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Comparative Nephroprotective Effects of Concomitant Administration of Ca, Mg and the Combination of Ca and Mg against Cd and Pb Co-intoxicated Rats

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Abstract: *This work studied the comparative nephroprotective effects of concomitant administration of calcium (Ca) alone, magnesium (Mg) alone and the combination of Ca and Mg against cadmium (Cd) and lead (Pb) co-intoxicated rats. Wistar rats were divided into five groups of four rats per group in metabolic cages. Group one was fed with tap water only; group two with the co-administration of Cd and Pb; group three with co-administration of Cd and Pb and concomitant addition of Mg; group four with co-administration of Cd and Pb and concomitant addition of Ca; while group five with co-administration of Cd and Pb and concomitant addition of Ca and Mg. All the groups fed and freely drank from the water meant for each group for a period of fourteen (14) days. The rats were humanely sacrificed under anaesthesia, sample of blood was obtained from each rat by decapitation. Serum was obtained by centrifugation of clotted blood for kidney biomarkers determination, while the kidney was identified and fixed in 10% formal saline for histopathological studies. Results show that kidney biomarkers were significantly different ($p<0.05$) between control and the groups treated with the combination of Cd+Pb and Cd+Pb+Mg, while there was no significant difference (($p>0.05$) between control and the groups treated with Cd+Pb+Ca and Cd+Pb+Ca+Mg. The histochemistry also show that there was mild damage to the kidney integrity of the group treated with Cd+Pb+Mg and a marked damage to the group treated with Cd+Pb. Results suggest that Ca has a better hepatoprotective property than Mg and the two metals have synergistic effect in mitigating the nephrotoxicities induced by co-administration Cd and Pb in rats.*

Keywords: *Comparative, Nephroprotective, concomitant, Calcium, Magnesium, Cadmium, Lead, Co-intoxicated.*

I. Introduction

Mining and smelting operations are important causes of heavy metal contamination in the environment due to activities such as mineral excavation, ore transportation, smelting and refining, and disposal of the tailings and waste waters around mines [1, 2, 3]. Literatures abound on the adverse environmental impact of excessive heavy metals dispersed from mine and smelter sites contamination of water and soil, phytotoxicity, soil erosion, and potential risks to human health [4, 5, 6, 7]. Studies on the mining sites of Plateau State, Nigeria, show that in the recent past decades, the natural environmental concentrations of several chemical elements (toxic and essential) have largely increased on the Jos Plateau, mostly as a result of anthropogenic activities, chief amongst them is mining.

Metals and metalloids have been reported to occur in the mining pond waters of Plateau State at levels above World Health Organisation tolerable limits for drinking water [8, 9, 10, 11, 12]. In solution, these elements may exist either as free ions or as various complexes associated with organic or inorganic ligands or as suspended colloidal particles. In the solid phase, they may be adsorbed (or absorbed) on organic and inorganic soil components, exist as minerals ions, or co-precipitated with other minerals. Generally, ions in solution are more available for plant and animal uptake, and immediately entering the food chain [13, 14, 15, 16].

In our previous work, we showed that Ca and Mg hepatoprotective effects are synergistic, while Ca alone had more hepatoprotective effect than Mg alone in rats as determined by liver biomarkers and the histochemistry of the liver [17], and graded concentrations of Ca and Mg had nephroprotective effect on the nephrotoxicity induced by a constant toxic concentrations of Cd and Pb [18]. The mining pond waters of Plateau state contain Cd and Pb in concentrations above WHO permissible limits, and also contain Ca and Mg in high concentrations. The local inhabitants of these areas use the pond waters for their domestic use (drinking, cooking and washing). What could be the effect of the concurrent occurrence of these four metals from using this pond water on the inhabitants? This present work seeked to compare the nephroprotective effects of calcium alone, magnesium alone and the combination of calcium and magnesium against the nephrotoxicity of a constant toxic concentration of the combination of Cd and Pb in rats. This is to determine whether calcium alone, magnesium alone or the combination of calcium and magnesium have more efficient nephroprotective effect against the nephrotoxicity induced by co-administration of cadmium and lead in rats.

II. Materials And Methods

2.1 Experimental Animals

Ethical Clearance was obtained from The University of Jos Committee on Care and Use of Laboratory Animals before the commencement of this work. Twenty (20) adult male Wistar strain rats weighing 178g on the average were obtained from the University of Jos Animal House. Commercial feed produced by Grand Cereal and Oil Mill Limited, Jos, Nigeria, was used to feed the animals.

2.1.2 Chemicals

Lead acetate and magnesium sulphate, both analar, were products of British Drug House (BDH), Poole, England. Bovine Serum Albumin (BSA) was a product of Sigma Chemicals. Cadmium chloride and calcium sulphate were products of May and Baker (M & B) Limited, Dagenham, England. All other chemicals used were of analytical grade purchased by the Department of Biochemistry, University of Jos, from reputable chemical companies in Jos, Plateau State, Nigeria.

2.2 Experimental design

The rats were randomly divided by body weight equally into five groups of four per group in metabolic cages. Group one (control) was placed on tap water only, while group two was placed on 0.327mg/L Pb and 0.079 mg/L Cd only; group three was placed on 0.327mg/L Pb and 0.079 mg/L Cd with the addition of 0.221mg/L of Mg; group four was placed on 0.327mg/L Pb and 0.079 mg/L Cd with the addition of 0.221mg/L of Ca; while group five was placed on 0.327mg/L Pb and 0.079 mg/L Cd with the addition of equal concentrations 0.221mg/L of Ca and Mg respectively as shown in table 1 below. The choice of Cd and Pb concentrations of (0.327mg/L Pb and 0.079 mg/L Cd) is based on the fact that the combination of the two concentrations caused the most damage to the kidney in our previous work, hence the need to comparatively test the protective effects of Mg alone, Ca alone and the combination of Ca and Mg. The mining pond waters of Plateau state contain Cd and Pb in concentrations above WHO permissible limits, and also contain Ca and Mg in high concentrations, which the inhabitants of the areas use for their domestic purposes.

Twenty-four (24) hours prior to the commencement of the experiment the rats were fasted to clear the gastrointestinal tract of any other food eaten before, according to Rodriguez-de Fonseca *et al* [19]. Their feed was mashed with the same water meant for each group. All the groups fed on the mashed vital growers' food, and freely drank from the water for a period of fourteen (14) days.

Table 1: Experimental design

Metals	Group1 (control)	Group 2	Group 3	Group 4	Group 5
Pb	-	0.327	0.327	0.327	0.327
Cd	-	0.079	0.079	0.079	0.079
Mg	-	-	0.248	-	0.248
Ca	-	-	-	0.248	0.248

Concentrations in mg/*L*

2.2.1 Blood Collection

The rats were humanely sacrificed, and five to ten milliliter sample of blood was obtained from each rat. To prevent mechanical lyses, the blood was allowed to flow along the wall of the tubes, which was brought close, to the bottom. The blood was allowed to clot at room temperature after which a gentle ringing was carried out to dislodge the clot from the walls of the tubes. The serum was then separated from the clot by centrifugation, using MSE Mistral 2L Centrifuge, and kept frozen until required for the measurement of the following biochemical parameters: urea and creatinine. The kidney was excised and fixed in 10% formal saline for histopathological studies.

2.2.2 Methods used in the determination of biochemical parameters

Urea estimation in serum was done by diacetyl monoxime method [20]. The principle of the method is based on the fact that under acidic conditions diacetyl monoxime react with water to form diactyl. Diacetyl will then react with urea to give a yellow diazine derivative. Estimation of creatinine in serum was done by Jaffe's method [21]. The principle of this method is based on the fact that creatinine reacts with alkaline picrate to form an amber yellow solution that is measured quantitatively with a photometer at 520nm.

2.2.3 Histopathological studies

The kidney was fixed in 10% neutral formalin solution. After a week of fixing, the kidney tissues were dehydrated with a sequence of ethanol solutions, embedded in paraffin, cut into 5µm section, stained with haematoxylin eosin dye (H & E stain) and observed under a microscope at x400 magnification. Morphological changes were observed including glomeruli necrosis and loss of nuclei within collecting ducts.

2.2.4 Statistical Analysis

Tukey-Kramer multiple comparisons test at 95% level of confidence was used to test for the significant differences in the concentrations of serum urea and creatinine, and results expressed as mean ± S.D. The INSTAT3 statistical software was used.

III. Results

The results are presented in Table 2 and Plates 1-5. When the combination of Cd and Pb only were administered, the result of urea was significantly ($P<0.05$) different from control. But when Cd, Pb and Mg were administered concomitantly, the significant difference observed in the first instance was drastically reduced. There was no significant difference in the value of urea when Ca alone or the combination of Ca and Mg were concomitantly administered. The same trend was observed for the values of creatinine (table 2). The histochemistry show that when Cd and Pb were administered without the addition of either Mg, Ca, or the combination of Ca and Mg, the kidney histochemistry showed necroses of glomeruli (left arrow), while the up-pointing arrow shows loss of nuclei within a collecting duct (Plate 2). There was necrosis of glomerulei (up-pointing arrow) of the kidney, while the down-pointing arrow shows a normal opening of a collecting duct when the combination of Cd and Pb where concomitantly administered with Mg alone (Plate 3). When Ca alone was added to the combination of Cd and Pb, the kidney histochemistry showed normal glomerulei (up-pointing arrow), while the down-pointing arrow shows a normal opening of a collecting duct (Plate 4). The addition of the Ca and Mg to the combination of Cd and Pb showed that the histochemistry of the kidney showed normal glomerulei (right-pointing arrow), while the left-pointing arrow shows a normal collecting duct with a normal opening.

Table 1: The Effect of Concurrent Administration of Cadmium and Lead with the Addition of Either Magnesium Alone, Calcium Alone or with the Combination of Calcium and Magnesium on the concentration of Urea and Creatinine in Rats.

Group	Treatment	UREA (mmol/L)	CREATININE (mg/dl)
1.	No metal Added	49.5 ±0.06	38.5±0.01
2.	Cd+Pb	68.9±0.07	45.5±0.02
3.	Cd+Pb+Mg	59.1±0.04	40.0±0.03
4.	Cd+Pb+Ca	51.7±0.02	37.8±0.01
5.	Cd+Pb+mg+Ca	50.1±0.08	39.0±0.01

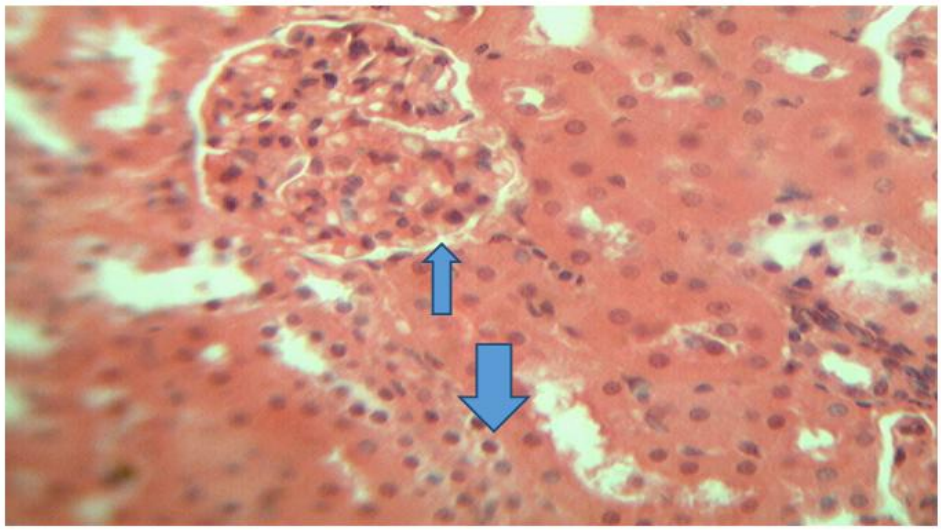

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Plate 1: Representative kidney section of the rats fed vital feed without the addition of any metal showing normal glomeruli (up arrow), while the down arrow shows normal nuclei arrangement within the cell and a normal opening within the collecting duct.

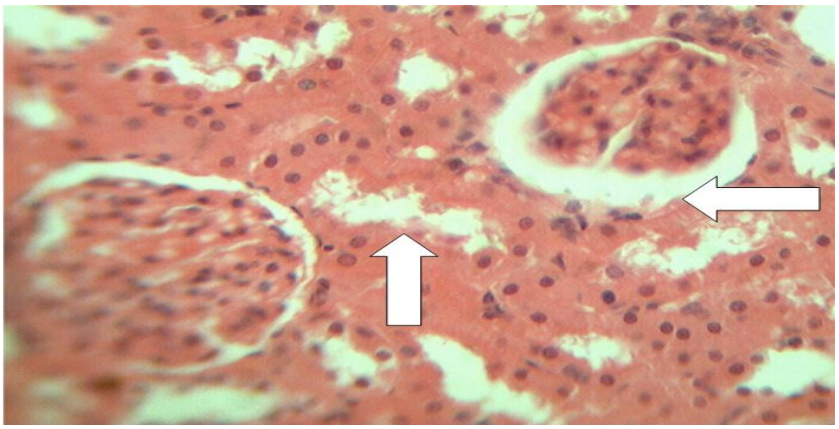

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Plate 2: Representative kidney section of the rats fed with the combination of cadmium and lead showing necroses of glomeruli (left arrow). The up-pointing arrow shows loss of nuclei within a collecting duct.

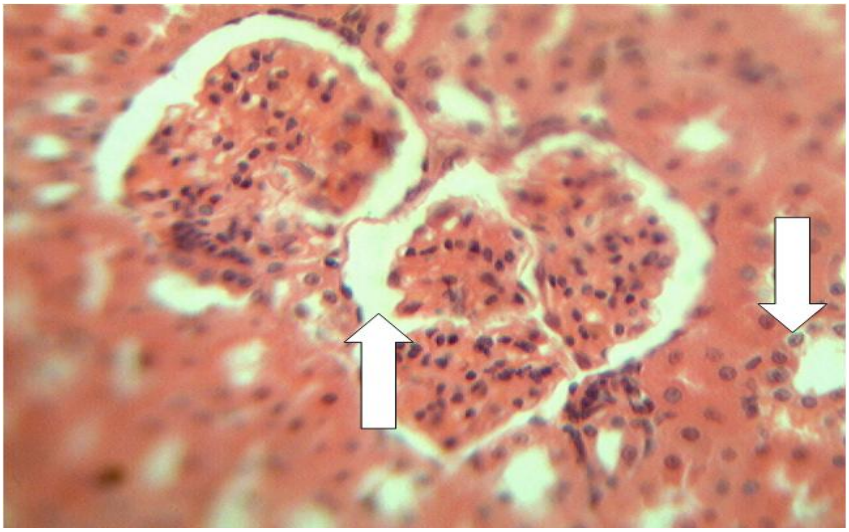

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Plate 3: Representative kidney section of the rats fed with the combination of cadmium, lead, and magnesium showing necrosis of glomeruli (up arrow). The down arrow shows a relatively normal opening of a collecting duct.

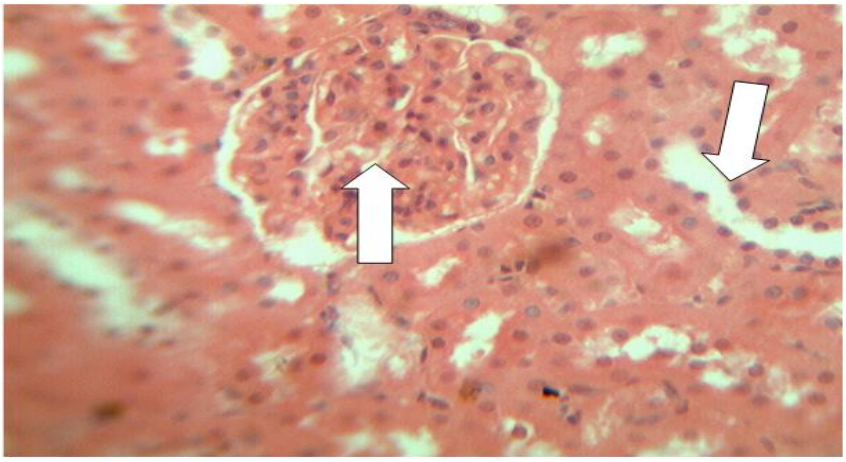

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Plate 4: Representative kidney section of the rats fed with the combination of cadmium, lead and calcium showing relatively normal glomeruli (up arrow). The down-pointing arrow shows a normal opening of a collecting duct.

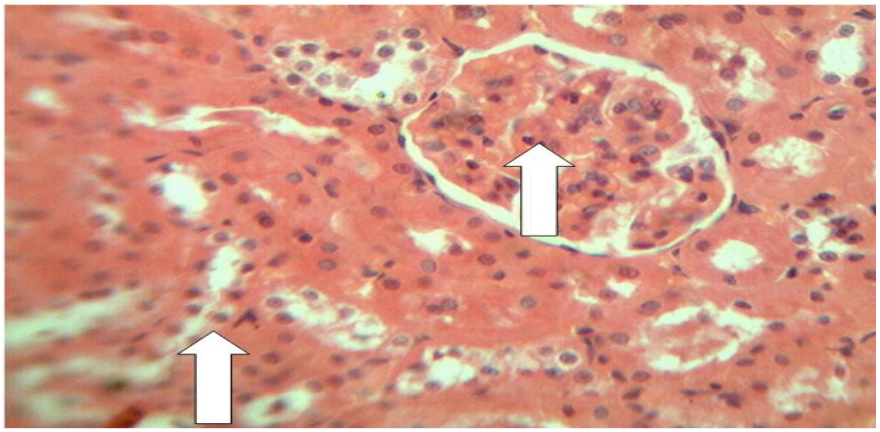

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Plate 5: Representative kidney section of the rats fed with the combination of cadmium, lead, calcium and magnesium showing relatively normal glomeruli (right arrow). The left arrow shows a normal collecting duct with a normal opening.

IV. Discussion

From the results, when 0.327*mg*/*L* of Pb and 0.079*mg*/*L* of Cd concentrations were administered without the addition of either Mg, Ca or the combination of Ca and Mg, there was significant difference between the kidney of control group with this group as indicated by kidney biomarkers and the histochemistry. This indicate that there was marked compromise of the kidney integrity of this group. This is in agreement with the fact that when Cd and Pb are ingested either in food, water, or breathe in the air beyond the WHO admissible limits kidney toxicity occurs [12, 22, 23]. Cadmium is known to induce tissue injury through creating oxidative stress [24], epigenetic changes in DNA expression [25], inhibition or upregulation of transport pathways [26] particularly in the proximal S1 segment of the kidney tubule [27]. Other pathologic mechanisms include competitive interference with the physiologic action of Zn or Mg [28], inhibition of haeme synthesis [29], and impairment of mitochondrial function potentially inducing apoptosis [30]. Depletion of glutathione and structural distortion of proteins is said to also occur due to Cd binding to sulfhydryl groups. These effects are magnified by interaction with other toxic metals such as Pb and As [31] and possibly ameliorated by Zn or Se [32]. But when the Cd and Pb concentrations above were administered concurrently with 0.248*mg*/*L of Mg alone*, there was necrosis of glomerulei of the kidney and normal opening of a collecting duct signifying that the severe damage that was observed in plate 2 was ameliorated but not obliterated. Increasing the availability of essential micronutrients had proved in various studies to decrease the toxicity of toxic heavy metals. Zinc can increase synthesis of Metallothionine (MT), a thiol-rich protein that sequester cadmium and prevent acute hepatotoxicity, leading to chronic kidney toxicity as Cadmium-MT is excreted from the liver and absorbed by the kidney. Gastrointestinal lead absorption and retention constitutes the major pathway of lead intake and depends on the micronutrients status of the individual. Adults are said to absorb approximately 10% of ingested lead and small children absorb approximately 50% of ingested lead. From this studies, magnesium decreased the susceptibility of cadmium and lead intoxication in rats. This could be as a result of decrease intestinal absorption of cadmium and lead as a result of competition for similar binding sites on intestinal proteins which are important in the absorptive process. These shared binding sites on absorptive proteins could explain why sufficient dietary magnesium could decrease lead and cadmium absorption [33, 34, 35].

When Ca was concurrently administered with Cd and Pb concentrations above, the histochemistry of the kidney showed normal glomerulei and normal opening of a collecting duct. There was no significant difference between the kidney biomarkers of this group and control. This means that calcium alone has more nephroprotective effect on Cd and Pb co-intixicated rat kidney than Mg alone. The interaction between calcium and cadmium was made clear in the case of the itai-itai disease in Japan where women developed bone deformities, osteomalacia and an increased in osteoporosis. It was discovered that the women normal diet consisted of mostly rice and other grains that were farmed on Cd polluted soils. This is in agreement with the work of Ahamed and Siddiqui [28,], who reported that Cd transport occurred by temperature-insensitive processes, probably Ca channel, and carriers that involved interaction with sulfhydryl groups. If that is so, then Ca channel will preferentially transport Ca leaving the other toxic metals Cd and Pb, since Ca was present in high concentration, leading to the insignificant difference between control and this group in the parameters analysed [36, 37].

When Ca and Mg were concurrently administered with the Cd and Pb concentrations above, there was no significant difference between the kidney biomarkers of control and this group. The histochemistry of this

group showed normal glomerulei and normal collecting duct with a normal opening which was not significantly different from that of control. This means that the combined nephroprotective effect of Ca and Mg against Cd and Pb co-intoxicated rats was higher than Ca or Mg alone. This could be as a result of the fact that Cd and Pb have no specific transport proteins, but rather rely on their similarities in chemical and physical properties to the essential metals Ca and Mg for their transport and uptake into the cells by a process referred to as "ionic and molecular mimicry" [38]. Some studies have demonstrated that Cd and Pb ions are taken up by the divalent metal transporter 1 (DMT1), and the metal transporter protein 1 (MTP1), which are located in the basolateral and the apical membranes of the enterocytes respectively [39, 40, 41]. This work therefore points to the fact that disruption of essential metals homeostasis can lead to kidney diseases and adequate intake of essential metals (Ca and Mg) can mitigate the toxicities of non-essential metals (Cd and Pb).

V. Conclusion

This study shows that the synergistic action of Ca and Mg have the greatest nephroprotective effect, followed by Ca alone and then Mg alone last, against Cd and Pb nephrotoxicities in rats. Based on these results, we recommend that people around the world who are at risk of exposure to toxic metals Cd and Pb should ensure a sufficient intake of Ca and Mg through enhance consumption of vegetables, fruits and foods which are known to be high in Ca and Mg. These metals are important natural antagonists to Cd and Pb toxicities and should be consumed on a regular basis. Providing livestock and farmed fish with the above-mentioned food interventions may also be helpful to reduce Cd and Pb exposure in humans through the food chain.

Ethical Approval

All authors hereby declare that the principles of laboratory animal care (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee"

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