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Cadmium Toxicity: An Experimental Study to Illustrate the Toxic Effects of Cadmium Exposure and the Role of BSA to Develop Autoimmunity in the Kidneys of Albino Mice

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ABSTRACT

Background: Cadmium is a toxic heavy metal that causes nephrotoxicity. Chronic exposures lead to cadmium accumulation in kidneys, causing histopathological and physiological dysfunction. **Objective:** To assess the nephrotoxic effects of chronic cadmium exposure on the kidneys of albino mice. **Study Design:** Randomized controlled trial. **Settings:** University of Health Science, Lahore Pakistan. **Duration:** Six months from 01-03-2014 to 31-08-2014. **Methods:** In this study, 48 albino mice were randomly divided into 4 groups (12 each): one control and three experimental groups (A, B, and C). Cadmium exposure, such as cadmium chloride ($CdCl_2$), was administered orally and intraperitoneally on alternate days for 8 weeks at a 10 mg/kg body weight. Bovine Serum Albumin (BSA) was introduced in the control group to observe the early devastating changes in the glomeruli. **Results:** The findings of present study presented the mesangial hypercellularity causing glomerular swelling, glomerular bonds, increased thickness of the glomerular capillaries, crescentic nephropathy, tubular dilatation, deterioration of renal tubules, interstitial inflammation and accumulation of protein cast in renal tubules along with many other histopathological changes. Biochemical changes were mainly proteinuria and alterations in serum creatinine. However, all the histopathological lesions and biochemical changes depended on the exposure route. **Conclusion:** In conclusion, the study found significant kidney histopathological and biochemical damage in mice exposed to cadmium chloride, emphasizing the nephrotoxic nature of cadmium. The route of cadmium administration influenced the extent of the kidney damage, accentuating the need to consider exposure routes in evaluating kidney damage.

Keywords: *Cadmium, Nephrotoxicity, Proteinuria.*

INTRODUCTION

Exposure to certain chemicals and drugs usually exhibits marked toxic effects in various tissues and organs in living organisms. The most susceptible organ is the kidney.[1] Numerous kidney compartments may experience intrinsic kidney disease due to exogenous nephrotoxins.[2,3]

Cadmium chloride is a white crystalline metal that is a mixture of cadmium and chlorine. 50% oral lethal dose (anhydrous cadmium chloride LD50) for rats is as 88mg/kg.[4] The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) has consistently ranked cadmium seventh out of 275 hazardous elements on its priority list for the last fifteen years.[5] The International Agency for Research on Cancer (IARC), a division of the World Health Organization, designated cadmium (Cd) and its containing complexes as category one human carcinogens in 1993 based on data obtained from human occupational exposure.[6]

Many possibilities lead the general public to encounter Cd. The tobacco plant actively absorbs cadmium metal from the surroundings.[7,8] There are several places in the world where the amount of Cd in the soil is noticeably high. Cadmium has a lengthy biological half-life—16 to even 30 years—and accumulates in the kidneys and liver of humans.[2]

The lungs and digestive system absorb cadmium, which is then carried by blood to the kidneys and liver. Evidence from animal tests shows that, upon exposure, cadmium in the blood initially binds to albumin and is absorbed by the liver. Cadmium stimulates the metallothionein-producing cells in the liver. Low molecular weight

protein metallothionein metabolizes copper, zinc, and cadmium. Its molecular weight is around 6500Da. The protein called metallothionein, which accumulates cadmium in the body, has been shown to detoxify cadmium and is essential for the blood's passage of cadmium from the liver to the kidneys.[9,10]

Cadmium nephrotoxicity may result from repeated inhalation or consumption. Research has shown that the kidneys are disproportionately affected by even low levels of Cd.[11] The first indication of glomerular damage from cadmium in the population exposed to work is increased excretion of large proteins such as albumin and iron-binding glycoproteins. The extent of the glomeruli's harm varies with dosage; once it begins, it's considered permanent. Chronic renal failure and a decreased glomerular filtration rate may also be brought on by significant cadmium exposure. In this instance, polyuria, aminoaciduria, hypercalciuria, glucosuria, hyperphosphaturia, and a diminished ability to buffer acids are signs of chronic renal failure.[12] Nephrotoxicity caused by cadmium has been documented in cases of industrial exposure and environmental contamination.[13]

Cadmium exposure levels in faces, hair, urine, blood, kidney, liver, and other tissues have been used as biological markers. Blood metal levels mostly indicate recent exposure to cadmium.[14] Urine cadmium concentrations mostly reflect the body's overall metal burden; however, they also somewhat correspond to new exposure. Nephrotoxicity is linked to urinary cadmium concentrations of 0.5 µg/g creatinine, and elevated creatinine values above 2.0 µg/g may result in widespread harm.[15]

So, the present study is aimed to determine the histopathological and biochemical changes resulting from different routes of cadmium administration.

METHODS

This randomized Control Trial (RCT) was conducted at University of Health Science, Lahore Pakistan. The duration of the study was 6 months from March 01, 2014 to August 31, 2014. Sample size was 48 albino mice by using simple random sampling technique.

Both male and female albino mice of BALB/c strain, aged 6-8 weeks and weighing 30 ± 5g were included in this study. Mice exhibiting illness or disease symptoms, having prior exposure to cadmium or BSA, or showing abnormal baseline biochemical parameters were excluded from the study.

Forty-eight albino mice meeting inclusion criteria were obtained from Veterinary Research Institute Lahore (VRI). They were housed by gender in the Animal House of the University of Health Sciences, Lahore, under controlled conditions (temperature 22-25˚C, humidity 65% ± 5) with a 12-hour light-dark cycle, and fed standard pellet rodent diet with tap water. After acclimatizing for one week, mice were weighed. Doses were given every other day for 8 weeks as outlined in Table 1.

Table 1: Experimental groups, interventions & dosages for albino mice undergoing cadmium exposure

Group	Mice	Intervention	Dosage on alternate day	Route
Control	12	Normal diet+ tap water	None	Oral
A	12	$CdCl_2$	10mg/kg	Oral
B*	12	BSA (single dose) + $CdCl_2$	250mg/kg +10mg/kg	Intraperitoneal + Oral
C	12	$CdCl_2$	10mg/kg	Intraperitoneal

**Group B received a single intraperitoneal dose of 250mg/kg Bovine Serum Albumin (BSA) followed by oral 10mg $CdCl_2$/kg.*

Biochemical parameters, such as serum creatinine and urinary proteins, were assessed. After 8 weeks, blood samples were collected, and the mice were euthanized. Serum creatinine levels were measured spectrophotometrically using Randox kits (Ref: CR510, LOT: 216982), while urinary proteins were determined using strip method (Ref: Roche Diagnostic GmbH).

The data was analyzed with SPSS 21.0. Mean values were used for quantitative variables like serum creatinine and urinary proteins, while frequencies and percentages were calculated for qualitative variables such as histopathological changes in the kidney. Fisher's exact test was used for analysis.

RESULTS

The current experiment was aimed to assess morphological and biochemical changes induced by $CdCl_2$ administered orally and intraperitoneally for 8 weeks. The kidneys showed no detectable abnormalities upon gross examination but significant histological changes were observed in the tubules, glomeruli, and interstitium. Fischer's exact test was used for analysis, revealing a significant P value across all variables (Table 2, 3, and 4).

Table 2: Histopathological changes in kidney tissues (Glomeruli and tubules) of mice

Variable	Group	Absent (%)	<25% (%)	25-50% (%)	>50% (%)	P Value	Fisher's Exact Test
Glomerular Adhesions	**Control**	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.000	55.830
	A	0 (0.0)	6 (50.0)	6 (50.0)	0 (0.0)		
	B	0 (0.0)	2 (16.7)	6 (50.0)	4 (33.3)		
	C	0 (0.0)	0 (0.0)	12 (100)	0 (0.0)		
	Total	12 (25.0)	8 (16.7)	24 (50.0)	4 (8.3)		
Tubular Necrosis	**Control**	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.000	51.692
	A	0 (0.0)	4 (33.3)	7 (58.3)	1 (8.3)		
	B	0 (0.0)	0 (0.0)	6 (50.0)	6 (50.0)		
	C	0 (0.0)	0 (0.0)	10 (83.3)	2 (16.7)		
	Total	12 (25.0)	4 (8.3)	23 (47.9)	9 (18.8)		
Tubular Vacuolar Degeneration	**Control**	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.000	43.834
	A	0 (0.0)	6 (50.0)	5 (41.7)	1 (8.3)		
	B	0 (0.0)	4 (33.3)	8 (66.7)	0 (0.0)		
	C	0 (0.0)	5 (41.7)	6 (50.0)	1 (8.3)		
	Total	12 (25.0)	15 (31.3)	19 (39.6)	2 (4.2)		

Table 3: Histopathological changes in kidney tissues (Mesengium, Interstitium and Blood vessels) of mice

Variable	Group	Normal (%)	Mild (%)	Moderate (%)	Severe (%)	P Value	Fisher's Exact Test
Mesangial Cellularity	**Control**	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.000	54.053
	A	0 (0.0)	0 (0.0)	7 (58.3)	5 (41.7)		
	B	0 (0.0)	0 (0.0)	0 (0.0)	12 (100)		
	C	0 (0.0)	0 (0.0)	1 (8.3)	11 (91.7)		
Interstitial Inflammation	**Control**	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.000	46.494
	A	0 (0.0)	8 (66.7)	4 (33.3)	0 (0.0)		
	B	0 (0.0)	0 (0.0)	4 (33.3)	8 (66.7)		
	C	0 (0.0)	1 (8.3)	3 (25.0)	8 (66.7)		
Vessel Thickness (Sclerosis)	**Control**	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0.000	39.889
	A	12 (100)	0 (0.0)	0 (0.0)	0 (0.0)		
	B	4 (33.3)	4 (33.3)	4 (33.3)	0 (0.0)		
	C	0 (0.0)	4 (33.3)	8 (66.7)	0 (0.0)		

Table 4: Glomerular capillary wall thickness after 8 weeks

Group	Normal (%)	Focally Thick (%)	Diffusely Thick (%)	P Value	Fisher's Exact Test
Control	12 (100)	0 (0.0)	0 (0.0)	<0.001	41.372
A	2 (16.7)	3 (25.0)	7 (58.3)		
B	0 (0.0)	0 (0.0)	12 (100)		
C	0 (0.0)	2 (16.7)	10 (83.3)		

Serum Creatinine and Proteinuria Levels: The proteinuria and serum creatinine levels in mice groups showed that after 3 and 5 weeks, Group B had lower proteinuria, while Groups C and D had higher levels. After 8 weeks, Group B maintained low proteinuria, but Groups C and D remained high. Serum creatinine levels after 8 weeks were lowest in the control group, increasing progressively in Groups B, C, and D, with Group C having the highest levels (Figure 1).

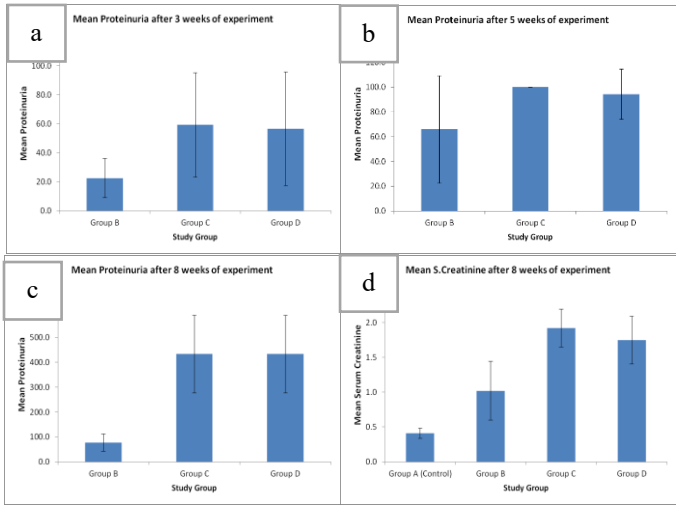
a) Displays mean proteinuria levels after 3 weeks with Groups B, C, and D. Group B has the lowest mean proteinuria, and Groups C and D are higher with substantial variability.

b) Shows mean proteinuria after 5 weeks with the same groups. The levels have generally increased, with Group C showing the highest mean proteinuria.

c) Illustrates mean proteinuria after 8 weeks. The levels have escalated significantly, especially for Groups C and D, with Group B remaining the lowest.

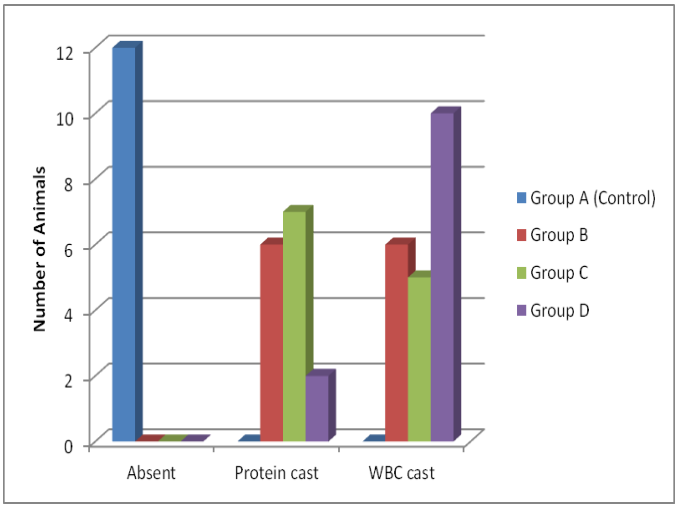
d) Depicts mean serum creatinine levels after 8 weeks, including a new Group A (Control). Here, Group C shows the highest mean serum creatinine level, while the control group has the lowest.

Figure 1: Mean Proteinuria after 3, 5 and 8 weeks and mean serum creatinine after 8 weeks of experiment



Urinary proteins Levels: The bar chart (Figure II) showed the presence of protein and WBC casts in kidney tissues of four groups of mice. The control group (Group A) had no casts. Group B and Group C showed a significant number of protein casts, while Group D exhibited the highest number of WBC casts.

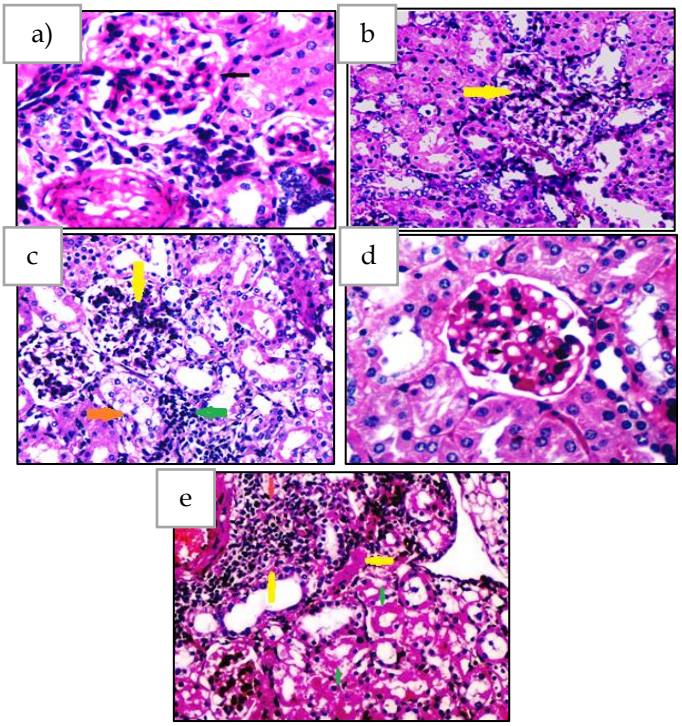
Figure 2: Urinary cast occurrence across four animal study groups



The figure is a clustered bar chart showing the number of animals with absent, protein cast, and WBC cast conditions across four groups (A, B, C, and D). Group A (Control) has the highest number of animals with absent conditions, and a high number with WBC cast. Groups B, C, and D have varying numbers of animals with protein casts and WBC casts, but all have fewer animals with absent conditions compared to the control group.

Following diagrams showed the histopathological changes in kidney tissues of mice (Figure 3, 4).

Figure 3: Photomicrographs showing histopathological examination of kidney tissue samples indicating various cellular changes



a) Glomerular adhesions (40 X H&E).

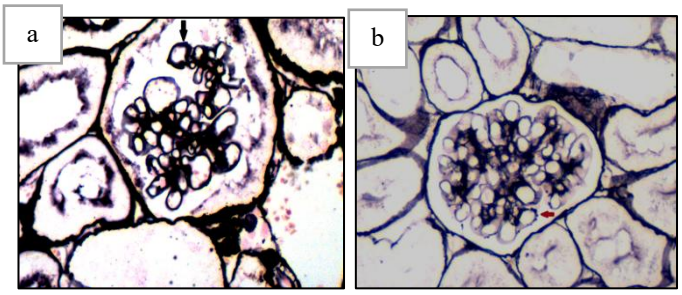
b) Mesangial hypercellularity (yellow arrow) (20 X H&E)

c) Mesangial hypercellularity (yellow arrow), tubular vacuolar degeneration (red arrow) and severe interstitial inflammation (green arrow). (20 X H&E).

d) Glomerular capillary wall thickness (20 X H&E).

e) Vascular sclerosis (20 X H&E)

Figure IV: Photomicrographs showing deposition of immune complexes (arrows) in glomerular basement membranes leading to Glomerular capillary wall thickness:



a) Glomerular capillary wall thickness (black arrow) (40 X JMS)

b) Deposition of immune complexes in glomerular basement membrane (red arrow) (40 X JMS)

DISCUSSION

This research had shown a strong correlation between proteinuria and the $CdCl_2$ pathway. Eight of the animals in group A had proteinuria of 100 mg/dl after eight weeks, but none of the animals in group A had proteinuria of 500 mg/dl. In relation to the function of BSA and intraperitoneal routes, 10 mice from groups B and C each displayed 500 mg/dl of proteinuria after 8 weeks. As a result, this research demonstrated that mice who received an intraperitoneal dosage of 250 mg BSA once at the beginning of the trial and 10 mg $CdCl_2$/kg body weight on alternate days had more severe kidney impairment than the mice that received an oral dose. Consequently, this experiment demonstrated that BSA induced autoimmunity in the form of serum sickness, which increased glomeruli's susceptibility to toxicant damage due to increased capillary permeability. Additionally, it was shown that group C, which received $CdCl_2$ intraperitoneally on alternate days, had more severe equivocal kidney damage than the oral group [Figure I(c)]. These results were in line with previous research showing that proteinuria is often the first sign of kidney damage.[16]

This study observed a significant increase in serum creatinine levels in Groups B and C, reaching up to 2.50 gm/dl in 10 animals from each group, compared to the normal range of 0.43 mg/dl + 0.14 mg/dl for male mice and 0.45 mg/dl + 0.07 mg/dl for female mice as reported by Fox *et al*. (2002) [Figure 1(d)]. These findings align with glomerular injury leading to proteinuria, consistent with Abdel-Moneim and Said observation of elevated serum creatinine after cadmium exposure.[17]

Additionally, $CdCl_2$ exposure caused dose dependent glomerular adhesions, with all animals in Group C and six and four animals from Group A and B respectively. showing >50% adhesions (Table 2). This highlights the role of exposure routes in kidney damage. Nagi and Khan[18] investigated BSA's role in glomerular injury, supported here by cadmium's harmful effects.[19] Mesangial cellularity increased significantly in 12 Group B and 11 Group C mice, compared to 5 in Group A, with moderate increase in 1 Group C and 7 Group A mice (Table 3). These morphological changes align with earlier findings.[20]

The thickening of the glomeruli's capillary walls was displayed in Table 4 showed diffuse capillary wall thickness established by all 12 mice of Group B, 10 mice of Group C and 7 mice of Group A. Kukner *et al*. previously reported on the thickening of the glomerular capillaries' basement membrane after exposure to Cd[21]. Cadmium deposition in the proximal convoluted tubules led to tubular necrosis and vacuolar degeneration according to this study. Table 2 indicated that six mice in Group B, ten in Group C, and seven in group A had 25–50% necrosis, while one in Group A, six in Group B, and two in Group C had > 50% necrosis. Liu Q, *et al*., demonstrated that cadmium adversely affected tubules, leading to tubular necrosis. High cadmium levels often caused renal tubular cell necrosis upon new exposure[22]. Furthermore, all experimental mice exhibited tubular vacuolar degeneration. This damage pattern was consistent with previous data, with Group B experiencing the highest damage, followed by Groups C and A (Table 3). The observed tubular vacuolar degeneration aligns with findings from other studies involving rats exposed to various toxicants, particularly cadmium.[21,23]

Cadmium also caused eosinophilic cast, mostly protein cast, to develop in the tubules of mice (Figure 2). A similar cast had previously been seen in quail renal tubules after fluoride treatment[24]. Additionally, several mice had the deposition of WBC cast. Moreover, severe interstitial inflammation was seen in 8 mice from Groups B and C, indicating the effects of BSA in Group D and intraperitoneal injection in Group E as shown in Table 3 and Figure 3 (c & e). Thus, our data supports the findings reported by Prozialeck *et al*., that cadmium caused interstitial inflammation in the kidneys of experimental mice.[20]

Blood vessels were seen to grow vascular thickness in addition to the effects of $CdCl_2$ on renal tubules, glomeruli, and the interstitium (Table 3). Messner and Bernhard have outlined the pathophysiological pathways of cadmium toxicity-induced vascular sclerosis. Additional morphological changes, including glomerular crescent formation, tubular dilatation, mesangial widening, swelling of the tubular epithelial cells' nuclei, fibroid change in the afferent arterioles, lobulation of glomeruli, and atrophy of glomeruli, were also observed in a few of the mice in this study.[25]

Analysis of the harmful effects of low ambient Cd exposure has shown significant deleterious effects on human glomerulus and renal tubular cell functioning.[26] Johri *et al*. highlighted that cadmium toxicity's clinical effects, particularly in stress-related renal illness, depend on the exposure route, such as ingestion or inhalation.[27]

CONCLUSION

Proteinuria was strongly associated with exposure to $CdCl_2$, showing varying levels among different experimental groups. Mice that received an intraperitoneal dose of bovine serum albumin (BSA) and $CdCl_2$ exhibited more severe kidney damage compared to those receiving an oral dose. This damage included glomerular injury leading to proteinuria, elevated serum creatinine levels, and glomerular adhesions. Cadmium exposure caused tubular necrosis, vacuolar degeneration,

consistent with previous studies. Additionally, cadmium induced eosinophilic cast formation, interstitial inflammation, and vascular changes in the kidneys of the experimental mice. These findings highlight the detrimental effects of cadmium exposure on renal health.

LIMITATIONS

One limitation of the study is that it focused on a specific dosage and route of cadmium exposure. This approach may not fully represent real-world exposure scenarios, where individuals are exposed to varying levels of cadmium through different routes such as inhalation, ingestion, and dermal contact. Additionally, the study used a relatively small sample size, which may limit the generalizability of the findings.

SUGGESTIONS / RECOMMENDATIONS

Further research should explore the mechanisms underlying the observed effects of cadmium on renal function. Studies could investigate potential interventions or treatments to mitigate the harmful effects of cadmium exposure. Long-term studies are needed to understand the chronic effects of cadmium on kidney health in various exposure scenarios. Comparative studies with different animal models or human samples could provide valuable insights into the human health implications of cadmium exposure.

CONFLICT OF INTEREST / DISCLOSURE

There was no conflict of interest.

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