <0.05)

a - Values were significant when compared to group A, b-Values were significant when compared to group B, c- Values were significant when compared to group C, d- Values were significant when compared to group D

A study also suggested that patients with essential hypertension had elevated concentrations of MDA and indicated increased lipid peroxidation due to an impaired oxidant/antioxidant status [21].

The decrease in the GSH level observed during this study can be attributed to the high MDA level. High MDA levels indicate higher free radicals, this benzene radical can suppress GSH consequently reducing its availability during hypertension [22]. In this study, SOD and CAT were significantly reduced, and SOD and CAT act as an antioxidant defense against oxidative stress in the body [23], the decrease in their levels during this study was a result of the oxidative stress in the hypertensive group.

Because of the antioxidant properties of calcium and captopril [24] GSH, SOD, CAT& MDA levels were restored to normal, and the combination of calcium and captopril had more therapeutic effect.

3.3 Effect of calcium- captopril combination on urea and creatinine levels in male Wistar rats

Table 4 presents the results of the effect of calcium-captopril interaction on urea and creatinine levels in male Wistar rats. The results show that the rats in Group B had significantly higher levels of urea and creatinine compared to the rats in Group A, indicating that dexamethasone-induced hypertension in the rats. However, the rats in Groups C, D, and E showed a decrease in urea and creatinine levels compared to Group B, indicating that calcium and captopril had a protective effect against dexamethasone-induced hypertension. Notably, the rats in Group E, which received all three treatments, showed the lowest levels of urea and creatinine, indicating that the combination of calcium and captopril had a synergistic effect in protecting against hypertension. Hypertension, or high blood pressure, can cause an increase in urea and creatinine levels in the blood [25]. Urea is a waste product that forms in the liver when the body breaks down proteins, while creatinine is a waste product that comes from muscle metabolism.

When blood pressure is high, it can damage the small blood vessels in the kidneys, impairing their ability to filter waste products from the blood [26]. As a result, urea and creatinine can build up in the bloodstream, leading to elevated levels [27].

The increase in urea and creatinine levels is often used as a marker of kidney damage or dysfunction, as the kidneys are responsible for removing these waste products from the body. In some cases, hypertension can lead to chronic kidney disease, which is a progressive loss of kidney function over time [28].

In addition, hypertension can also cause damage to the glomeruli, which are the tiny blood vessels in the kidneys responsible for filtering waste products from the blood [29]. When blood pressure is high, it can cause the glomeruli to become damaged or even destroyed, impairing their ability to filter waste products from the blood. This, in turn, can lead to an increase in urea and creatinine levels [30].

During our study, calcium attenuated the elevated levels of urea and creatinine induced by hypertension. Several mechanisms have been proposed to explain the effect of calcium on hypertension-induced urea and creatinine levels. One proposed mechanism is the renin-angiotensin-aldosterone system (RAAS). The RAAS is a hormonal system that regulates blood pressure by controlling the amount of sodium and water reabsorbed by the kidneys. When blood pressure is low, the kidneys secrete the enzyme renin, which converts angiotensinogen (produced by the liver), into angiotensin I. Angiotensin I is then converted to angiotensin II by the enzyme angiotensin-converting enzyme (ACE), which is primarily produced in the

lungs. Angiotensin II is a potent vasoconstrictor that causes the blood vessels to narrow, increasing blood pressure. It also stimulates the secretion of aldosterone, a hormone that causes the kidneys to retain sodium and water, leading to an increase in blood volume and blood pressure. Calcium has been shown to inhibit the secretion of renin, thereby decreasing the production of angiotensin II and aldosterone, leading to a decrease in blood pressure.

Calcium has also been shown to improve endothelial function. The endothelium plays a crucial role in regulating blood pressure. When the endothelium is healthy, it produces a molecule called nitric oxide, which causes the blood vessels to dilate, leading to a decrease in blood pressure. Calcium has been shown to enhance the production of nitric oxide and improve endothelial function, leading to a decrease in blood pressure.

Captopril is a type of medication known as an angiotensin-converting enzyme (ACE) inhibitor. ACE is an enzyme that plays a role in the production of angiotensin II, a hormone that causes constriction of blood vessels and increases blood pressure. By inhibiting ACE, captopril reduces the production of angiotensin II, leading to the relaxation of blood vessels and a decrease in blood pressure. This mechanism of action is the primary reason why captopril is used to treat hypertension.

However, captopril has also been found to affect urea and creatinine levels. Urea and creatinine are waste products that are normally filtered out of the blood by the kidneys and excreted in the urine. When the kidneys are damaged, their ability to filter out these waste products is reduced, leading to an increase in their levels in the blood. Captopril has been found to improve kidney function in patients with hypertension-induced kidney damage. One possible explanation for this is that captopril increases blood flow to the kidneys, which can improve their function. This is because hypertension can cause damage to the blood vessels in the kidneys, leading to reduced blood flow and impaired function. By reducing blood pressure, captopril can improve blood flow to the kidneys, which can improve their ability to filter out waste products.

Another possible mechanism of action of captopril on urea and creatinine levels is through its effect on the RAAS. The RAAS is a complex system that plays a role in regulating blood pressure and fluid balance in the body. When blood pressure is low, the kidneys release an enzyme called renin, which converts angiotensinogen (a protein produced by the liver) into angiotensin I. Angiotensin I is then converted to angiotensin II by ACE, which causes constriction of blood vessels and an increase in blood pressure. Captopril inhibits ACE, which reduces the production of angiotensin II. This can lead to a decrease in the constriction of blood vessels and a decrease in blood pressure. By reducing the production of angiotensin II, captopril can decrease the release of aldosterone, leading to increased excretion of sodium and water in the urine. This can improve fluid balance in the body and reduce the workload on the kidneys, which can improve their function and reduce urea and creatinine levels.

The interaction between calcium and captopril has also been studied in the context of hypertension-induced urea and creatinine levels [31]. Captopril works by inhibiting the conversion of angiotensin I to angiotensin II, leading to a decrease in blood pressure. Calcium has been shown to enhance the effectiveness of captopril from our study, leading to a further decrease in blood pressure and a decrease in urea and creatinine levels.

Table 4. Effect of calcium- captopril combination on urea and creatinine levels in male Wistar rats

Groups	Urea	Creatinine
A	40.33±4.51	1.4±0.2
B	53.67±8.02	1.87±0.3
C	45.33±13.32	1.7±0.45
D	40.00±13.53	1.57±0.49
E	39.00±2.65	1.3±0.1

Each value is an expression of mean ± SEM. ($P < 0.05$)

a - Values were significant when compared to group A, b-Values were significant when compared to group B, c- Values were significant when compared to group C, d- Values were significant when compared to group D

3.4 Effect of calcium- captopril combination on the histo-architecture of the kidney in male Wistar rats.

Within group A, the renal histology was in place, with all the structures characterized well, including the renal capsular space (CS), glomerular podocytes, and tubules (shown by blue arrowheads). On the other hand, the hypertension group displayed fibrinoid necrosis and erosion of the glomeruli tuft layer (demonstrated by dark thick arrows), hypertrophied tubules (demonstrated by dark arrowheads), and capsular space with loss of capacities. However, the renal histology of Group C progressed, with mild expansion of the glomerular tuft layer (shown by dark thick arrows), regenerated proximal and distal tubules (shown by blue thick bolts), and well-differentiated capsular space (CS). Moreover, Group D appeared a well-improved recovery of the glomerular layer (demonstrated by dark thick arrows), capsular space (CS), and atrophied tubules (demonstrated by dark lean bolts). Finally, Group E displayed a well-improved

renal morphology, with the glomerular tuft layer (demonstrated by dark thick arrows), capsular space (CS), and tubules (demonstrated by blue thin arrows) being well-defined without any disorientation. Hypertensive group B manifests fibrinoid necrosis as a result of pressure in the arterioles that weakens blood vessels leading to their death, hence the ischemia and subsequent fibrinous necrosis. The high pressure in hypertensive individuals can also destroy the blood vessels that supply the glomeruli, causing insufficient blood flow [32].

Fibrinoid necrosis observed in the hypertensive group B was a result of pressure in the arterioles leading to the weakening of blood vessels and consequently death of blood vessels [32], this high pressure can damage the blood vessels that supply the glomeruli, leading to ischemia (inadequate flow of blood) and subsequent fibrinous necrosis. Another mechanism is related to the increased workload that is placed on the glomeruli due to hypertension. The glomeruli are responsible for filtering the blood, and when hypertension causes the heart to pump harder and faster, the glomeruli are forced to work harder to maintain their filtration function [33]. Over time, this increased workload can lead to degeneration and damage to the glomeruli.

Generally, hypertension can lead to damage in the blood vessels in the kidneys, which can in turn lead to decreased blood flow and oxygen delivery to the kidney tissue. This can cause damage to the nephrons, leading to hypertrophied tubules and capsular space, as well as other changes such as thickening of the glomerular basement membrane and scarring. Over time, this damage can result in a loss of kidney function, which can manifest as proteinuria, reduced urine output, and eventual kidney failure if left untreated. Increased calcium levels may lead to a decrease in the concentration of lipid peroxidation products, this helps in the treatment of hypertension and thereby restoring blood flow to the kidneys causing a repair of the kidney blood vessels [34]. It has been demonstrated that endothelium-dependent relaxation is attenuated in hypertension (a phenomenon referred to as endothelial dysfunction) and contributes to the increase of peripheral resistance [35], ACE inhibitors improve kidney function by reducing the peripheral resistance as observed in the group administered with captopril during our study. The combination of both calcium and captopril brought about more effectiveness showing the synergy between both.

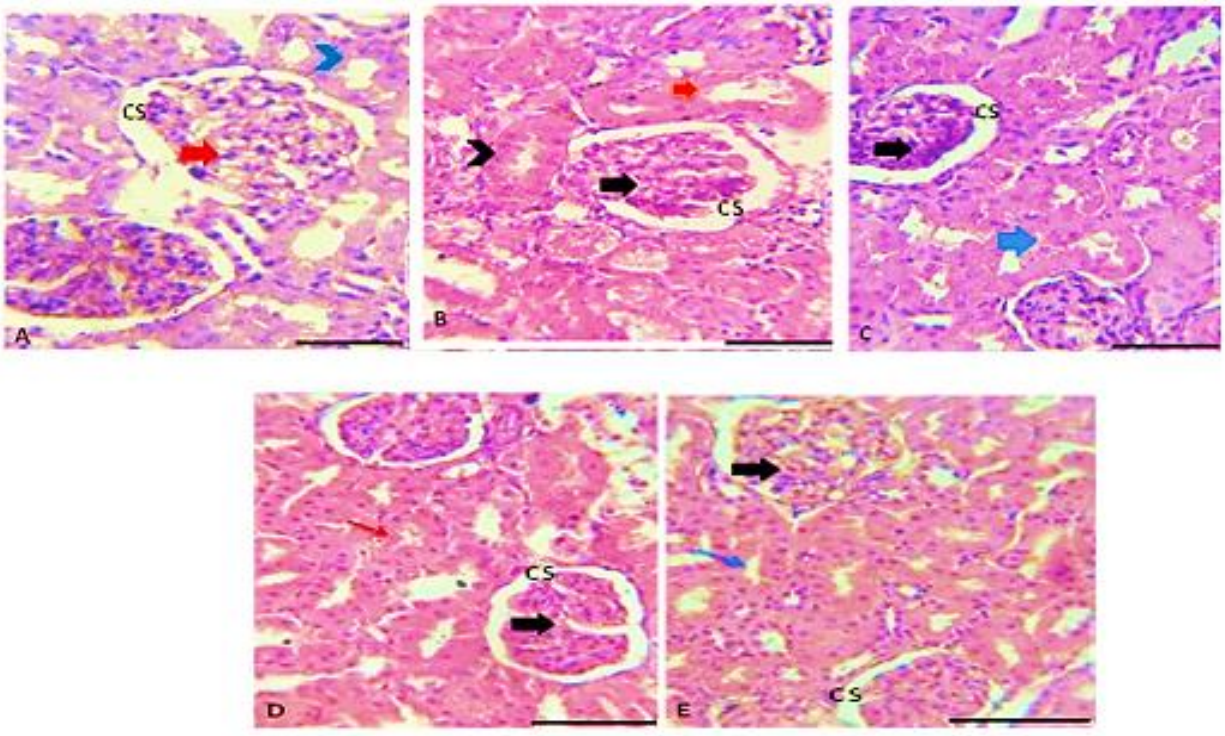

Figure 1. Effect of calcium- captopril interaction on the histo-architecture of the kidney in male Wistar rats. Scale Bar =120µm. A; Distilled water only, B; 0.5 mg/kg of dexamethansone injection (S. C), C; 0.5 mg/kg of dexamethansone injection (S.C) and 150 mg/kg of calcium (P.O), D; 0.5 mg/kg of dexamethansone injection (S.C) and 40 mg/kg of captopril tablet (P.O), E; 0.5 mg/kg of dexamethansone injection (SC) and 40 mg/kg of captopril tablet (P.O) and 150 mg/kg of calcium (P.O) after thirty minutes

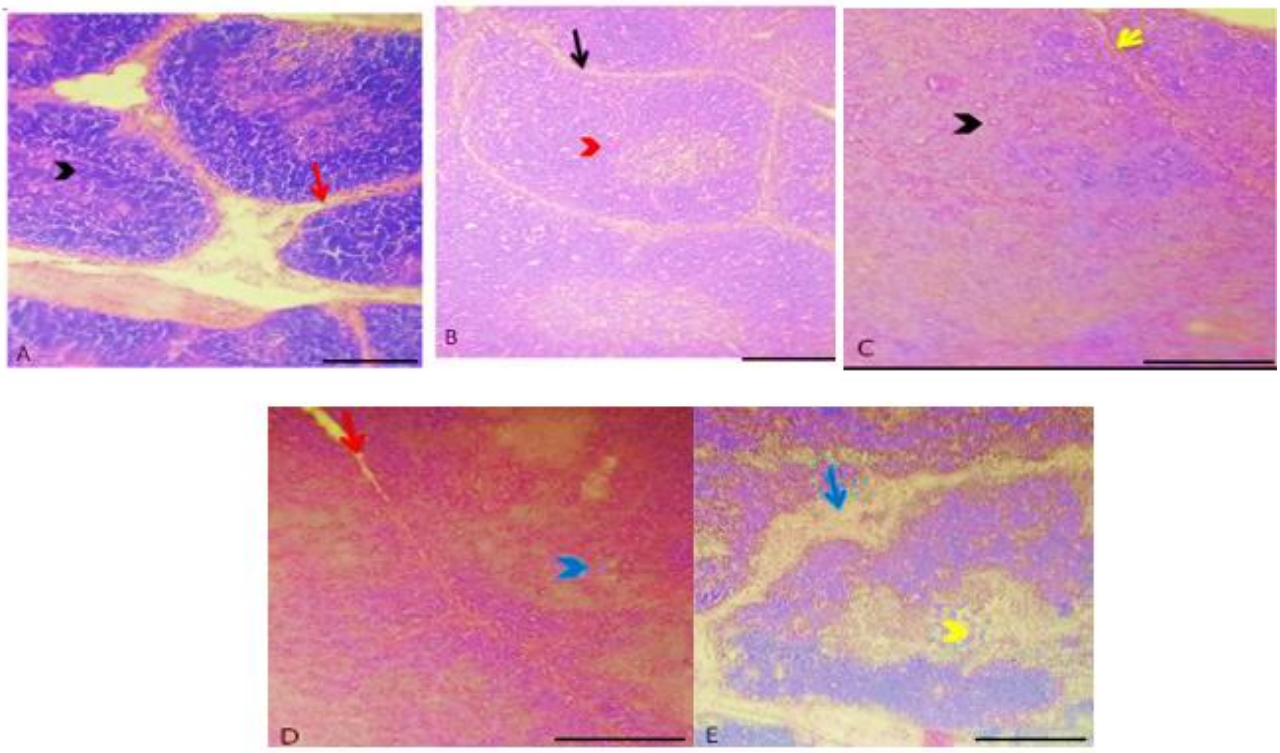

Figure 2. Effect of calcium- captopril interaction on the histo-architecture of the thyroid gland in male Wistar rats. Scale Bar =120µm. A; Distilled water only, B; 0.5 mg/kg of dexamethansone injection (S. C), C; 0.5 mg/kg of dexamethansone injection (S.C) and 150 mg/kg of calcium (P.O), D; 0.5 mg/kg of dexamethansone injection (S.C) and 40 mg/kg of captopril tablet (P.O), E; 0.5 mg/kg of dexamethansone injection (SC) and 40 mg/kg of captopril tablet (P.O) and 150 mg/kg of calcium (P.O) after thirty minutes

3.5 Effect of calcium- captopril interaction on the histo-architecture of the thyroid gland in male Wistar rats

In the control group, there was normal thyroid gland tissue histology showing organized and well-differentiated tissue, the interlobular connective tissue (red thin arrow), follicles (black arrowhead), and epithelial cells are well differentiated without any disorientation. In the hypertensive control group, there was damaged and hypochromatic thyroid gland tissue with loss of function, the interlobular connective tissue (black thin arrow), and the follicles (red arrowhead) were constricted. Group C shows improved thyroid gland histology with constricted interlobular connective tissue (yellow thin arrow), and regenerated follicles (black arrowhead). Group D shows well-improved regeneration of the cardiac muscle (yellow thin arrow) and the cardiomyocytes (blue circle) without any loss of inflammatory response. Group D shows well-improved thyroid gland tissue, the connective tissue (blue thin arrow) and the follicles (yellow arrowhead) are intact. H/E X200.

Hypothyroidism has been associated with increased peripheral resistance and decreased cardiac output, which can lead to an increase in blood pressure [36]. Hyperthyroidism, on the other hand, has been associated with an increase in cardiac output and a decrease in peripheral resistance, which can also lead to an increase in blood pressure [37]. Thyroid disorders induce several hemodynamic changes leading to elevated BP as a consequence of their interaction with endothelial function, vascular reactivity, renal hemodynamics, and the renin-angiotensin system [38]. The elevated blood pressure in the dexamethasone-induced hypertension led to damaged thyroid tissues and constricted connective tissue. In thyroid pathologies, calcium is important for the regulation of proliferation and invasion [39], this supports the observed regeneration seen in the group administered with calcium. The hypertensive group treated with captopril showed a well-improved thyroid gland histoarchitecture. Proper treatment of hypertension can often control both the high blood pressure and the condition that causes it [40] hence, a reason for the well-improved thyroid gland histology.

4. Conclusion

This study shows that the use of Captopril abated high systolic blood pressure, while the combination of calcium and captopril improved the damage caused to the histoarchitecture of the kidney and thyroid gland due to hypertension during this study, and also caused a decrease in the urea and creatinine level. GSH, SOD, CAT, and MDA were restored to normal levels.

References

[1] M.E. Rubio-Ruiz, I. Pérez-Torres, M.E. Soto, G. Pastelín, V. Guarner-Lans Aging in blood vessels. Medicinal agents FOR systemic arterial hypertension in the elderly. Aging research reviews, 18, (2014) 132-147. [DOI]

[2] Q. Jiang, Q. Zhang, T. Wang, Q. You, C. Liu, S. Cao, Prevalence and risk factors of hypertension among college freshmen in China. Scientific Reports, 11(1), (2021) 1-8. [DOI]

[3] S.E. Kjeldsen, Hypertension and cardiovascular risk: General aspects. Pharmacological Research, 129, (2018) 95-99. [DOI]

[4] C. Guerrero-García, A.F. Rubio-Guerra, Combination therapy in the treatment of hypertension. Drugs in context, 7, (2018) 212531. [DOI]

[5] M. Jadhav, C. Yeola, G. Zope, A. Nabar Aliskiren, the first direct renin inhibitor for the treatment of hypertension: the path of its development. Journal of Postgraduate Medicine, 58(1), (2012) 32-38.

[6] S. Man, L. Yang, H. Xiang, G. Lu, Y. Wang, C. Liu, W. Gao, Antihypertensive and renal protective effect of Shunaoxin pill combined with captopril on spontaneous hypertension rats. Biomedicine & Pharmacotherapy, 125, (2020) 109977. [DOI]

[7] M. Hashemzadeh, S. Park, H. Ju, R. Movahed, A novel design of combining the angiotensin-converting enzyme (ACE) inhibitor captopril with the angiotensin receptor blocker (ARB) losartan using homo coupling via PEG diacid linker. Recent Patents on Cardiovascular Drug Discovery (Discontinued), 8(3), (2013) 221-225. [DOI]

[8] L.M. Moreira, R.P. Araujo, F.P. Leonel, H.V. Machado, A.O. Teixeira, F.V. Santos, J.P. Lyon, The biological roles of calcium: nutrition, diseases, and analysis. Royal Society of Chemistry, (2015) 21-29. [DOI]

[9] E.O. Erhirhie, N.E. Ekene, D.L Ajaghaku, Guidelines on dosage calculation and stock solution preparation in experimental animals' studies. Journal of Natural Sciences Research, 4(18), (2014) 100-106.

[10] Y. Zhang, K. D. Croft, T. A. Mori, C.G. Schyvens, K.U. McKenzie, J.A. Whitworth, The antioxidant tempol prevents and partially reverses dexamethasone-induced hypertension in the rat. American journal of hypertension, 17(3), (2004) 260-265. [DOI]

[11] S.L. Ong, J.J. Vickers, Y. Zhang, K.U. McKenzie, C.E. Walsh, J.A. Whitworth, Role of xanthine oxidase in dexamethasone-induced hypertension in rats. Clinical and experimental pharmacology & physiology, 34(5-6), (2007) 517-519. [DOI]

[12] D.M. Valerino, J.J. Mccormack, Xanthine oxidase-mediated oxidation of epinephrine. Biochemical Pharmacology, 20(1), (1971) 47-55. [DOI]

[13] J. Sedlak, R.H. Lindsay, Estimation of total protein bound and nonprotein sulfhydryl groups in tissues with Ellman's reagent. Anal of Biochemistry, 25, (1968) 192-205. [DOI]

[14] D.J. Jollow, J.R. Mitchell, N. Zampaglione, J.R. Gillette, Bromobenzene-induced liver necrosis. Protective role of glutathione and evidence for 3, 4-bromobenzene oxide as the hepatotoxic metabolite. Pharmacology, 11(3), (1974) 151-169. [DOI]

[15] A.K. Sinha, Colorimetric assay of catalase. Analytical Biochemistry, 47(2), (1972) 389-394. [DOI]

[16] V. Ádám-Vizi, A. Seregi, Receptor independent stimulatory effect of noradrenaline on Na, K-ATPase in rat brain homogenate: Role of lipid peroxidation. Biochemical pharmacology, 31(13), (1982) 2231-2236. [DOI]

[17] J.L. Tan, K. Thakur (2021) Systolic hypertension. *StatPearls Publishing*.

[18] I.F. Alexa, M. Ignat, R.F. Popovici, D. Timpu, E. Popovici, In vitro, controlled release of antihypertensive drugs intercalated into unmodified SBA-15 and MgO modified SBA-15 matrices. International journal of pharmaceutics, 436(1-2), (2012) 111-119. [DOI]

[19] A. Puzserova, I. Bernatova, Blood pressure regulation in stress: focus on nitric oxide-dependent mechanisms. Physiological rvar, S., & Nasiri Amiri, F. (2017). Association of lipid peroxidation and antioxidant status with metabolic syndrome in Iranian healthy elderly women. Biomedical Reports, 7(4), (2016) 331-336. [DOI]

[20] G.V. Naregal, B.B. Devaranavadagi, S.G. Patil, B.S. Aski, Elevation of oxidative stress and decline in endogenous antioxidant defense in elderly individuals with hypertension. Journal of clinical and diagnostic research JCDR, 11(7), (2017) BC09. [DOI]

[21] Bakhtiari, K. Hajian-Tilaki, S. Omidvar, & F. Nasiri Amiri (2017). Association of lipid peroxidation and antioxidant status with

metabolic syndrome in Iranian healthy elderly women. Biomedical Reports, 7(4), 331-336.

[22] W. Domej, K. Oettl, W. Renner, Oxidative stress and free radicals in COPD–implications and relevance for treatment research, 65, (2014) 1207-1224. [DOI]

[23] O. M. Ighodaro, O.A. Akinloye, First-line defense antioxidants-superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defense grid. Alexandria journal of medicine, 54(4), (2018) 287-293. [DOI]

[24] K.A. Ahmad, D. Yuan Yuan, W. Nawaz, H. Ze, C. X. Zhuo, B. Talal, D. Qilong, Antioxidant therapy for management of oxidative stress-induced hypertension. Free radical research, 51(4), (2017) 428-438. [DOI]

[25] A.C. Webster, E. V. Nagler, R.L. Morton, P. Masson, Chronic kidney disease. The Lancet, 389(10075), (2017) 1238-1252. [DOI]

[26] B.M.I. Cabral, S.N. Edding, J.P. Portocarrero, E.V. Lerma, Rhabdomyolysis. Disease-a-Month, 66(8), (2020) 101015. [DOI]

[27] S. Pasala, J.B. Carmody, How to use serum creatinine, cystatin C, and GFR. Archives of Disease in Childhood-Education and Practice, 102(1), (2017) 37-43. [DOI]

[28] S. Vadakedath, V. Kandi, Dialysis: a review of the mechanisms underlying complications in the management of chronic renal failure. Cureus, 9(8), (2017) e1603. [DOI]

[29] J.A. Kellum, P. Romagnani, G. Ashuntantang, C. Ronco, A. Zarbock, H.J. Anders, Acute kidney injury. Nature reviews Disease primers, 7(1), (2021) 1-17. [DOI]

[30] P. Sobczuk, C. Szczylik, C. Porta, A.M. Czarnecka, (2017). Renin angiotensin system deregulation as renal cancer risk factor. Oncology Letters, 14(5), 5059-5068. [DOI]

[31] J.M. Wardlaw, C. Smith, M. Dichgans, Small vessel disease: mechanisms and clinical implications. The Lancet Neurology, 18(7), (2019) 684-696. [DOI]

[32] Y. Ohn, Y. Kanno, T. Takenaka, Central blood pressure and chronic kidney disease. World journal of nephrology, 5(1), (2016) 90. [DOI]

[33] W.C. Lee, H.Y. Wong, Y.Y. Chai, C.W. Shi, N. Amino, S. Kikuchi, S. H. Huang, Lipid peroxidation dysregulation in ischemic stroke: plasma 4-HNE as a potential biomarker? Biochemical and biophysical research communications, 425(4), (2012) 842-847. [DOI]

[34] J. Jiang, J.P. Zheng, Y. Li, Z. Gan, Y. Jiang, D. Huang, Y. Ke, Differential contribution of endothelium-derived relaxing factors to vascular reactivity in conduit and resistance arteries from normotensive and hypertensive rats. Clinical and Experimental Hypertension, 38(4), (2016) 393-398. [DOI]

[35] M. Udovcic, R.H. Pena, B. Patham, L. Tabatabai, A. Kansar Hypothyroidism and the heart. Methodist DeBakey Cardiovascular Journal, 13(2), (2017) 55. [DOI]

[36] B. Afsar, R. Elsurer, The relationship between magnesium and ambulatory blood pressure, augmentation index, pulse wave velocity, total peripheral resistance, and cardiac output in essential hypertensive patients. Journal of the American Society of Hypertension, 8(1), (2014) 28-35. [DOI]

[37] F. Vargas, I. Rodriguez-Gomez, P. Vargas-Tendero, E. Jimenez, M. Montiel, The renin–angiotensin system in thyroid disorders and its role in cardiovascular and renal manifestations. Journal of Endocrinology, 213(1), (2012) 25-36. [DOI]

[38] J.K. Huang, L. Ma, W.H. Song, B.Y. Lu, Y.B. Huang, H.M. Dong, R. Zhou, MALAT1 promotes the proliferation and invasion of thyroid cancer cells by regulating the expression of IQGAP1. Biomedicine & Pharmacotherapy, 83, (2016) 1-7. [DOI]

[39] E. Lurbe, E. Agabiti-Rosei, J. K. Cruickshank, A. Dominiczak, S. Erdine, A. Hirth, A. Zanchetti 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. Journal of hypertension, 34(10), (2016) 1887-1920. [DOI]

[40] F.D. Fuchs, P.K. Whelton, High blood pressure and cardiovascular disease. Hypertension, 75(2), (2020) 285-292. [DOI]

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Conflict of interest

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