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## Effect of Dietary Zinc Supplementation on Salt Induced Hypertension in Rats

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**Abstract:** The present study was undertaken to investigate the effect of dietary zinc supplementation on salt induced hypertension in rats. This study was carried out due to the paucity of information on the clear role of zinc in treatment of hypertension. Plasma electrolytes, hematological parameters and changes in their body weight were assessed. Adult male Wistar rats were used. They were divided into four groups: control, zinc-fed, salt-loaded and salt-loaded-zinc-fed. The control rats were given the standard rat chow, the zinc-fed rats were given the standard rat chow plus zinc sulphate (50 mg/kg/day), the salt-loaded rats were given a diet containing 8% NaCl and the salt-loaded-zinc-fed rats were given a diet containing 8%NaCl plus 50 mg/kg/day zinc sulphate supplementation. Rat feed and tap water were given *ad libitum* for 10 weeks. Blood pressure measurement was done in anaesthetised animals through a direct invasive method using a 2 Channel Recorder Polygraph. Salt loading significantly increased the mean arterial pressure, but zinc sulphate supplementation prevented hypertension in salt-loaded rats. Salt loading also led to increase in hematocrit, number of red blood cells, hemoglobin concentration and the mean corpuscular volume. Zinc supplementation reduced the values of these hemetological parameters. There was also a significant decrease in plasma potassium level and no significant changes in plasma sodium and zinc in salt-loaded rats. Zinc sulphate supplementation prevented the decrease in plasma potassium in salt-loaded rats. Furthermore, high diet led to a low percentage weight gain compared with rats given a normal rat diet, but zinc supplementation reduced the extent of this weight loss during salt loading. These results suggest that zinc has antihypertensive effects associated with maintaining the plasma potassium, number of red blood cell and body weight.

**Key words:** Hypertension, dietary zinc supplementation, salt induced hypertension rats

### INTRODUCTION

Zinc ion has been found to be very important in the body. The coordination flexibility makes it highly adaptable to meeting the needs of proteins and enzymes that carry out diverse biological functions and are involved in the metabolism of proteins, nucleic acids carbohydrates and lipids as well as in control of gene transcription and other fundamental biological processes such as cell division, differentiation and receptor activity etc. Zinc supplementation has been reported to enhance body immunity (Erickson, 2000), reduce the attack of malaria (Shankar, 2000) reduce blood sugar in diabetes (Chen and Lin, 2000), increase sperm count and improve sperm motility, prevent osteoporosis and reduce acne inflammation (Jacqueline *et al.*, 2002).

Hiruyuki *et al.* (2001) reported that zinc deficiency might be a crucial factor in the development of genetic hypertension presumably through the oxidative stress caused by superoxide. Low maternal zinc level has been associated with pregnancy induced hypertension.

(Swanson and King, 1987). Furthermore, it was reported that zinc plays a role in the pathogenesis of hypertension, but its role was not known. Serum zinc was lower and erythrocyte zinc was higher in essential hypertension than in normotensives (Pol Arch Wemn [Poland], 1996). An increase in zinc absorption from the alimentary tract has been found in patients with essential hypertension (Tubek, 2001). Garcia *et al.* (1985) reported that there was an increase in urinary excretion in patients suffering from essential hypertension. They found no clear explanation for this phenomenon.

The lack of evidence for the clear role of zinc in the treatment of hypertension prompted this study. It is known that zinc deficiency is associated with hypertension; therefore this project aims at checking the effect of zinc sulphate supplementation in the diet. It is assumed that zinc supplementation, which may increase both extracellular and intracellular zinc content may through its effect on various body enzymes, hormones, cell membranes be able to stabilize factors whose derangement result in the pathogenesis of hypertension,

hence, preventing the development of hypertension or it may lower an already existing hypertension. It is proposed that dietary zinc supplementation would prevent or delay the development of salt induced hypertension. If this hypothesis is proved to be correct, then the advocacy of dietary zinc supplementation in adolescent offspring of hypertensives may be encouraged to prevent the development of hypertension in a large population of people who are prone to the development of hypertension later.

## **MATERIALS AND METHODS**

Experiments were performed in male Wistar rats initially weighing between 170-300 g. They were randomly divided into four groups i.e control, zinc-fed salt-loaded and salt-loaded-zinc-fed respectively. The control rats (group A) were given the standard rat chow, which contains 0.3% NaCl. The zinc-fed rats (group B) were given a standard rat chow plus 50 mg/kg/day zinc sulphate solution administered orally using intragastric tube. The salt-loaded rats (group C) were given a rat chow containing 8% NaCl, while the salt-loaded-zinc-fed rats (group D) were given a diet containing 8% NaCl plus 50 mg/kg/day zinc sulphate supplementation administered orally as above. Food regimen and tap water for each group were given ad libitum for 10 weeks.

**Preparation of altered sodium diet:** A sodium loaded diet containing 8% NaCl (Analar BDH Laboratory Supplies, Poole BDH Ltd. England) was prepared by adding appropriate quantities of salt to the standard rat feed containing 0.3% NaCl (supplied by Ladokun feeds, Ibadan) (Sofola *et al.*, 2002).

**Preparation of zinc sulphate solution:** The dose of zinc sulphate (Analar BDH Laboratory Supplies, Poole BDH Ltd. England) that was given was 50 mg kg<sup>-1</sup> (Select Committee on GRAS Substances, 1973). It was prepared by dissolving 10 g of zinc sulphate in 1 L of normal saline. By calculation 1 mL of this solution was given to a rat weighing 200 g. From this stock solution appropriate volume of zinc sulphate was given to rats daily according to their body weights.

**Measurement of arterial blood pressure:** At the end of the 10th weeks of feeding period, rats were randomly picked from each group for blood pressure measurement using a pressure transducer connected to a polygraph [2-channel recorder Gemini 7070 UGO BASILE]. The machine was calibrated with a mercury manometer before each experiment. The rats were anaesthetized by

intraperitoneal injection of urethane at a dose of 3 mL/100 g body weight. This unconscious animal was fastened to the small operation table. The trachea and left carotid artery were exposed by blunt dissection. The trachea was cannulated for spontaneous respiration. Threads were passed under the carotid arteries and it was cannulated for blood pressure measurement. Heparin (500 iu/kg- body weight) was infused into the cannulated artery immediately to prevent intravascular coagulation. The cannula on the already cannulated rat was now connected to the pressure transducer. Immediately a pressure pulse is seen. The upper limit of the pulse corresponds to the systolic blood pressure while the lower limit corresponds to the diastolic blood pressure in the rat. The rats were allowed 30 min for the BP to stabilize before reading, was obtained from the animal. To obtain the reading the paper was allowed to run for 1 min with the recording pen recording the pressure pulse. The mean arterial pressure (MAP) is calculated from the relationship: MAP = diastolic + 1/3 pulse pressure (pulse pressure = systolic minus diastolic blood pressure).

**Haematological studies:** Eight rats were randomly selected from each group on the 8th week for the collection of blood Hematological parameters such as RBC, WBC, hematocrit and haemoglobin concentration were determined from the sample collected.

**Blood collection:** The tail of each rat was sterilized using methylated spirit and cotton wool. The rat was held at the mid-region with the left hand. With a pair of scissor the tip of the tail was cut. With the right hand the whole length of the tail was squeezed from proximal attachment to the body to the distal cut. Using this method 1 mL of blood was collected from the tail artery of the rats into a container containing anticoagulant (Ethylene-diamine-tetra-acetic acid; EDTA) and the study began immediately.

**Measurement of plasma zinc, sodium and potassium:** Five milliliter of blood was collected from rats after the completion of the measurement of arterial blood pressure through the cannulated left carotid artery into the EDTA container. The blood was immediately centrifuged at 300 rpm for 5 min. The plasma was aspirated and used for the measurement of plasma electrolyte. Plasma zinc, sodium and potassium were measured using atomic absorption spectrophotometer [BUCK Scientific atomic absorption spectrophotometer Model 200 A].

**Sodium and potassium level in plasma:** Plasma Na and K were analyzed by flame absorption technique using

atomic absorption spectrophotometer. Three sets of standards; 100, 50 and 25 ppm, respectively were used to calibrate the equipment. After this the samples were aspirated directly into the flame and the absorbance reading recorded. The calibration curve was plotted as concentration against absorbance and a slope calculated from the graph. The slope multiplied by the absorbance value for each sample is the concentration of the element in the sample.

**Zinc level in plasma:** Flame absorption technique was used as above. Zn cathode lamp was inserted into the equipment. The lamp current and the wavelength were set. The equipment was calibrated using two point calibrations. The zinc concentrations of the sample were then determined.

**Data analysis:** The values were recorded as mean±SEM. The student t test was used to compare variable between two groups. Confidence interval of 95% was taken as statistically significant.

## RESULTS

**Effect of diet on mean arterial blood pressure (map):** The MAP of Group C (salt-loaded rats) was significantly higher compared with rats in Groups A (control) and B (zinc-fed) ( $p < 0.01$ ). There was no significant difference in the MAP between rats in Groups A and B ( $p > 0.05$ ). Zinc supplementation significantly decreased the MAP in Group D (salt-loaded-zinc-fed rats) compared with Group C ( $p < 0.01$ ). There was no significant difference in the MAP of rats in Groups A and D ( $p > 0.05$ ) (Table 1).

### Effect of diet on hematological parameters:

**Effect of diet on hematocrit level:** There was a significant increase in the hematocrit in the salt loaded rats of Group C compared with Groups A and B ( $p < 0.01$ ). Only zinc supplementation in diet in Group B rats did not cause any significant difference in the hematocrit compared with Group A ( $p > 0.05$ ). Also, zinc supplementation significantly reduced the hematocrit in Group D rats compared with Group C rats that were both given high salt diet ( $p < 0.01$ ). There was a significant increase in the hematocrit of Group D rats compared with Group A ( $p < 0.01$ ) (Table 2).

**Effect of diet on number of Red Blood Cells (RBCs):** The effect of salt loading and zinc supplementation on the number of RBCs is shown in Table 2. Salt loading resulted into a significant increase in the number of RBCs in Group C rats compared with rats in Groups A and C

Table 1: Effect of diet on mean arterial blood pressure in rats

Groups	Mean ±SEM [mm Hg]
Group-A	118±8.45
Group-B	120±1.22
Group-C	145±3.66*
Group-D	121±5.71 <sup>#</sup>

Data are presented as mean±SEM, \* $p < 0.01$  compared with control rats, <sup>#</sup> $p < 0.01$  compared with salt loaded rats, Group A, Control rats; Group B, Zinc-fed rat; Group C, salt-loaded rats; Group D, Salt-loaded-zinc-fed rats. N = 6

( $p < 0.01$ ). Zinc supplementation in Group D rats caused a decrease in the number of RBCs compared with Group C rats (both were given a salt loaded diet), but this reduction was not significant ( $p > 0.05$ ). The increase in the number of RBCs between rats in Groups A and B was not significant ( $p > 0.05$ ). There was a significant increase in the number of RBCs in Group D compared with Group A rats ( $p < 0.05$ ). And the high salt diet given to Group D rats caused a significant increase in the number of RBCs compared with Group B rats ( $p < 0.05$ ) (they both had zinc supplementation in their diet) (Table 2).

### Effect of diet on hemoglobin (Hb) Concentration:

Salt loading caused a significant increase the Hb concentration in the Group C rats compared with Group A and B rats ( $p < 0.01$ ). Zinc supplementation resulted into a significant reduction in the Hb concentration in rats in the Group D rats compared with rats in Group C rats (both groups were given high salt diet) ( $p < 0.01$ ). There was no significant difference in the Hb concentration between Group A and B rats ( $p > 0.05$ ). And there was a significant increase in the Hb concentration in rats in Group D compared with Groups A ( $p < 0.01$ ) and B ( $p < 0.05$ ) rats (Table 2).

### Effect of diet on Mean Corpuscular Volume (MCV):

There was an increase in the MCV in Group C rats compared with rats in Group A and B, but this increase was not significant ( $p > 0.05$ ) (Table 2). Zinc alone did not cause a significant difference in the MCV ( $p > 0.05$ ). The Group D rats had a significant decrease in their MCV compared with Group C rats ( $p < 0.01$ ). There was no significant difference in the MCV of Group D compared with Group A ( $p > 0.05$ ) and Group B ( $p > 0.05$ ) rats.

### Effect of diet on the number of white blood cells:

There was no significant difference in the number of WBCs between Group A and C rats ( $p > 0.05$ ) (Table 2). Compared with Group A rats there was a significant increase in number of WBCs of Group B ( $p < 0.05$ ) and D ( $p < 0.01$ ) rats. The difference in the number of WBCs between Group B and D rats was not significant ( $p > 0.05$ ), likewise between Group C and D rats ( $p > 0.05$ ).

Table 2: Effect of diet on Hematocrit

	Group A	Group B	Group C	Group D
PCV (%)	27.68±1.33	29.00±3.03 <sup>#</sup>	42.90±0.29 <sup>*</sup>	35.25±0.31 <sup>#*</sup>
RBC (X10 <sup>6</sup> μL <sup>-1</sup> )	5.60±0.28	5.92±0.40 <sup>#</sup>	8.11±0.21 <sup>*</sup>	7.58±0.14 <sup>#</sup>
HB (g dL <sup>-1</sup> )	8.75±0.53	9.38±1.01	13.90±0.14 <sup>*</sup>	11.75±0.41 <sup>#*</sup>
MCV (fL)	49.46±1.31	48.49±2.48	53.11±1.30	46.60±0.88 <sup>#</sup>
WBC (cell μL <sup>-1</sup> )	8575±804	12000±1337 <sup>#</sup>	10975±1067	13131±439 <sup>*</sup>
PLATELET (cell ccm <sup>-1</sup> )	124750±10754	129250±4866	144000±12596	154500±14240

Data are presented as mean±SEM. <sup>#</sup>p<0.01 compared with control rats <sup>\*</sup>p<0.01 compared with salt loaded rats, <sup>\*</sup>p<0.01 compared with salt-loaded-zinc-fed rats. Group A, Control rats; Group B, Zinc-fed rat; Group C, Salt-loaded rats; Group D, Salt-loaded-zinc-fed rats. N = 8

Table 3a: Effect of diet on body weight

	Week 1	Week 2	Week 4	Week 6	Week 8
Group A (g)	187.5±2.12	208.5±2.03	219.5±2.18	227±2.21	255.7±3.39
Group B (g)	175.7±0.87	193.5±1.83	206.9±1.60	203.3±1.83	235±2.00
Group D (g)	180.2±1.28	185.3±1.32	202.8±1.98	211.5±1.63	230±4.72
Group D (g)	190.7±0.6	200.4±1.0	215±1.63	232±1.4	248±3.1

Data are presented as mean±SEM. Group A, Control rats; Group B, Zinc-fed rat; Group C, Salt-loaded rats; Group D, Salt-loaded-zinc-fed rats. N = 14

Table 3b: Effect of diet on body weight

	Initial weight (g)	Final weight (g)	Weight gain (g)	(%) Weight gain
Group A	187.5	255.7	68.2	36.4
Group B	175.7	235	59.3	33.8
Group C	180.2	230	49.8	27.6
Group D	190.7	248	57.3	30.0

Data are presented as mean±SEM. Group A, Control rats; Group B, Zinc-fed rat; Group C, Salt-loaded rats; Group D, Salt-loaded-zinc-fed rats. N = 14.

**Effect of diet on platelet count:** There was no significant difference in the platelet count among the four groups of rats; Groups A, B, C and D (p>0.05) (Table 2).

**Effect of diet on total body weight:** The four groups of rats; Groups A, B, C and D had a significant increase in their TBW over 8 weeks period of feeding (p<0.01) (Table 3a). Table 3b shows that the rats in group A had the highest weight gain and percentage weight gain compared with the other three groups, followed by rats in Group B. The Group D rats had a higher weight gain and percentage weight gain compared with Group C rats.

**Effect of diet on plasma electrolyte level**

**Effect of diet on plasma zinc level:** There was an increase in the plasma zinc level in Group B rats compared with rats in the Group A, C and D, but this increase was not significant (p>0.05). There was no significant difference in the plasma zinc level among the four groups of rats (p>0.05) (Fig. 1).

**Effect of diet on plasma sodium level:** There was no significant change in the plasma level of sodium between Group A and B (p>0.05); A and C (p>0.05) and C and D (p>0.05) (Fig. 2). The plasma sodium level was significantly decreased in the Group D rats compared with

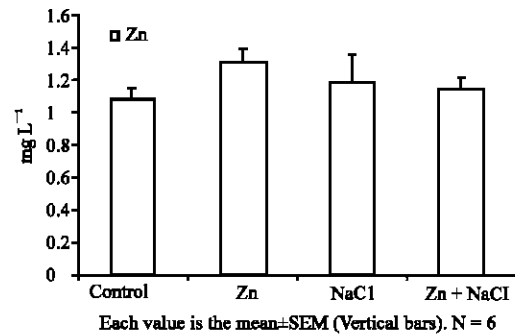


Fig. 1: Bar chart showing the effect of diet on plasma zinc level

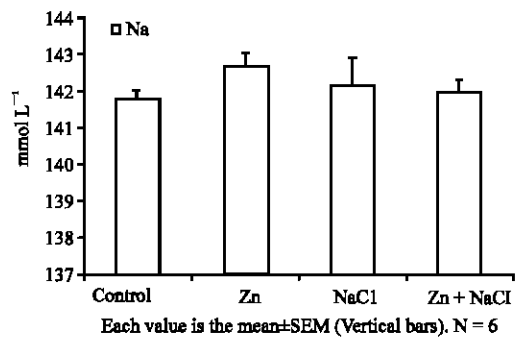


Fig. 2: Bar chart showing the effect of diet on plasma sodium level

Group A (p<0.05). Furthermore there was a significant decrease in the Group D rats compared with Group B rats (p<0.05).

**Effect of diet on plasma potassium level:** There was no significant difference in the plasma potassium level between rats in Groups A and B (p>0.05) and between

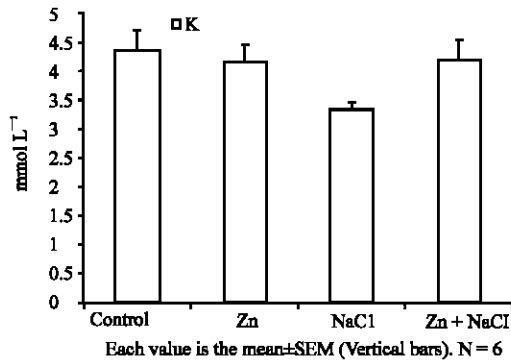


Fig. 3: Bar chart showing the effect of diet on plasma potassium level

Group A and D ( $p > 0.05$ ) (Fig. 3). The plasma potassium was significantly reduced in the Group D compared with Group A ( $p < 0.05$ ). There was a significant increase in the plasma potassium level in Group D compare with Group C ( $p < 0.05$ ). There was also a significant difference in the potassium level between group B and C rats ( $p < 0.05$ ).

### DISCUSSION

A diet containing 8% NaCl was used in this study to induce hypertension in Wistar rats for a period of 10 weeks. Eight percent NaCl has been reported to cause hypertension in Wistar rats over a period of 70 days (Adigun and Akinyanjuola, 1991). Moreover, zinc sulphate was used because dietary zinc supplements usually are prescribed as zinc sulphate and is the most frequently use as supplement (Jacqueline *et al.*, 2002). A dose of 50 mg/kg/day zinc sulphate was used, which has been reported to show no adverse effect in rats (Select Committee on GRAS Substances, 1973). The recorder used to measure blood pressure in the rats was calibrated before each experiment. Moreover, the blood samples used in the analysis of plasma electrolytes were centrifuged immediately after collection before hemolysis occurred. Hemolysis interferes with the plasma electrolyte level (Bergstrom, 1973).

The result of the present study shows that salt loading increased the arterial blood pressure of normotensive rats and zinc supplementation prevented this salt-induced elevation of blood pressure. This observed salt-induced elevation of blood pressure in this study confirms the report that salt loading to various strains of rats is known to result in increased arterial blood pressure. This effect was reported to be greatest in genetically selected Dahl sensitive animals (Dahl *et al.*, 1962), but it also occurs in other animals including weanling Sprague-Dawley rats (Nwaigwe and Sofola,

1989), Wistar rats (Kagota *et al.*, 2001) and chimpanzees (Denton *et al.*, 1995). Zinc sulphate supplementation (50 mg/kg/day) prevented this increase in the arterial blood pressure. (Pol, Arch Wemn [POLAND], 1996) reported that zinc plays a role in the pathogenesis of hypertension, but its role was not known. This study has demonstrated that dietary zinc supplementation can prevent the development of hypertension.

This present study also show that salt induced hypertension caused an increase in the hematocrit, number of red blood cells, hemoglobin concentration and mean corpuscular volume. The increase in the mean corpuscular volume might be due to increased or high intracellular sodium ion in the red blood cell, which causes inward movement of water by osmosis. Increased intracellular sodium ion in the red blood cells of hypertensives had been reported by Aderounmu and Salako (1979). The increase in these hematological parameters might expands the blood volume, increase the demand on the heart to pump more volume (increase cardiac output) and thus, raise the blood pressure. The increase in PCV and red blood cell presumably causes an increase in the blood viscosity (Gross and Hathaway, 1973). Letcher *et al.* (1981), reported that the blood viscosity was higher in hypertensive patients. The increase in blood viscosity was attributed to increase in hematocrit value. Zinc supplementation significantly reduced the hematocrit, number of red blood cells, hemoglobin concentration and mean corpuscular volume. These might indicate a decrease in the blood volume and blood viscosity, which may lead to a lowering of the blood pressure that was caused by increased salt loading.

The zinc fed and salt-loaded-zinc-fed rats had a significant increase in the number of white blood cells, which are important in the immune system of the body. This is consistent with the report that zinc supplementation enhances immune system activity and protect against a range of infections including cold and upper respiratory infections such as bronchitis (Erickson, 2000). Zinc has been reported to enhance activity of lymphocytes (Erickson, 2000). Boost the immunity of the body in sickle cell anemia, elderly, HIV/AIDS (Mocchegiani and Muzzioli, 2000). It is used in the treatment of diarrhea and it reduces malaria attack (Shankar, 2000).

This present study also show that the rats in the control group had the highest percentage weight gain, followed by zinc-fed and then by salt-loaded-zinc-fed rats. The salt-loaded rats had the least percentage weight gain. It was also observed that the salt-loaded and salt-loaded-zinc-fed rats consumed more water than the other two groups during feeding period. Thus, the weight loss in these rats may be attributed to large water consumption

at the expense of food intake. This indicates that the thirst center overrides those of hunger during salt loading. Brum *et al.* (1991) reported the stimulation of the thirst center in the brain of salt loaded rats. This probably might be due to the mediating action of angiotensin II, which has been reported as acting on the central nervous system to stimulate drinking (Jackson *et al.*, 2000). The fact that salt-loaded-zinc-fed rats gained more weight than the salt-loaded rats suggests that dietary zinc supplementation blocked the effect of salt on the feeding and thirst center. It was also observed that the salt-loaded and salt-loaded-zinc-fed rats excreted more urine than the other two groups. They wet their beddings such that the beddings needed to be replaced more regularly than those of control and zinc-fed rats. The salt-loaded zinc fed rats must have excreted more urine than the salt-loaded rats (they ate the same salt diet), because they have less blood volume than salt-loaded rats as reflected in their hematological parameters and blood pressure (reduced). Hence, Group D rats have increased renal excretion of salt and water than rats in Group C. This might be due to the antihypertensive effect of zinc.

The decrease in the plasma potassium concentration in the salt-loaded rats may be a possible factor for the development of hypertension in this group of rats. Aderounmu and Salako (1979) reported that there is a fall or low serum/plasma potassium in hypertensives. The plasma potassium level in the salt-loaded-zinc-fed rats was significantly higher compared with the salt-loaded rats, indicating that zinc supplementation caused a stability of plasma potassium. This may be an antihypertensive effect of zinc. Since correction of hypokalemia by supplementary potassium abolishes the hypertensive response to salt loading (Nwaigwe and Sofola, 1989), Hypokalemia has also been shown to enhance cardiac activity and slow conduction in the heart (Roden and Iansmith, 1987).

The result of this present project work did not show a significant difference in the plasma sodium level between hypertensive and control rats. This is in line with report of Sofola *et al.* (1991), that the plasma sodium levels in the hypertensive rats and control were not significantly different, but plasma potassium were significantly reduced in hypertonic saline rats (1.2% NaCl) and high salt rats (8% NaCl).

There was no significant difference in plasma zinc level in the four groups of rats. The high salt did not lead to reduce plasma zinc level. This is consistent with the report of Rubio *et al.* (1995) that there was no significant difference between control and hypertensive patients in serum and intraerythrocyte concentration of zinc. The

difference in plasma zinc level in the four groups of rats was not significant. Thus hypertension can be induced in the presence of normal plasma zinc. Further studies on the antihypertensive effects of zinc sulphate may focus on the vascular effects of zinc in preventing hypertension

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