The Protective Roles of Zinc and Magnesium in Cadmium-Induced Renal Toxicity in Male Wistar Rats

*Nasim Babaknejad [*1], Ali Asghar Moshtaghie [1], Kahin Shahanipour [1], Somaye Bahrami [1]*

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ABSTRACT

Background: Cadmium (Cd) is a heavy metal that has widespread use. It enters the food chain in different ways, including soil and water. Cadmium can cause dysfunction of different body organs. Zinc (Zn) and magnesium (Mg) supplementation can have protective effects against cadmium toxicity due to their antagonistic and antioxidants properties. This study examines the influence of supplemental Zn and Mg on Cd renal toxicity.

Methods: Young male Wistar rats were divided into six groups of five. The Cd group received 1 mg Cd/kg and the control group received 0.5 mg/kg normal saline (i.p.). The other four groups were administered 1 mg/kg Cd+0.5 mg/kg Zn, 1 mg/kg Cd+1.5 mg/kg Zn, 1 mg/kg Cd+ 0.5 mg/kg Mg, and 1 mg/kg Cd+ 1.5 mg/kg Mg (i.p.) for 21 days. Then, serum sodium, potassium, urea, creatinine, and protein levels were measured.

Results: The results indicated that creatinine and protein levels decreased while urea, sodium, and potassium levels increased as a result of Cd exposure. Co-administered Cd and Zn and Mg decreased urea and increased sodium serum level in comparison to the cadmium group. Treatment by Mg, contrary to co-administered Cd and Zn, reduced serum protein level compared to the cadmium group. Compared to the cadmium treated group, Zn and Mg treatment enhanced serum creatinine level and reduced serum potassium level.

Conclusion: The findings seem to suggest that zinc and magnesium compounds, due to their antagonistic and antioxidant activities, can protect Cd renal toxic effects in a dose-dependent manner.

Keywords: Cadmium, Magnesium, Renal Function, Zinc.

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INTRODUCTION

Cadmium (Cd) is a widespread industrial and environmental pollutant that may induce adverse harmful effects on humans and animals. Apart from smoking, the major sources of cadmium exposure in the general population are contaminated foods and water and industrial fumes and dusts [1]. The kidneys and liver are among the major target organs of cadmium accumulation and intoxication where it induces metallothionein (MT) synthesis. The kidney has been considered the critical organ for Cd toxicity. Cadmium-induced kidney injury is primarily characterized by proximal tubular dysfunction [2]. The cytotoxic action of Cd mainly occurs in the main tubules and partially in the renal glomeruli [3]. The molecular mechanism responsible for the toxic effects of Cd is not well-understood. Various studies have pointed to Cd oxidative stress role, since this metal can alter the antioxidant defense system in several animal tissues [4,5]. No effective therapy of Cd poisoning has yet been developed since the application of known chelate agents does not produce satisfactory results. Therefore, a great deal of attention has been paid to finding natural therapy for cadmium poisoning [6]. Previous studies have demonstrated that compounds, such as vitamins A, C, and E as well as selenium, can be used to prevent or reduce many toxic effects of cadmium on various organs and tissues, including liver, kidney, skeleton, and blood [7-9]. In fact, zinc and magnesium are elements with multiple clinical applications [10]. Zinc (Zn) is the unique trace intracellular element required for a number of cellular processes, including cell proliferation, reproduction, immune function, and defense against free radicals [11,12]. Zinc is an essential trace element has an important role in cell signaling,

1. Department of Biochemistry, Falavarjan Branch, Islamic Azad University, Isfahan, Iran.
*Corresponding Author: E-mail: n.babaknejad@gmail.com

enzyme function, nucleic acid metabolism, growth, and cellular repair, especially in pregnant women and newborns [12-14]. Enhanced daily Zn intake has been noted to protect the organism from Cd accumulation and its effects, especially to prevent kidney damage [15,16]. A number of studies have indicated that zinc affects Cd-induced changes in the antioxidative enzymes genes expression, such as SOD, CAT, and Gpx [17,18]. Mg is an essential cofactor to activate many enzyme systems in humans. It is involved in carbohydrate, lipid, protein, and DNA metabolism, interacting either with the substrate or the enzyme directly [19]. Increasing evidence suggests that Mg modifies Cd absorption in the gastrointestinal system and thus reduces peripheral blood Cd [20,21]. Mg's protective activity against Cd toxicity may be due to either the antagonistic effect of Mg and/or the stimulatory effect of Mg in producing de novo GSH [21]. However, the exact mechanism behind the protective effects of Zn and Mg against cadmium remains largely unexplored. The most recommended mechanism is the interaction between these metals in intestinal absorption stage (Cd, Zn and Mg) and sometimes the same ability to induce metallothionein [22-24].

Consequently, this study was performed to elucidate the protective role of Mg and Zn in renal Cd toxicity of male Wistar rats.

MATERIALS AND METHODS

Chemicals

Cadmium chloride, zinc chloride, and magnesium chloride were obtained from Acros Organics (New Jersey, USA). Kits for urea, creatinine, and protein estimation were purchased from the ZiestChem Company (Tehran) Iran. All other reagents and chemicals were of analytical grade quality or higher purity.

Animals

A total of 30 adult (10-week-old) male Wistar rats (initial body weight: 200±50 g) were used in this study. The animals were housed in conventional conditions at a temperature of 25±1°C, with a relative humidity of 50±10% and a 12-h/12-h light/dark cycle. They were maintained on Ad libitum diet and water throughout the experimental period. The empirical protocols of this experimental study were approved by the Department of Physiology, University of Isfhan, and were performed according to guidelines for the care and use of animals, prepared by the Council of the American Physiological Society.

Experimental Protocol

The rats were allocated randomly to six experimental groups of five animals each. The Cd group were given intraperitoneal injection with cadmium (as $CdCl_2 \cdot 2\ 1/2H_2O$, 1 mg/kg). Four experimental groups in the protection experiment were administered either 1 mg/kg Cd+ 0.5 mg/kg Zn (as $ZnCl_2$), 1 mg/kg Cd+ 1.5 mg/kg Zn, 1 mg/kg Cd+ 0.5 mg/kg Mg (as $MgCl_2$), and 1 mg/kg Cd+ 1.5 mg/kg Mg intraperitoneally for 21 days. Control rats received equal volumes of 0.9% NaCl solution (saline). The treatment in all groups was continued for 21 consecutive days. All animals were anaesthetized 24 h after the administration of the final dose and blood samples were withdrawn directly from their hearts. Serum samples were collected by centrifugating at 2000 rpm for 20 minutes. The serum samples were used in the present study to estimate the concentrations of parameters related to renal function, such as urea, creatinine, potassium, sodium and protein. Serum urea, creatinine and protein concentrations were determined by routine laboratory methods and kits. Serum sodium and potassium were analyzed by flame photometry (Corning 408). All experiments were repeated twice with similar results.

Statistical Analysis

SPSS software version 20 was used for data analysis. The results of all measurements are presented as mean± S.E. for ten rats in each group. A one-way analysis of variance (ANOVA) was conducted to determine whether there were statistically significant ($P<0.05$) differences among the six experimental groups. Furthermore, the LSD multiple-range post-hock test was performed for making comparisons between individual groups and to determine which means differed significantly ($P<0.05$).

RESULTS

Body and Kidney Weight

The body and kidney weights of rats during exposure to Cd, Cd+Zn (0.5 and 1.5 mg/kg), and Cd+Mg (0.5 and 1.5 mg/kg), and in control conditions are shown in Table 1. Intraperitoneal injection of Cd reduced body

weight gain. At the end of the experiment (day 21), a 13% reduction in body weight was noted in the Cd group compared with controls. Cotreatment with 1.5 mg/kg Mg and Zn produced a significant increase in body weight of rats in these two experimental groups compared with the Cd group. The only statistically significant reduction in body weight gain was observed in 0.5 mg/kg Mg treated group. There were statistically significant differences in kidney weight of rats among the six experimental groups. During the experiment, an increase in the kidney weight of the Cd group rats was noted, which was caused by the decrease in body weight gain. Administration of Zn and Mg during chronic Cd intoxication produced a significant decrease in kidney weight compared with the Cd group (Table 1).

Serum and Urinary Markers of Renal Toxicity

Applied cadmium dose of 1 mg/kg for 21 days had no statistically significant effects on serum urea and creatinine. In rats exposed to 1 mg/kg cd, concentration of protein and sodium in the serum decreased, while serum potassium increased in comparison to the control group. The administration of Zn at both concentrations in conjunction with 1 mg/kg Cd decreased serum urea level compared to the group receiving Cd alone. In rats receiving 0.5 or 1.5 mg/kg Zn with 1mg/kg Cd for three weeks, serum creatinine and sodium concentrations were significantly higher compared to the respective groups treated with Cd alone.

In the 1 mg/kg Cd+ 0.5 mg/kg Zn group, the serum potassium concentration was higher by 12-13% compared to the 1 mg/kg Cd group; however, there were no differences in the potassium concentration between the rats receiving Cd alone and those receiving Cd and 1.5 mg/kg Zn. The coadministration of 0.5 mg/kg Zn with 1 mg/kg Cd had no influence on protein concentration in the serum compared to the cadmium group, whereas serum protein concentration increased as a result of cotreatment with 1.5 mg/kg Zn in comparison to the Cd group. The positive effect of Zn at both levels of exposure to Cd was dependent on Zn concentration (Table 2).

The results presented in Table 2 show a statistically significant decrease in urea concentration in the serum of mice in the group given 0.5 or 1.5 mg/kg Mg with 1 mg/kg Cd compared with the group receiving only Cd. Mg supply (0.5 mg/kg) had no significant effect on serum creatinine level but when rats were concomitantly exposed to 1 mg/kg Cd and 1.5 mg/kg Mg, serum creatinine concentration was significantly higher than that in Cd-exposed animals. In rats supplemented with Mg (0.5 and 1.5 mg/kg Mg) during exposure to 1 mg/kg Cd, the serum concentrations of sodium were higher and did not differ compared with respective values noted in the rats not receiving Mg supplementation during treatment with Cd.

The administration of Mg at the two concentrations (0.5 and 1.5 mg/kg) totally prevented Cd-induced changes in the serum concentrations of potassium and decreased serum level of this parameter compared to the Cd group. The treatment of Cd-exposed rats with 1.5 mg/kg Mg had no significant effect on the protein level of the serum. However, 0.5 mg/kg Mg decreased serum protein concentration compared to the cadmium group.

Table 1. The mean body weight of rats exposed for 21 days to cadmium (Cd), 1 mg / kg cadmium+zinc (0.5 and 1.5 mg / kg, cadmium+ magnesium (0.5 and 1.5 mg / kg).

Groups	Body weight		Kidney weight
	Initial body weight	Final body weight	
Control	239.00±4.26	264.00±3.39	0.86±0.00
Cd 1 mg/kg	235.00±11.45	228.00±10.85[a*]	1.06±0.01[a*]
Cd+Zn 0.5 mg/kg	242.00±6.79	235.20±7.45[a*]	0.76±0.01[a*d*]
Cd+Zn 1.5 mg/kg	233.00±14.20	247.60±13.05[d*]	0.80±0.01[d*]
Cd+Mg 0.5 mg/kg	235.00±11.45	202.00±9.74[a* d*]	0.79±0.04[d*]
Cd+Mg 1.5 mg/kg	240.00±5.57	251.00±5.20[a*d*]	0.88±0.83[d*]

Means±SE of five separate experiments performed twice; significance from C: a; Significance from Cd: d
*p<0.05, *p<0.001

Table 2. Biochemical tests of kidney function in rats exposed for 21 days to cadmium (Cd), 1 mg / kg cadmium+zinc (0.5 and 1.5 mg / kg, cadmium+ magnesium (0.5 and 1.5 mg / kg).

Parameters	Groups					
	Control	Cd	Cd+Zn 0.5	Cd+Zn 1.5	Cd+Mg 0.5	Cd+Mg 1.5
Urea (mg/dl)	20.95±1.22	23.81±1.20	22.09±2.46 ^{d*}	20.03±0.69 ^{d*}	19.70±1.05 ^{d*}	17.46±1.39 ^{a*d*}
Creatinine(mg/dl)	0.59±0.03	0.55±0.01	0.75±0.05 $^{a* d*}$	0.63±0.04 ^{d*}	0.50±0.00 ^{a*}	0.64±0.01 ^{d*}
Sodium(meq/L)	134±0.78	138.30±0.55 ^{a*}	140.30±0.73 $^{a* d*}$	141.20±0.48 $^{a* d*}$	142.00±0.33 $^{a* d*}$	137±0.00 ^{a*}
Potassium(meq/L)	4.20±0.02	4.97±0.13 ^{a*}	5.61±0.36 $^{a* d*}$	4.75±0.08 ^{a*}	4.66±0.07 ^{a*}	4.50±0.00 ^{d*}
Protein (g/dl)	6.48±0.05	5.92±0.04 ^{a*}	5.92±0.02 ^{d*}	6.34±0.07 ^{d*}	5.14±0.15 $^{a* d*}$	6.11±0.04 ^{a*}

Means±SE of five separate experiments performed twice; significance from C: a.; significance from Cd: d. *p<0.05, *p<0.001

DISCUSSION

In recent years, a great deal interest has been drawn to the interaction between biological elements of toxic and essential elements [24]. This interaction involves biological elements, such as Zn, Cu, Se, Fe, and Ca and toxic elements, such as cadmium [25]. The present study, conducted on the rat model, focused on the potential benefits of treatment with Zn and Mg in reversing Cd-induced renal toxicity. The degree of kidney damage was evaluated biochemically by measuring serum parameters related to renal function.

Effects of Cd on Renal Function

Three-weeks following Cd administration, body weight gain decreased. Weight loss of the Cd-treated group is probably because of serum proteins reduction and severe diarrhea. Several studies have shown that cadmium inhibits growth [26]. The increase in the weight of kidney was caused by the decrease in body weight gain and probably hypertrophy induced by the nephrotoxicity of $CdCl_2$ and cadmium accumulation in the kidney [27-29].

Serum creatinine and urea are used for assessing renal glomerular function. For this purpose the levels of creatinine and urea were assessed. It was found that after intraperitoneal injection of 1 mg/kg of cadmium chloride to rats for three weeks, serum urea concentration increased. It should be noted that this increase was not statistically significant. Also, there was no statistically significant reduction in serum creatinine. The serum concentrations of urea and creatinine changed when about 50-70% of nephrons are destroyed [30]. Thus, a common test of kidney function is not sufficient to show nephropathy. This finding agrees with the report by Asagaba *et al*. [31].

In Cd-exposed rats, sodium and potassium serum levels significantly increased. According to several reports, electrolyte disturbances are due to cadmium toxicity in renal tubules [32]. Cadmium increased the retention of sodium and decreased water excretion. In fact, Cd increases sodium reabsorption [33-35]. Cadmium also leads to cell membrane depolarization and decreases cell membrane resistance; it stimulates potassium channels and increases extracellular potassium concentration [36]. Serum protein concentration in Cd-treated animals was significantly lower than that in the control group. These observed changes are in accordance with the results of other studies. Decrease in serum proteins following Cd exposure may be due to many reasons. One of the most toxic effects of Cd on kidney is proteinuria. Proteinuria has been observed in man and animals and has been shown to be due to renal tubular dysfunction [37-39]. Cadmium damage is typically located in the proximal tubule and it decreases proteins reabsorption [40]. Moreover, liver damage induced by Cd caused serum protein decrease [41]. Moshtaghie *et al.* made a similar observation [42].

Several hypotheses have been proposed to explain cadmium nephrotoxicity, particularly the role of the metal binding metallothionein [18]. Metallothionein is induced by a number of metals, including cadmium. Cadmium in both forms, free or bound to metallothionein, can cause the renal dysfunction [42].

Following exposure, cadmium is transported to the liver where it stimulates the synthesis of metallothionein. Cd–metallothionein complex is transported to the kidneys via blood. Next, the Cd–Mt complex is taken up from the tubular filtrate and is transported into lysosomes where it is degraded. The free Cd^{2+} ions released are transported to the cytoplasm where Mt molecules synthesis is induced, which bind and retain Cd in the kidney for a very long time. Before reabsorption, Cd^{2+} ions are released into tubular lumen and cause damage to the membrane proteins of renal tubular cells [43, 44].

Furthermore, cadmium induced the production of oxygen-free radicals in the cells. Many reports have suggested that Cd toxicity is mediated by a decrease in antioxidant enzymes, production of reactive oxygen species, and lipid peroxidation [17, 18, 44].

Zn and Mg Protection during Exposure Cd

Several lines of research indicate that treatment with Mg or Zn during Cd exposure prevented or decreased the harmful effects of Cd [20]. Consistent with these reports, the current study shows that treatment of Cd-exposed rats with Zn significantly increased serum creatinine and sodium concentrations and reversed Cd-induced increase in urea level. It also partially prevented Cd-induced decrease in serum protein concentration, but it did not reverse Cd-induced increase in potassium.

According to the related literature, cotreatment with Zn during Cd administration completely prevented the changes in renal function produced by the toxic metal [15, 16, 43]. Among the possible mechanisms, Zn might reduce the renal uptake of Cd by competition for a common transporter [45]. Moreover, zinc induced the synthesis of metallothionein in the liver, which caused Cd accumulation in the liver and delayed its transfer to the kidney [46]. On the other hand, along the terminal nephron segments, Zn inhibited Cd transport [21]. Jacquillet *et al.* demonstrated that Cd induces apoptosis by the activation of caspase 3, in a kidney cortex and Zn prevents apoptosis and necrosis by inhibition of caspase-3 and apoptosis [47]. Previous studies have demonstrated that Zn is a well-established antioxidants and it can protect against Cd-induced oxidative stress [14 ,15].

The results of this study show that Mg treatment was effective in reducing serum urea and potassium concentration. Mg cotreatment had positive effects on Cd-induced reduction of serum creatinine concentration. Magnesium treatment did not have any significant influence on serum level sodium and protein.

Various studies have demonstrated the protective effect of Mg against the toxic effects of Cd compounds [20, 22, 24]. This effect of Mg could be explained by competitive antagonism between Cd and Mg at the level of GIT [21]. Matovic *et al.* [48] showed that Mg supplementation could reduce organ Cd accumulation, especially in kidney. The effect of Mg supplementation on renal Cd retention could be explained by Cd-Mg competition during reabsorption. Furthermore, increased Mg in the lumen of the distal nephron can disable the uptake of Cd by intercellular transport and increase Cd elimination via urine [49]. In addition, Buha *et al*. [50] showed the beneficial effects of Mg on parameters of oxidative stress in the liver of Cd-exposed rats. In fact, Mg is a cofactor of enzymes which are involved in synthesis of GSH which is an important cellular antioxidant [19].

CONCLUSION

This study contributes to investigations on the protective effects of zinc and magnesium on renal toxicity of cadmium. Furthermore, in order to predict the effect of Zn and Mg on Cd-induced toxicity serum biochemical parameters related to renal functions were assayed. The present study revealed that enhanced consumption of Zn and Mg during exposure to Cd can prevent disorders in serum parameters related to renal function induced by this toxic metal. Based on the results, it seems that the protective Zn and Mg influence is dose-dependent. Zinc was also found to be more effective than magnesium in reducing the toxic effect of Cd in our study.

As shown in the present study on a rat model, Zn and Mg supply had a protective effect against toxic Cd action on kidney. Thus, these bioelements could be used as a therapeutic agent against cadmium renal toxicity; however, further studies are necessary to explain the possible

protective effect of Zn and Mg in subjects exposed to Cd and to establish the most effective dose of these elements.

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