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Effects of Potassium and Magnesium on Some Hemodynamic and Renal Function Related Parameters in 2k1c Hypertensive Rats

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Abstract—The present study was done to investigate the effect of potassium and magnesium on aldosterone level, systolic blood pressure (SBP), heart rate (HR); renal function test parameters, serum nitric oxide (NO) and malondialdehyde (MDA) in 2-kidney, 1-clip (2K1C) hypertensive rats. The experimental rats were divided into six groups, each with seven rats and the treatments were continued for 4 weeks: Group 1: Control, Group 2: Sham operated surgery rats ,Group 3: 2K1C hypertensive rats , Group4: 2K1C + Potassium chloride ,KCl (80 gms/Kg diet) , Group5: 2K1C + Magnesium sulphate ,MgSO4 (80 gms/Kg diet), Group6: 2K1C +KCl+MgSO4 (160 gms/Kg diet). The results showed that renal artery constriction caused significant elevation in SBP and HR. Furthermore, serum levels of aldosterone, serum MDA, sodium ions (Na^+), chloride ions (Cl^-), creatinine and urine Na^+ levels were also elevated significantly in 2K1C hypertensive rats. On the other hand, administration of potassium decreased significantly SBP,HR, serum level of aldosterone, MDA, serum $Na^+$and creatinine, while, serum levels of NO, K^+ and glomerular filtration rate (GFR) significantly increased compared with values in 2K1C hypertensive rats. Magnesium supplementation in 2K1C hypertensive rats caused significant decrease in SBP, HR, serum aldosterone level, serum MDA, Cl^-, calcium ions (Ca^{2+}) and increased serum levels of NO and magnesium ions (Mg^{2+}) levels compared with 2K1C hypertensive group. Moreover, administration of potassium in combination with magnesium in 2K1C hypertensive rats caused significant decrease in SBP, serum aldosterone level, HR, serum MDA, Na^+, Cl^-, Ca^{2+}, creatinine and serum levels of NO, K^+, Mg^{2+} and GFR were increased significantly, while, no significant change recorded in urine Na^+ levels compared all values with 2K1C hypertensive rats. Conclusion: The blood pressure lowering characteristic of potassium and magnesium was attributed to increase serum NO levels. The reduced serum MDA levels in hypertensive rats suggest that potassium and magnesium have antioxidant properties by reducing oxidative stress and preventing lipid peroxidation.

Keywords—Potassium, Magnesium, Two-Kidney One-Clip hypertensive rats, Renin-angiotensin system, Nitric oxide.

I. INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular disease, atherosclerosis, coronary artery disease, cerebrovascular accidents, heart and renal failure and it is the leading cause of death worldwide (61). Studies show that the renin-angiotensin-aldosterone system (RAAS) is responsible for the regulation of systemic blood pressure, as well as, salt and water homeostasis and the maintenance of vascular tone (66). In the RAAS, renin, generated in the juxtaglomerular apparatus of the kidney, catalyzes the conversion of angiotensinogen to angiotensin I (Ang I). Then, angiotensin converting enzyme (ACE), converts the inactive decapeptide angiotensin I (Ang I) to the octapeptide angiotensin II (Ang II). Ang II stimulates the production of aldosterone, a mineralocorticoid that exerts sodium and water retaining effects on the distal tubule (8).

The well known model for generating hypertension dependent Ang II secretion is 2K1C Goldblatt model. (47), through it one renal artery chronically constricted by clip process and the other one untouched to reduce renal perfusion (49). After reduction in renal perfusion pressure renin synthesis and release increases from the juxtaglomerular cells and some time from the principal cells of collecting tubules, cortical and medullary collecting ducts of renal constricted kidney (51). (38),

It was found that after 4 weeks of renal artery stenosis in rats, the increased Ang II releases aldosterone from adrenal cortex leading to salt and water retention(38). Also Ang II increases the activity of the sympathetic nervous system stimulates vasopressin secretion, and enhances NaCl reabsorption in the kidney (41). while, in non-clipped kidney progressive elevations in arterial pressure causes renin depletion the phenomenon of pressure natriuresis (10)

Potassium ion has low concentration in the extracellular fluid compare with intracellular fluid. Therefore increase dietary K has benefits in the treatment of hypertension ,arrhythmia , decrease renal vascular damage and inhibiting oxygen free radical formation from vascular endothelial cells (7).

The second high intracellular ion and the the fourth abundant cation in the body is magnesium (6). It has many functions in the body. Magnesium attenuates generation of reactive oxygen species (ROS) and stimulates production of prostacyclins and NO that have vasodilatation properties (60). The present study was done to investigate the effect of potassium and magnesium on aldosterone level, SBP, HR; renal function test parameters, serum NO and MDA in 2K1C hypertensive rats

II. MATERIALS AND METHODS

A-Animals and housing

Forty two adult male albino rats of about (150-250gms) body weight and (6-8) weeks old were used in the present study. Animals were housed in plastic cages bedded with wooden chips. They were housed under standard laboratory conditions, 12:12 light/dark photoperiod at 22 ± 2 C^0. The animals were given standard rat pellets and tap water *ad libitum*

B-Experimental design

This experiment was designed to study the effects of KCl, $MgSO_4$ and their combination on some hemodynamic and renal function test parameters in 2-kidney 1-clip (Goldblatt) hypertensive rats. The experimental rats were divided into six groups, each with seven rats and the treatments were continued for 4 weeks

Group 1: Control
Group 2: Sham operated surgery rats
Group 3: 2K1C hypertensive rats
Group4: 2K1C +KCl (80 gms/Kg diet)
Group5: 2K1C +$MgSO_4$ (80 gms/Kg diet)
Group6: 2K1C +KCl+$MgSO_4$ (160 gms/Kg diet).

C- Clipping procedure

The left renal artery was detached from male albino rats under anesthesia with combination of ketamine hydrochloride and xylazine intra-peritoneally in a dose of 35 mg/kg and 5mg/kg body weight, respectively, (Laird *et al*., 1996)and a silver clip of a 0.25 mm width was placed on the artery for inducing stenosis in the renal artery, to make hypertensive rats (2K1 clip rats)(37).

D. Collection of blood samples

At the end of the experiment, the rats were anesthetized with ketamine hydrochloride (50mg/kg). Blood samples were taken by cardiac puncture into chilled tubes and centrifuged at 3000 rpm for 20 minutes; then sera were stored at -85C^0 until assay.

E-Collection of urine samples.

On the 30th day of experiments, 24-h urine samples were collected from all rats. After volume measurements, the samples were stored at -80 C^0 (Sanyo, Japan) until assay.

F. Blood pressure and heart rate measurements

Measurements of SBP and HR were obtained at the end of experiment by the tail-cuff method in all groups using NIBP controller system 125 ML.R connected to power Lab (AD Instruments, power lab 2/25).Rats were placed in a restraining chamber and warmed to an ambient temperature of approximately 37C^0, typically taking about 10-15 minutes, after that occluding cuffs and pneumatic pulse transducers were placed on the rats' tails. Six readings were taken for each rat, the highest, lowest and any associated with excess noise or animal movement were discarded. The average was taken of the remaining readings to generate a value for a given rat for that week.

G. Biochemical determination *1.Determination of serum malonaldehyde (MDA)*

The level of serum MDA was determined spectrophotometrically with a thiobarbituric acid (TBA) solution. In brief to 150µl serum sample added the followings: 1ml trichloroacetic acid (TCA)17.5 %, 1ml of 0.66 % TBA, mixed well by vortex, incubated in boiling water for 15 minutes, and then allowed to cool. Then add 1ml of 70 % TCA, and let the mixture to stand at room temperature for 20 minutes, centrifuged at 2000 rpm for 15 minutes, & take out the supernatant for scanning spectrophotometrically. The concentration of MDA was calculated as follow:

MDA (µmol/L) = Absorbance at 532 nm x D/ L x Eo
Where L: light bath (1cm)
Eo: Extinction coefficient 1.56 x 105 M-1.Cm-1
D: Dilution factor = 1 ml Vol. used in ref. / 0.15 =6.7

2-Determination of serum aldosterone (pg/ml) by Enzyme linked immunosorbent assay (ELISA) kit for rat aldosterone

Serum aldosteron level was measured using the ELISA kit which is a sandwich enzyme immunoassay for the *in vitro* quantitative measurement of rat aldosteone in serum, plasma and other biological fluids.

3- Serum total nitric oxide measurement

Serum total NO was determined by NO non–enzymatic assay kit (US Biological, USA).

H-Assay of electrolytes

1-Determination of serum and urine electrolytes

Serum levels of Na^+, K^+ and Cl^- and urine level of Na^+ were determined by electrolyte analyzer (ElITE), electra biomedical corporation (USA).

2-Determination of serum magnesium

Magnesium level in serum and urine was determined by spectrophotometer magnesium kit(Biolab, France).

3-Determination of serum total calcium

Spectrophotometric method was used for serum calcium determination. In alkaline solution, CPC (O-Cresol Phtalein Compleone) reacts with calcium to form a dark-red colored complex(Biolab, France).

I-Determination of serum and urine creatinine

Serum and urine creatinine level was determined by spectrophotometer creatinine kit(Biolab, France).

J-Glomerular filtration rate (GFR) determination:

Glomerular filtration rate was determined by measuring the renal clearance of endogenous creatinine. During experiments, blood and urine samples were taken as described previously. Chemical analysis of diluted urine and blood samples for creatinine was performed using the methods quoted by (65). The GFR was calculated as follow: GFR =U*V/P (17)

Where,

U and **P** = the concentration of the creatinine in urine and plasma respectively**.**

V = the rate of urine flow in ml/min

III. STATISTICAL ANALYSIS

Analysis of data was performed by using {statistical package for social science (SPSS) version 11.5}. Results are expressed as mean ± standard error (mean ± SE). Statistical differences were determined by Ducan's test for multiple comparisons after analysis of variance (ANOVA)(14).

IV. RESULTS

The SBP of 2K1C Goldblatt hypertensive rats increased significantly ($p<0.01$) and reached (149.1± 3.52 mmHg) after 4 weeks of operation as compared with control (111.5 ± 0.56 mmHg). On the other hand, SBP decreased significantly ($p<0.01$) in 2K1C animals that were provided with diet supplemented with KCl, $MgSO_4$ and their combination (115.5 ± 0.36 mmHg), (110.5 ± 0.42 mmHg) and (107.3 ± 0.42 mmHg), respectively, compared with 2K1C hypertensive rats (Table 1).The 2K1C hypertensive rats showed a significant ($P<0.01$) increase in HR (471.1 ± 4.9 beats/min) when compared with control (341.1 ± 6.7 beats/min), while, a significant ($p<0.01$) reduction occurred in HR of 2K1C hypertensive rats treated with KCl , $MgSO_4$ and their combination (397.6 ± 3.4 beats/min), (406.8 ± 1.7 beats/min) and (395.1 ± 4.1 beats/min) respectively, in comparison with 2K1C hypertensive rats (Table 1).

Statistical analysis revealed non significant changes in serum total NO level in 2K1C hypertensive rats compared with control group. On the other hand, 2K1C hypertensive rats treated with (KCl, $MgSO_4$ and their combination) showed significant ($p<0.05$) increases in serum total NO levels (9.27 ±0.13 µmol/L), (9.43 ± 0.28 µmol/L) and (9.00 ± 0.23 µmol/L), respectively, compared to 2K1C hypertensive (8.22 ± 0.11 µmol/L) group (Table 1). Serum aldosterone level in 2K1C hypertensive rats increased (59.61 ± 10.0 pg/ml) significantly ($p<0.05$) as compared with control (12.96 ± 1.05 pg/ml) group. On the other hand, supplementation of KCl, $MgSO_4$ and their combination in 2K1C hypertensive rats prevented the rise in serum aldosterone level significantly ($p<0.05$) (7.8 ± 2.0 pg/ml), (14.52 ± 1.18 pg/ml) and (14.56 ± 2.13 pg/ml), respectively, in comparison with 2K1C hypertensive rats (Table 1).

The level of MDA was increased significantly ($P<0.05$) in 2K1C hypertensive group (5.57± 0.23 µmol/L) compared with control (2.09 ± 0.04 µmol/L) group, while, a significant ($P<0.05$) reduction occurred in MDA level (3.11 ± 0.06 µmol/L) in 2K1C hypertensive rats supplied with KCl. However, a greater reduction in

serum MDA levels recorded in rats supplied with $MgSO_4$ and combination of (KCl and $MgSO_4$) (2.5 ± 0.10 µmol/L) and (2.42 ± 0.15 µmol/L), respectively, compared all with 2K1C hypertensive rats (Table 1).

Serum Na^+ concentration of the 2K1C hypertensive group (129.33 ± 1.76 mmol/L) was significantly higher ($P< 0.05$) than that of the control (127.85 ± 1.14 mmol/L) group. In 2K1C hypertensive rats along with KCl treatment had significantly ($p<0.05$) decreased serum Na^+ concentration (123.05 ± 1.7 mmol/L), whereas, $MgSO_4$ treatment did not change serum Na^+ concentration, co-administration of KCl along with $MgSO_4$ significantly ($P<0.05$) decreased serum Na^+ concentration (124.6 ± 1.2 mmol/L) compared all with 2K1C hypertensive rats (Table1).

Two- kidney, one-clipped hypertensive rats showed non significant change in serum K^+ concentration in compared with control group. On the other hand, treatment by KCl alone and in combination with $MgSO_4$ in 2K1C hypertensive rats caused significant increase ($p<0.01$) in serum K^+ concentration (5.11 ± 0.10 mmol/L) and (5.30 ± 0.18 mmol/L), respectively, whereas, rats treated with $MgSO_4$ showed no significant differences in serum K^+ concentration compared all with 2K1C hypertensive rats, (3.82 ± 0.15 mmol/L) (Table 2).

Serum Cl^- level was increased significantly ($P<0.05$) in 2K1C hypertensive rats (115.4 ± 0.5 µmol/L) compared with control (104.6 ± 0.7 mmol/L) group. Moreover, in 2K1C hypertensive rats KCl caused non significant change in serum Cl^- level, however, a significant decrease in serum Cl^- levels recorded in rats supplied with $MgSO_4$, and combination of (KCl and $MgSO_4$) (108.6 ± 0.21 mmol/L) and (109.6 ± 0.7 mmol/L), respectively, compared all with 2K1C hypertensive rats (Table 2). No significant differences in serum Mg^{2+} levels were recorded among 2K1C, control group.

Also, in 2K1C rats KCl treatment caused non significant change in serum Mg^{2+} level, whereas, $MgSO_4$ alone and in combination with KCl significantly increased ($p<0.01$) serum Mg^{2+} level (2.11 ± 0.06mg/dL) and (2.16 ± 0.06 mg/dL), respectively, compared with 2K1C hypertensive rats (1.38± 0.14 mg/dL) (Table.2).

Two kidney one clip hypertensive rats showed non significant change in serum total $Ca^{2+}$when compared with control group. Potassium chloride treatments in 2K1C hypertensive rats caused non significant change in serum total Ca^{2+}, while, $MgSO_4$ alone and in combination with KCl decreased serum total Ca^{2+} significantly ($p<0.05$) (7.07 ± 0.17 mg/dL) and (7.16 ±0.19 mg/dL), respectively, compared all with 2K1C hypertensive rats (9.39± 0.08 mg/dL) (Table 2).

Concentration of urine Na^+ significantly increased ($p<0.05$) in 2K1C hypertensive rats (206.66 ± 1.33 mmol/L) compared to control (199.71 ± 0.99 mmol/L) group, respectively. Moreover, a significant increase ($p<0.05$) in Na^+ concentration was recorded in 2K1C hypertensive rats treated with KCl in diet (212.00 ± 0.81 mmol/L), while, $MgSO_4$ and combination of (KCl and $MgSO_4$) treatment caused non significant changes in urine Na^+ concentrations compared with 2K1C hypertensive rats (Table 2).

A significant increase ($p<0.05$) in serum creatinine level was recorded in 2K1C hypertensive rats (2.661 ± 0.12 mg/dL) when compared to control (0.953 ± 0.03 mg/dL), group, while, serum creatinine level significantly decreased in 2K1C hypertensive rats treated with KCl and combination of KCl and $MgSO_4$ (1.15± 0.03 mg/dL), (0.7± 0.16 mg/dL) when compared with 2K1C hypertensive rats. On the other hand, $MgSO_4$ caused non significant changes in serum creatinine level when compared with 2K1C hypertensive rats (Figure 1).

Renal artery constriction in 2K1C hypertensive rats had non significant effect on GFR when compared with control group, while, GFR was increased significantly ($P<0.01$) in 2K1C hypertensive rats that were treated with KCl and combination of (KCl and $MgSO_4$) with mean values (2.27 ± 1.13 ml/min) and (2.57 ± 0.12 ml/min), respectively. Moreover, $MgSO_4$ had no significant effect compared with 2K1C hypertensive group (1.52 ± 0.05 ml/min) (Figure 2).

V. DISCUSSION

The renal artery constriction in 2K1C rats caused marked increase in SBP. Previous studies showed that unilateral renal artery stenosis in 2K1C rat can lead to hypertension, returninig this to the renal atrophy, and reduced renal function (43; 49). A reduced renal perfusion pressure after clipping of arenal artery in the early (2-to 4 week) 2K1C rat model of Goldblatt hypertension increases Ang II concentrations in both kidneys and causes Ang II- dependent hypertension(44)

The present results show that renal artery constriction for four weeks caused an increase in plasma aldosterone concentration, suggesting that aldosterone could play a pathophysiological role in 2K1C hypertension subsequent to activation of the RAAS and as demonstrated by (5), renal artery occlusion creates ischemia, which triggers the release of renin. Hyperreninemia promotes production of Ang II, causing severe vasoconstriction and release of aldosterone.

Our results also show that experimentally induced-hypertension in 2K1C rats produced a significant increase in HR. The mechanism by which 2K1C rats showed an increase in HR may be due to interactions between RAS and sympathetic nervous system since it has been well recognized that strong sympathetic stimulation can increase the HR (57). Moreover, a role for changes in sympathetic nervous system in 2K1C

hypertension has been suggested. (34) reported that sympathetic tone is inappropriately increased and this sympathetic tone ameliorates hypertension and HR in Goldblatt animals. However, involvement of oxidative stress in early 2K1C Goldblatt hypertensive rats has been demonstrated by prolonged administration of Tempol (free radical scavenger) to reduce ROS (44).

The present results show that potassium treatment attenuated the development of hypertension and also led to decrease of existing hypertension in 2K1C Goldblatt hypertensive rats. The antihypertensive effect of K^+ was accompanied by suppression of plasma aldosterone activity. Different potential mechanistic pathways may explain how increasing K^+ intake reverses BP status. One Potential pathway involves that potassium activate the Na^+-K^+ pump in the central nervous system and lower BP by neurogenic mechanisms involving central adrenergic as well as dopaminergic pathways (19). Other studies indicated that the vasodilatation induced by potassium results from hyperpolarization of the vascular smooth muscle cells subsequent to potassium stimulation by the ion of the electrogenic Na^+-K^+ pump and/or by activating the inward rectifying potassium channels(K_{ir}) (9). This hyperpolarization decreases the open probability of-voltage-activated Ca^{2+} channels, which in turn reduces cytosolic Ca^{2+} levels and promotes vasodilation (45).

A significant reduction in HR observed in potassium treated rats, this declining of HR is almost related to the long treatment of rats with KCl in this study, and this is consistent with study of (20) reporting that raising serum K^+ concentrations may improve depolarization in patients with inherited or acquired long QT syndrome.
This study revealed that KCl supplementation increased NO production in hypertensive rats. Potassium causes the relaxation of arteries through release of several factors from endothelial cells, the most prominent autacoids being NO and prostacyclin (39). Moreover, High K^+ intake may enhance NO production in endothelial cells which may be due to prevention of the vascular hypertrophic change with K^+ supplementation and the another possible mechanism is that K^+ supplementation inhibits free radical formation and protects endothelial cells from oxidative stress, leading to the increase in the NO production (26).

In the present study, the dietary supplementation of KCl significantly decreased serum aldosterone level in the hypertensive rats. The mechanisms for inhibition of aldosterone by potassium are probably associated to the indirect interaction between potassium and factors that regulate aldosterone production.
(47) showed that K^+ ions suppress the secretion of renin and Ang II in hypertensive rats. On the other hand, it has been shown that Ang II activates glomerulosa cells and increases aldosterone production (15), so the decrease in Ang II will decrease the aldosterone production (50) and this may explain the lower range of baseline serum aldosterone concentrations seen in the KCl treated rats. Moreover, (23) showed that the suppression of hyperaldosteronesim in 2K1C with Ang II receptor blockers and ACE inhibitors resulted in significant improvement in hypertension. Also, (67) showed that K^+ exhibits direct ACE inhibitor activity.

Also, administration of ACE inhibitor to hypertensive patients produced sustained reductions in both plasma aldosterone and urine aldosterone excretion and at the same time caused marked K^+ retention that's directly related to the fall in aldosterone and changes in both plasma and urine aldosterone suggest that K^+ reduces secretion of aldosterone by the adrenal cortex (2).

The present study shows that dietary $MgSO_4$ supplementation prevented development of hypertension in hypertensive rats. Magnesium is thought to decrease vascular tone and blood pressure by reducing Ca^{2+} concentration in smooth muscle cells (64). Inhibition of calcium entry from the extracellular space and calcium release from intracellular stores are believed to be the main mechanisms operating in the vasorelaxant effect of Mg^{2+} (27).

Supplementation of $MgSO_4$ in diet for 4 weeks produced a significant decrease in HR, suggesting that $MgSO_4$ treatment could be useful in reducing the risk of cardiovascular disease in renovascular and salt loaded hypertension, because HR decreased in these cases. The effects of Mg^{2+} on HR are related to its ability to influence the movement of other ions across the sarcolemma of the atrial myocytes. The elevation in the Mg^{2+}concentration could increase the atrial cycle length as a result of its 'interference' with the fine balance between inward Ca^{2+} and outward K^+ currents during repolarization of the action potentials in the atrial muscle (24).

Furthermore, supernormal levels of Mg^{2+} act as type one inward rectifying potassium channels(I_{K1}) channel blocking agent to plug the open channel in a voltage dependent manner, and decrease the outward K^+ current density. Translated into changes in action potential, a prolongation of the final repolarization will occur, accompanied by a slight depolarization of the atrial resting membrane potential and these changes will cause prolonged refractoriness and decreased conduction velocity in the atrial muscle, which in turn could increase the atrial cycle length (25).

Results show that dietary $MgSO_4$ supplementation increased serum NO level induced by Mg^{2+}in hypertensive rats. This finding indicates that NO generated by endothelium may potentiate the vasorelaxant effect of magnesium on the vascular smooth muscle cells. Nitric oxide is known to cause relaxation of the vascular smooth muscle through numerous pathways. It activates soluble guanylate cyclase, thus increasing cyclic guanosine monophosphate(cGMP) formation (13).An increase in cGMP causes smooth muscle relaxation by

various pathways, including inhibition of the calcium influx through the voltage-gated calcium channels and activation of calcium-activated potassium channels, thereby, causing hyperpolarization (11). Therefore, the NO-cGMP pathway affects calcium influx and release through numerous cellular mechanisms, and these may be the sites of synergistic interaction between $Mg^{2+}$and the NO-cGMP system (33).

Our study showed that dietary intake of $MgSO_4$ caused marked decrease in serum aldosterone concentration. Magnesium has been reported to decrease cytosolic calcium concentration (12). Furthermore, magnesium has been shown to activate membrane Na^+-K^+ase in muscle cells, increased Na^+-K^+ pump activity results in decreased intracellular Na^+ ion. The Ca^{2+} ion concentration in the cell would also be decreased as a result of Na^+/Ca^{2+} exchanges (35). Moreover, (3) reported that Ca^{2+} is an intracellular messenger of Ang II in adrenal glomerulosa cells and since Mg^{2+} preferentially inhibits Ang II induced aldosterone production, thus, Mg^{2+} may inhibit aldosterone production by influencing the intracellular concentration of free Ca^{2+} in the glomerulosa cells.

In the current results, potassium chloride supplementation reduced MDA level significantly in hypertensive rats. In a study,(36) showed that, dietary K^+ supplementation counteracted salt and Ang II induced acceleration of vascular injury, possibly, *via* its antioxidant effect mediated through inactivation of nicotinamide adenine dinucleatid phosphate (NADPH). It has been postulated that an increase in extracellular K^+ can boost the membrane sodium pump activity, hyperpolarizing the cell membrane and "turning off" NADPH oxidase activation, because membrane depolarization up-regulates the activity of this enzyme complex (29)

supplied with $MgSO_4$. The mechanism by which Mg^{2+} decreased MDA is that Mg^{2+} has important role in the activation of some enzymes involved in the redox reactions (54). Moreover, Mg^{2+} may directly prevent the production of free radicals or it may facilitate the scavenging of free radicals (16), and Afanas'ev *et al*., (1995) showed that Mg^{2+} inhibits reduced NADPH oxidase, an enzyme that produces superoxide radical.

In the present study, concentration of Na^+ decreased in urine, while, increased in serum in the 2K1C rats. These findings correlate with investigations found by (1), confirming that urinary excretion of Na^+ was higher in normotensive rats than hypertensive rats. Moreover, (28) demonstrated that the mechanism of Na^+ retention in hypertensive rats is through increased aldosterone activation of the mineralocorticoid hormone receptor in the distal kidney tubules producing Na^+ and fluid retention and volume expansion, on the other hand, Ang II can increase release of norepinephrine from the adrenals and terminal nerve ending, adrenergic receptor stimulation has been shown to cause increased sodium reabsorption in the renal proximal tubule. The present study shows that KCl supplementation reduced serum Na^+ and increased urine excretion Na^+ concentrations in hypertensiverats. This finding is consistent with, (40), showing that K^+ has diuretic and natriuretic effects *in vivo*. Furthermore, (62) concluded that potassium can directly inhibit the release of renin by the juxtaglomerular apparatus, and inhibit proximal tubular Na^+ reabsorption. Moreover, (59) reported that the release of atrial natriuretic peptide might be increased by K^+ supplementation, leading to both natriuresis and vasodilation

A significant elevation in serum K^+ levels was observed in KCl treated rats, this elevation of K^+ is almost related to decline in serum aldosterone levels recorded in this study. Studies reported that the increased of serum K^+ is usually seen when aldosterone concentrations have decreased (30).

Results show that the serum Cl^- level was higher in 2K1C rats. This result may indicate that overall renal handling of Na^+, Cl^- and K^+ in our hypertensive rats was abnormal. Handling of electrolytes may be modulated by a variety of substances such as aldosterone and the RAAS(36). Furthermore, as it is mentioned in the review of literature, under the effect of aldosterone , Na^+ ions are reabsorbed, negative ions such as Cl^- and bicarbonate $HCO3^-$ follow the Na^+ ions back to the blood (56). On the other hand, it was found that increased Cl^- transport probably caused by augmented Na^+-K^+-2Cl cotransport activity in the thick ascending limb of Henle's loopin the hypertensive rats (4).

In this study, a significant decrease of serum calcium and increase in serum Mg^{2+} level was observed in hypertensive rats when they were provided with diets supplemented with $MgSO_4$ alone and in combination with KClthe decrease of serum calcium level may be caused by Mg^{2+} because of its actions on PTH, a hormone which increases calcium reabsorption in the distal parts of the nephron. Therefore, increased plasma Mg^{2+} would reduce PTH secretion and so reduce distal reabsorption of calcium (42).

Significant increase in serum creatinine was observed in hypertensive rats. This result suggests the role of Ag II in the development of renal injury in this study since it is believed that ROS, Ang II and endothelin are key mediators of kidney damage (63), and also increased serum creatinine and blood urea nitrogen were associated with excessive ROS (32).(31) recorded that renal artery constriction caused local generation of Ang II and up regulation of AT1-receptor density, up-regulation of endothelin system and oxidative stress. Also, renal tubule cell apoptosis has been consistently observed in models of renal injury (55).On the other hand, reduced bioavailability of NO is considered to be a key mechanism for renal endothelial dysfunction in various experimental models of hypertension and renal damage since, (22) reported that pronounced renal NO-mediated vasodilation is associated with protection against the development of renal damage in several models of renal injury. Also, (58) found that the ability of K^+ and Mg^{2+} to NO production may improve renal function.

In the current study, dietary supplementation of KCl significantly increased GFR in hypertensive rats. The increase in GFR in hypertensive rats treated with potassium may relate to the increase in NO production. This result is in agreement with the finding of (21) who observed a slight increase in renal blood flow and GFR with the production of local vasodilating agents such as NO. (53) indicated that non selective inhibition of NOS with L-NAME was clearly detrimental to renal function and infact resulted in acute renal failure (decreased GFR accompanied by decreased renal blood flow and tubular dysfunction). Also, it was found that potassium loading enhances the glomerular synthesis of prostaglandins PGE2 and PGI2 (hormones that cause vasodilation and increase renal blood flow and GFR) in normotensive rats (52). Moreover, PGE2 and PGI2 may dampen the renal vasoconstrictor effects of the sympathetic nerves or Ang II, especially their effects to constrict the afferent arterioles and by opposing vasoconstriction of afferent arterioles, the prostaglandins may help prevent excessive reductions in GFR and renal blood follow (18). In conclusion, potassium could improve the renal damage in both models of hypertension by decreasing serum uric acid, urea and increased GFR (which are indications for kidney function) in hypertensive and normotensive rats. Our findings show that oral magnesium supplementation reduced blood pressure in hypertensive rats, while, it could not reduce blood pressure in normotensive rats. Magnesium has an inhibitory action on aldosterone production in hypertensive rats and this suggests that Mg^{2+} may be involve in physiological regulation of aldosterone production.

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Table (1): Effects of potassium, magnesium and their combination on SBP, HR, serum NO, serum aldosterone level and MDA in 2K1C hypertensive rats.

Parameters / **Treatments**	**SBP(mmHg)**	**HR(beats/min)**	Serum NO(**µmol/L**)	Serum aldosterone(**(pg/ml)**	Serum MDA((**µmol/L)**
Control	111.5±0.56^{ab}	341.1±6.7 ^{ab}	8.16 ±0.04 ^{a}	12.96 ±1.05 ^{a}	2.09±0.04^{a}
Sham	113.8±0.8^{b}	400.0±5.3 ^{b}	8.29±0.04 ^{a}	11.14 ±0.4 ^{a}	2.19±0.10 ^{a}
2K1C	149.1±3.52^{d}	471.1±4.9 ^{c}	8.22 ±0.11 ^{a}	59.6 ±10.0 ^{b}	5.57±0.23 ^{c}
2K1C+ KCl (80gms/kg diet)	115.5±0.36^{bc}	397.6±3.4 ^{b}	9.27 ±0.13 ^{b}	7.8±2.0 ^{a}	3.11±0.06 ^{b}
2K1C+ $MgSO_4$ (80gms/kg diet)	110.5±0.42 ^{a}	406.8 ±1.7 ^{b}	9.43 ± 0.28 ^{b}	14.52±1.18 ^{a}	2.50 ±0.1 ^{a}
2K1C+ KCl+ $MgSO_4$(160gms/kg diet)	107.3 0.42 ^{a}	395.1 ± 4.1 ^{b}	9.00 ± 0.23 ^{b}	14.56 ± 2.13 ^{a}	2.42±0.15 ^{a}

The data presented as mean ± SE measured after 4 weeks of the treatments in all groups (Control , Sham operated surgery rats , Two kidney-one clip (2K1C) hypertensive rats , 2K1C + Potassium chloride ,KCl , 2K1C + Magnesium sulphate ,MgSO4 , 2K1C +KCl+MgSO4 .
The same letters mean non significant differences while the different letters mean significant differences * =p<0.05 ** =p<0.01

Table (2): Effects of potassium, magnesium and their combination on serum Na^+, K^+, Cl^-, Mg^{2+} Ca^{2+} and urine Na^+ concentration in 2K1C hypertensive rats.

Parameters / Treatments	Serum Na^+(mmol/)	Serum K^+ (mmol/L)	Serum Cl^- (mmol/L)	Serum Mg^{2+} (mg/dL)	Serum Ca^{2+}(mg/dL)	Urine Na^+(mmol/L) *
Control	127.8±1.14 [a]	3.87 ±0.7 [a]	104.6±0.7 [a]	1.30±0.18 [a]	9.37 ± 0.07 [b]	199.71± 0.99 [a]
Sham	128.0 0.58 [a]	4.13±0.20 [a]	106.2±0.7 [ab]	1.3 ±0.14 [a]	9.43 ±0.13 [b]	201.5 ± 1.23 [a]
2K1C	129.33 1.7 [c]	3.82±0.15 [a]	115.4±0.5 [c]	1.38±0.14 [a]	9.39 ±0.08 [b]	206.6 ± 1.33 [b]
2K1C+ KCl (80gms/kg diet)	123.05±1.7 [a]	5.11±0.10 [b]	116.4±0.6 [c]	1.48 ±0.24 [a]	9.42 ±0.05 [b]	212.0 ± 0.81 [c]
2K1C+ $MgSO_4$ (80gms/kg diet)	131.0 ±1.34 [c]	3.70±0.15 [a]	108.6±0.21 [b]	2.11±0.06 [b]	7.07±0.17 [a]	203.8 ± 0.83 [b]
2K1C+KCl+$MgSO_4$(160gms/kg diet)	124.6 ± 1.2 [b]	5.30±0.18 [b]	109.6±0.7 [b]	2.16 ±0.06 [b]	7.16 ± 0.19 [a]	206.3 ± 1.97 [b]

The data presented as mean ± SE measured after 4 weeks of the treatments in all groups (Control , Sham operated surgery rats , Two kidney-one clip (2K1C) hypertensive rats , 2K1C + Potassium chloride ,KCl , 2K1C + Magnesium sulphate ,MgSO4 , 2K1C +KCl+MgSO4 .The same letters mean non significant differences while the different letters mean significant differences * =$p<0.05$ ** =$p<0.01$