Toxicological And Immunological Adverse Effects Of Cadmium Chloride In Adult Male Albino Rats

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ABSTRACT

Forty adult male albino rats weighted (100-140g), were assigned randomly and divided into 4 equal groups (one control and three treated groups). The control group received only dis. water, while the treated groups received 5 ppm, 50 ppm and 100 ppm of cadmium chloride ($CdCl_2$) for 90 days. Some toxicological parameters (body weight, organ relative weight and cadmium level in tissue) were evaluated in adult male albino rats. In addition, immunological parameters (lysozomal, bactericidal activities, nitric oxide and tumor necrosis factor- α) were measured in the serum of treated rats after 90 days of the experiment. Serum lysozyme was determined via turbidimetric assay. Determination of bactericidal assay was assessed by agar diffusion bio-assay. Nitric oxide was determined by enzymatic colorimetric method by readymade kits. TNF-α was measured by ELISA. Data were analyzed by one-way analysis of variance. The body weight gain was reduced significantly ($P<0.001$) in rats exposed to 100 ppm of $CdCl_2$ than that of control. There were no significant difference in the organ relative weight of liver in control and treated rats. However, in rats treated with 100 ppm of $CdCl_2$, kidney relative weight was significantly increased ($P<0.001$) than that of control. The level of lysozomal and bactericidal activities showed significant increase to 5 ppm of $CdCl_2$, however, the pattern of these values were declined in response to 50 and 100 ppm of $CdCl_2$. The level of nitric oxide was correlated to the level of TNF-α in the serum. In conclusion, different doses of $CdCl_2$ in drinking water for 90 days could affect several toxicological parameters including reduction of growth rate particularly in rats exposed to 100 ppm of $CdCl_2$. Furthermore, $CdCl_2$ at 5 ppm has immunostimulatory effect; however, the 50 and 100 ppm of $CdCl_2$ inhibited the immune function in adult male albino rats.

INTRODUCTION

Cadmium (Cd) is a non-essential toxic metal. It is ubiquitous, it has a very long biological half-life of 20-30 years in humans *(1)* and it is bioaccumulable in organisms and ecosystems. Besides occupational exposure, it enters the body through food and drinking water as well as through inhalation. Cadmium causes renal *(2)* and hepatic toxicity *(3)*. The effects of Cd^{2+} are not limited to direct cytotoxicity. Cd^{2+} can also act at sub-toxic concentrations, which are far more likely to occur *in vivo* resulting from normal *(4)* or occupational exposure *(5)*. Whereas the most widely investigated effect of sub-toxic exposure to cadmium is its carcinogenicity, this metal also modulates the immune response.

Lysozyme is a ubiquitous enzyme present in biological secretions (serum, urine, tears, seminal fluid, and milk) and leukocyte. Lysozyme hydrolyzes glucosidic linkages between *N*-acetylmuramic acid and *N*-acetyl-D-glucosamine residues present in the mucopolysaccharide cell wall of a variety of microorganisms. It has been shown that treatment of rodents with Cd^{2+} can induce inflammation *(6)*. Rats injected intraperitoneally with Cd^{2+} show a rise in activity of the pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 *(7)*. Furthermore, culture of human peripheral blood mononuclear cells (PBMC) in the presence of Cd^{2+} led to gene expression of TNF-α, detected by RT-PCR *(8)*. Nitric oxide (NO) is a gaseous free radical species with pleiotropic functions in

pathophysiology. NO is synthesized by means of an enzymatic reaction involving two-step oxidation of the terminal guanidine nitrogen of L-arginine, the result being formation of NO and L-citrulline *(9)*. Low micromolar Cd^{2+} concentrations induced constitutive NO formation in macrophages *(10)*. Therefore Cd^{2+} effects on NO formation are medically significant because Cd^{2+} may interfere with defense functions of macrophages against infection and tumor formation. The aim of the present study was to assess the toxicological and immunological parameters in adult male rats exposed to different doses of CdCl2 in drinking water for 90 days.

MATERIALS AND METHODS

Experimental animals

Forty male albino rats weighted (100-140g) were assigned randomly and divided into 4 equal groups (one control and three treated groups). All groups received distilled water for one week. From the second week of the experiment, the control group received only distilled water, while the treated groups received 5 ppm, 50 ppm and 100 ppm of CdCl2 (Oxford Company, Mumbai, India) for 90 days.

Body weight

The body weight of control and treated male albino rats was measured at the start of the experiment (Day 0), Day 30, Day 60 and the time of scarification by cervical dislocation (Day 90).

Organ relative weights

At the end of the experimental period, rats were sacrificed and organ is dissected. Liver and kidney are removed and weighed. The organ relative weight (organ weight / body weight X 100) was measured for each treated and control groups. Portions of the liver and kidney were kept frozen at – 20 °C for the determination of cadmium and zinc levels.

Determination of cadmium and zinc in serum, liver and kidneys

At laboratory, the tissue samples wrapped separately in acid washed polyethylene bags. The samples were identified and kept frozen at -20°C till the analysis was carried out using UNICAM 969 Atomic Absorption Spectrometer *(11-12)*.

Determination of serum lysozomal activity

Serum lysozyme was determined via turbidometric assay. Serum lysozyme values were expressed as µg/mL *(13)*.

Determination of bactericidal assay

Agar diffusion bio assay method was done according to Lorian *(14)*.

Determination of nitric oxide

Nitric oxide was determined by enzymatic colorimetric method by using readymade kits provided by Biodiagnostic. The resulting azo dye has a bright reddish – purple color which can be measured at 540 nm *(15)*.

Quantitative measurement of rat TNF-alpha

Rat TNF-alpha was measured by ELISA kit (Cat#: ELR-TNFalpha-001) which is an *in vitro* enzyme-linked immunosorbent assay for the quantitative measurement of Rat TNF-alpha in serum, the intensity of the color is measured at 450 nm *(16)*.

Histopathological examination

Immediately after killing of the rats, the rats were necropsied and portions of liver and kidney were fixed in 10% neutral buffered formalin. They were gradually dehydrated and embedded in paraffin; 5-µm sections were stained with hematoxylin and eosin (H&E) for histopathological examination *(17)*.

Statistical analysis

Body weight, organ relative weights, cadmium and zinc levels in serum and tissues and immunological parameters were analyzed by one-way analysis of variance followed by Tukey's posttest using GraphPad Prism version 3 for Windows (GraphPad Software, San Diego California, USA). A p-value below 0.05 was considered statistically significant.

RESULTS

Body weight

The results of body weight gains of adult male albino rats given different doses (5, 50 and 100 ppm) of CdCl2 in drinking water for 90 days showed that the body weight gain in control rats was increased significantly than that of the

rats treated with 50 ppm ($P<0.05$) and 100 ppm ($P<0.001$). However, there was no significant difference in the body weight gain between the rats treated with 5 ppm and control rats (Table 1 and Fig. 1).

Table 1. Effect of CdCl2 (5, 50 and 100 ppm in drinking water) on body weight gains (means ± SE) in male albino rats from the Day 0 to Day 90 of the experiment

Groups and treatment	Body weights (g)				Body weight gain*
	Day 0	Day 30	Day 60	Day 90	
Control	95.3±2.9	102.2±3.1	133.9±4.8	195.5±13.1	98.6±40.1[a]
5 ppm	107.6±4.7	117.9±4.9	125.8±14.7	170.4±7.2	62.8±31.2[ab]
50 ppm	121.9±5.7	117.8±5.8	143.6±6.8	170.7±9.3	48.8±33.7[b]
100 ppm	136.2±3.4	125.7±5.1	145.2±8.1	162.4±12.7	26.6±18.9[b]

Superscripts with dissimilar values are significantly different within the same line

* Body weight gain is the difference between the body weight of the rats at the start of the experiment (Day 0) and body weight at Day 90

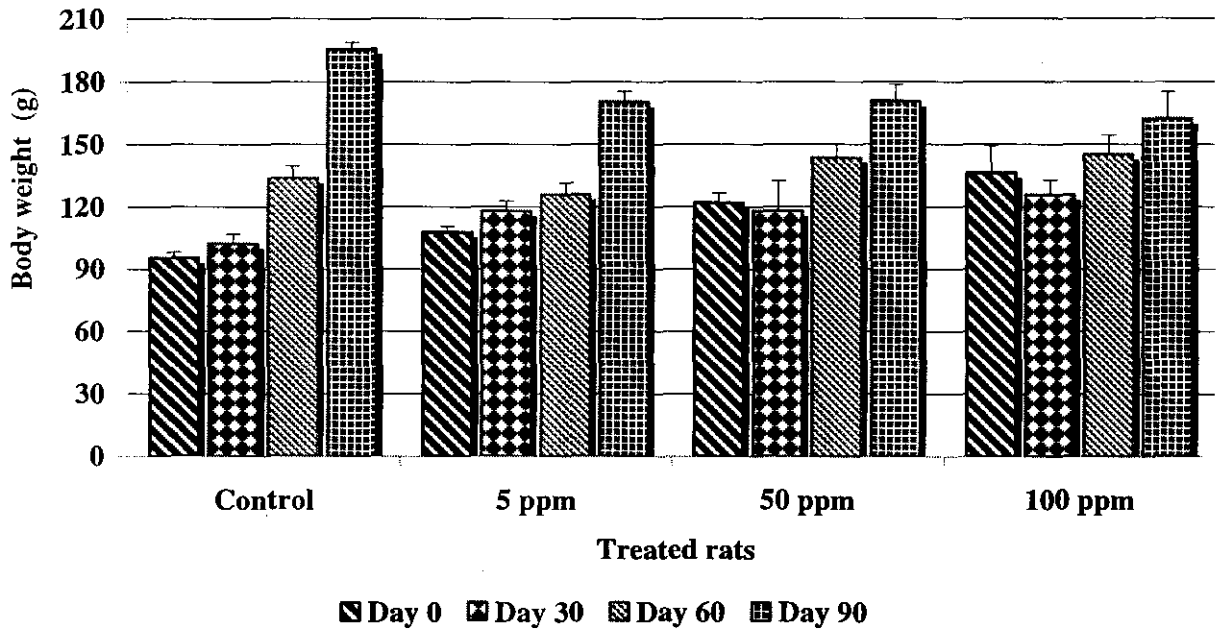

Figure 1. Changes in the body weights within the group of control and treated male albino rats with CdCl2 at the start of the experiment (Day 0), Day 30, Day 60 and Day 90. Data are expressed as means ± SE

Organ relative weights

There were no significant difference in the organ relative weight of liver in control and rats treated with 5, 50 and 100 ppm CdCl2. However, the kidney relative weight was significantly increased ($P<0.001$) in rats treated with 100 ppm, than that of control. Moreover, the relative weight of kidneys in rats treated with 50 ppm is significantly increased ($P<0.05$) than that of control rats (Table 2).

Table 2. Effect of CdCl2 (5, 50 and 100 ppm in drinking water) on relative organ weight (means ± SE) in male adult albino rats

Organs	Control	5 ppm	50 ppm	100 ppm)
Liver	2.12±0.07	1.95±0.06	2.01±0.06	1.87±0.07
Kidneys	0.39±0.02[a]	0.41±0.01[ab]	0.45±0.01[b]	0.49±0.02[b]

Superscripts with dissimilar values are significantly different within the same line

Cadmium and zinc level in serum and tissues

Cadmium level in serum of treated adult male albino rats for 90 days showed significant increase in rats treated with 5 and 100 ppm of CdCl2, while the zinc level was markedly lowered in rats treated with 100 ppm of cadmium chloride. The cadmium accumulation in liver was significantly ($P<0.001$) increased in rats treated with 50 and 100 ppm of cadmium chloride than that of control rats. Moreover, the zinc levels in liver of treated rats with 5, 50 and 100 ppm was higher ($P<0.05$) than that of the control group. The cadmium level in kidney was significantly increased in rats treated with 100 ppm ($P<0.001$) and 50 ppm ($P<0.01$) than the level in kidney of control rats. Furthermore, the level of zinc in kidney of all rats showed no significant differences among the groups (Table 3).

Table 3. Effect of CdCl2 (5, 50 and 100 ppm in drinking water) on level of cadmium and zinc (ppm) in serum, liver and kidney of treated male albino rats at Day 90. Data are expressed as means ± SE

	Control	5 ppm	50 ppm	100 ppm
Serum Cd	0.08±0.001[a]	0.2±0.004[b]	0.07±0.002[a]	0.1±0.001[ab]
Serum Zn	2.3±0.03[a]	2.5±0.02[a]	2.3±0.01[a]	1.5±0.01[b]
Liver Cd	1.8±0.2[a]	6.0±0.5[a]	17.0±1.2[b]	24.2±4.3[c]
Liver Zn	18.5±0.9[a]	28.0±2.2[b]	29.0±1.4[b]	25.9±1.1[b]
Kidney Cd	2.8±0.5[a]	7.3±0.7[ab]	9.6±0.9[b]	12.1±2.2[b]
Kidney Zn	15.8±1.3	17.4±1.9	19.0±1.3	18.9±1.0

Superscripts with dissimilar values are significantly different within the same line

Lysozomal and bactericidal activities

The pattern of serum lysozomal and the bactericidal activities showed an increase in response to 5 ppm of CdCl2 in drinking water for 90 days, however, the pattern of these values were declined in response to 50 ppm and 100 ppm of CdCl2. Rats exposed to 100 ppm of CdCl2 had the lowest level of lysozomal and bactericidal activities (Table 4 and Fig. 2).

Nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α)

The level of nitric oxide measured in the serum of treated rats was correlated to the level of TNF-α. The rats administrated 5 ppm of CdCl2 showed rise in NO and TNF-α production, while their levels were declined in rats treated with 50 ppm and 100 ppm of CdCl2 (Table 4 and Fig. 2).

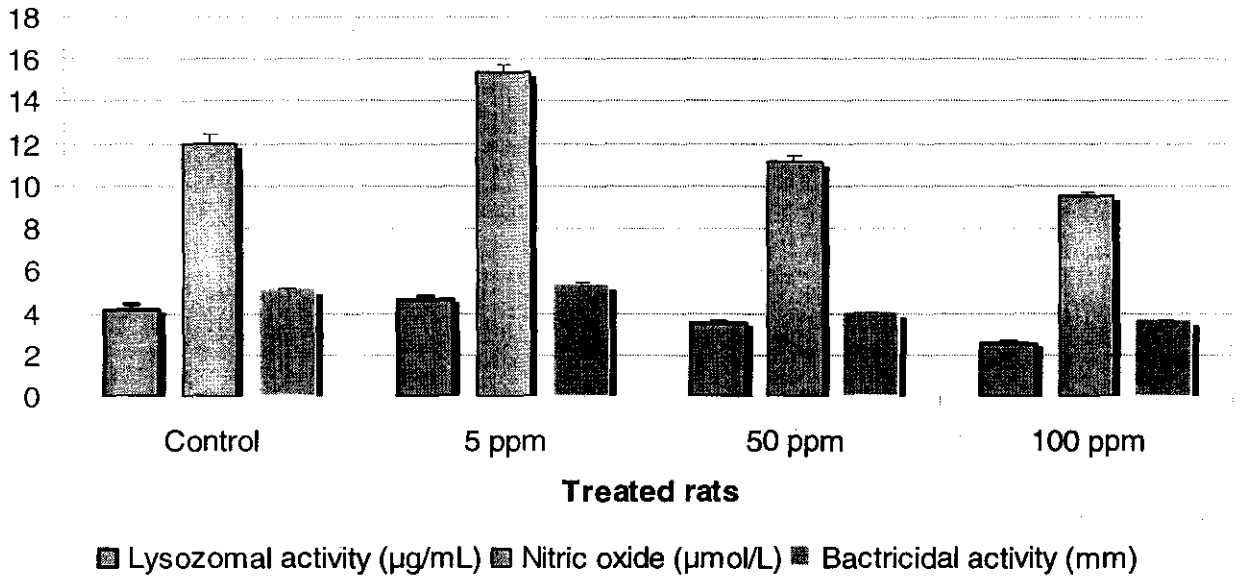

Figure 2. Effect of CdCl2 (5, 50 and 100 ppm in drinking water) on lysozomal activity, nitric oxide and bactericidal activity (mean ± SE) in rats at Day 90 of experiment

Table 4. Effect of CdCl2 (5, 50 and 100 ppm in drinking water) on lysozomal activity, bactericidal activity, nitric oxide and tumor necrosis factor-α (mean ± SE) in treated rats with after 90 days of treatment

	Control	5 ppm	50 ppm	100 ppm
Lysozomal activity (µg/mL)	4.1 ± 0.3^{ab}	4.6 ± 0.2^{b}	3.5 ± 0.1^{ac}	2.5 ± 0.1^{d}
Bactericidal activity (mm)	5.1 ± 0.11^{a}	5.3 ± 0.13^{ab}	4.0 ± 0.04^{c}	3.6 ± 0.11^{d}
Nitric oxide (µmol/L)	12.0 ± 0.4^{a}	15.4 ± 0.3^{b}	11.1 ± 0.3^{ac}	9.5 ± 0.2^{d}
Tumor necrosis factor-α (pg/ml)	70.8 ± 3.7^{a}	179.6 ± 4.9^{b}	128.6 ± 3.9^{c}	41.6 ± 4.1^{d}

Superscripts with dissimilar values are significantly different within the same line

Histopathology

The liver of rats exposed to 50 ppm of CdCl2 showed multifocal hepatic cells suffered from vacuolation within the cytoplasm. These vacuoles were small in size sharply demarcated border with centrally located nuclei. Some hepatocytes showed different stages of necrosis that was evident by nuclear pykosis, karyorhexis and karyolysis. In contrast the control rats showed normal hepatic architecture. The necrotic hepatocytes were randomly disrupted within the hepatic lobules (Fig. 3 a & b). In rats exposed to 100 ppm of CdCl2, the hepatic architecture showed multifocal disruption especially at the periphery of the hepatic lobules. The hepatic cells showed mild to moderate cytoplasmic irregular border vacuoles with centrally located nuclei. Some hepatic cells showed necrosis that was evident by karyolysis (Fig. 4 a & b).

Kidney of rats exposed to 50 ppm of CdCl2 showed proteinous casts within the lumen of many renal tubules. However, the rats exposed to 5 ppm showed no histopathological findings like the control untreated rats (Fig. 5).

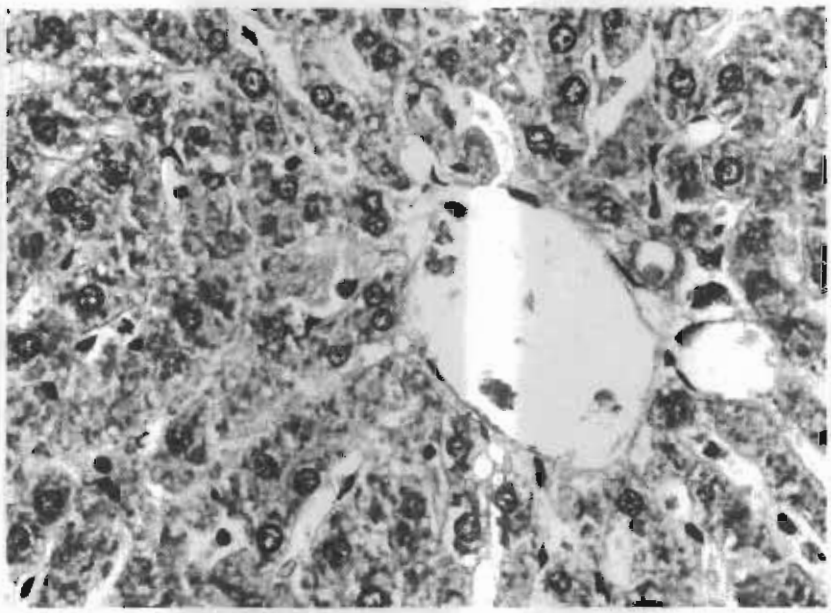

Figure 3 a. Section in liver of control rats showing normal hepatic architecture. H&E 400 X

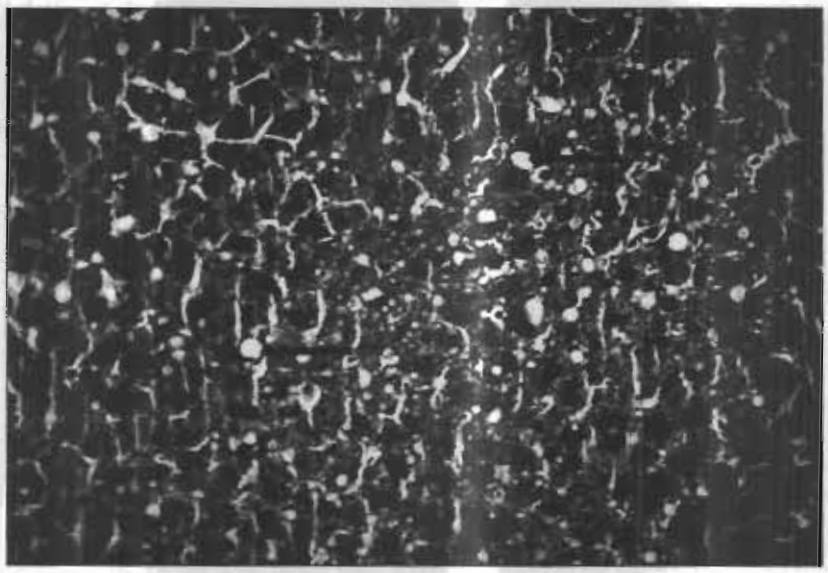

Figure 3 b. Section in liver, of rats treated with 50 ppm of CdCl2 showing unstained vacuoles within the hepatocyte cytoplasm displacing the nucleus to the peripbery (arrows). H&E 400 X

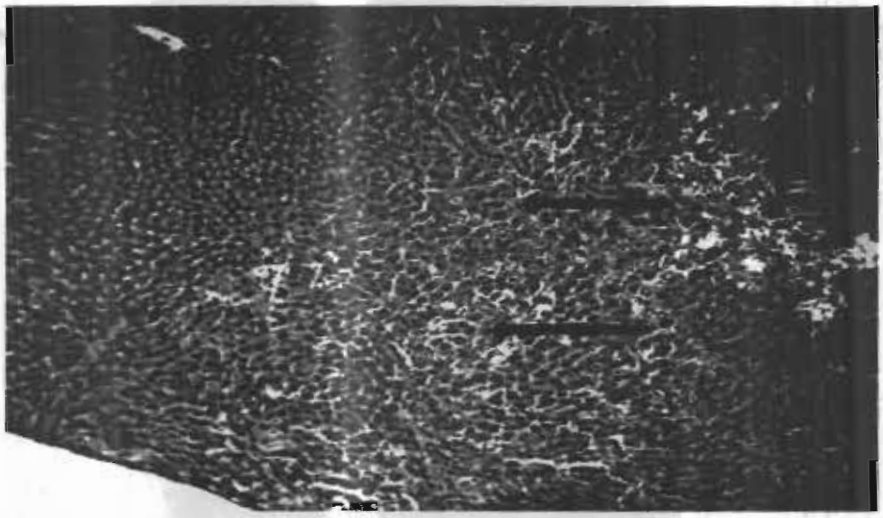

Figure 4 a. Section in liver, of rats treated with 100 ppm of CdCl2 showing disruption of the hepatic architecture (thick arrows) in comparison to normal architecture (thin arrows). H&E 100 X

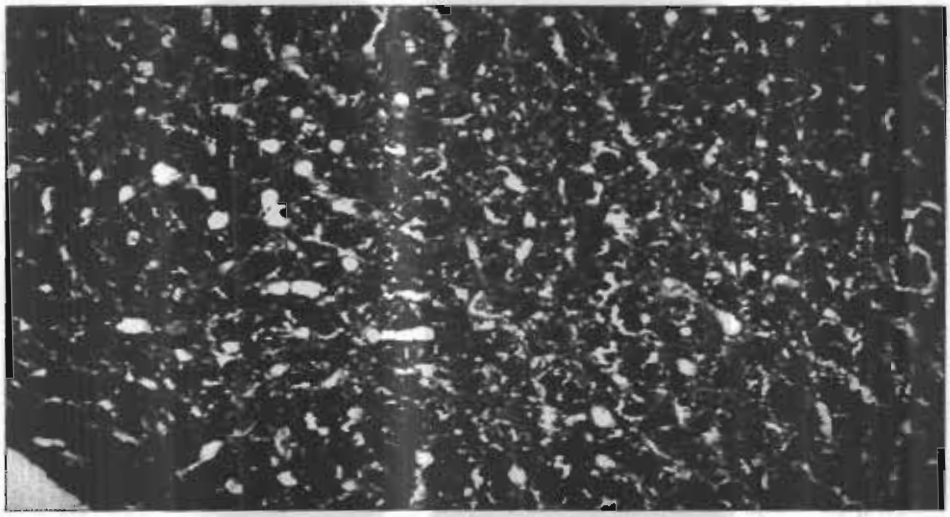

Figure 4 b. Section in liver, of rats treated with 100 ppm of CdCl2, showing vacuoles within hepatocytes cytoplasm (arrow). H&E 400 X

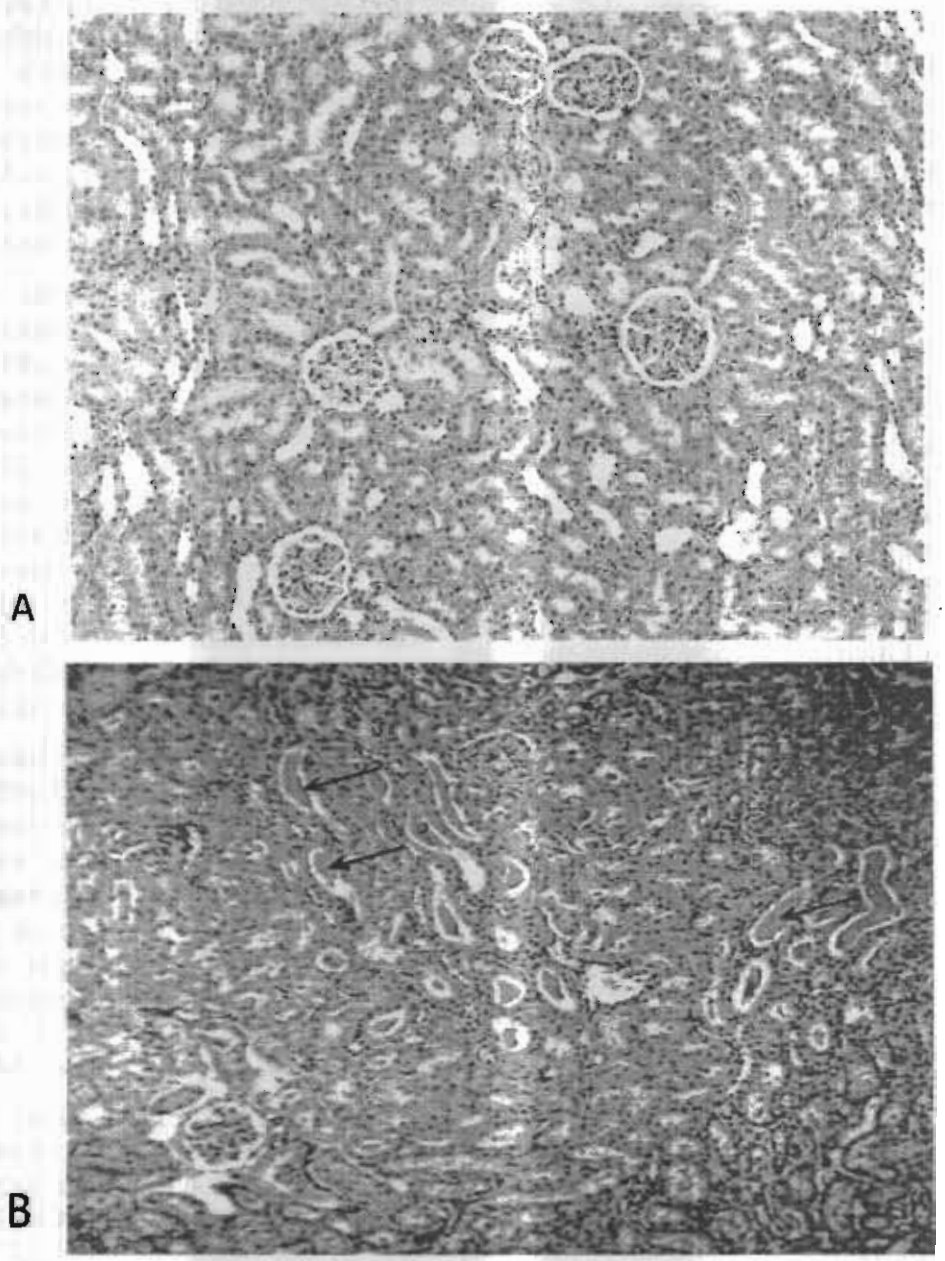

Figure 5. Section in kidney of control rats showed normal kidney tissue (A) while section in kidney of treated rats with 50 ppm of CdCl2 (B) showed casts within the many renal tubules (arrows). H&E 100 X

DISCUSSION

The importance of cadmium as an industrial and environmental pollutant and due to high amounts of Cd in cigarettes, smokers and passive smokers are exposed to high amount of Cd *(18)* for that reasons, the present study tried to clarify the effect of CdCl2 on some toxicological and immunological parameters of adult male albino rats. The results reported in this study showed that rats treated with 50 and 100 ppm of CdCl2 in drinking water showed a significant reduction in body weight gain compared to control. These results indicated that high concentration of CdCl2 affected the growth rate in male albino rats. The effect of cadmium on body weight gain observed in this study is consistent with previous reports *(19-20)*. Weight gain is influenced by the availability and absorption of nutrients. Recent studies show that cadmium decreases nutrient digestion and absorption *(21)*.

There was no significant difference in the relative weight of the liver in rats treated with different dosed of CdCl2, however, in rats treated with 100 ppm of CdCl2, the kidney relative weight is significantly increased. Cd did not affect the weight of liver in pups chronically exposed to cadmium. The liver is not very susceptible to Cd toxicity during chronic low level exposure because of its ability to synthesize metallothionein at a rate sufficient to prevent accumulation of the free ions in this organ *(22)*.

In the present study, the cadmium residue was increased significantly in rats treated with 5, 100 ppm of CdCl2. Blood-Cd levels showed a dose and time-dependent increase in cadmium treated rats. Liver-Cd data showed a similar behavior. Kidney-Cd content on the other hand showed a time- and concentration-dependent increase, indicating that the kidney indeed is the final storage space with no mechanisms to get rid of the Cd. It may be stated that kidney -Cd concentrations are closely correlated with the exposure history while liver and blood data might be misleading *(23)*. Zinc level tended to increase when the cadmium level in liver and kidney is increased. This result was supported by the finding of Brzoska and Moniuszko-Jakoniuk *(24)* who stated that the main accumulation sites for cadmium in humans are kidney and liver. Cd accumulation in the organism is accompanied by changes in levels of some essential elements, including Zn result in an increased retention of Zn in the liver and/or kidneys. A highly positive correlation between Cd and Zn concentrations in liver and kidneys has been noted *(25-26)*.

Studies supporting a role of cadmium in immune modulation demonstrated that heavy metals can increase the susceptibility of affected individuals to bacterial and viral infections *(27-28)*. This has been attributed to suppression of the phagocytic activities *(29)*, defect of macrophage recruitment to sites of infection *(30)*, suppression of NK cell activity *(31)*, or the general suppression of humoral and cell-mediated immune responses *(6)*. In contrast to our results, chronic exposure of B6C3F1 mice to 10–250μg/ml of CdCl2 for 90 days, revealed no changes in humoral immunity *(32)*.

The adult male rats administrated 100 ppm of CdCl2 showed a lower level of TNF-α and nitric oxide which might be due to inability of macrophage or monocyte to secrete TNF-α or NO in response to CdCl2 treatment. Cd^{2+} can directly induce the secretion of TNF-α in monocytes and macrophages of human and murine origin *(33)*. Monoclonal antibody-activated cells exposed to Cd showed a significant decrease in TNF-α *(34)*.

The liver of rats exposed to 50 ppm of CdCl2 showed multifocal hepatic vacuolation within the cytoplasm. Furthermore, in rats exposed to 100 ppm of CdCl2, the hepatic architecture showed multifocal disruption. In agreement of our results, liver of rats treated with Cd^{2+} showed cellular infiltration and vacuolation. The hepatocytes showed different degrees of degeneration *(35)*. In the present study, kidney of rats exposed to 50 ppm of CdCl2 showed proteinous casts within the lumen of many renal tubules. Edema was usually found *(36)* as well as proximal tubular necrosis and apoptosis, tubular degeneration, atrophy of some glomeruli and glomerular swelling *(37)*. The renal cortex showed clear evidence of tubulo-interstitial nephritis whereas the medulla is intact *(38)*.

In conclusion, different doses of CdCl2 in drinking water for 90 days could affect several toxicological parameters as growth rate reduction and increase the level of cadmium in liver and kidney of treated rats. Moreover, CdCl2 has immuomodulatory effect as low doses enhanced some immunological parameters; while, high doses inhibited these parameters in adult male albino rats.

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الملخص العربى
تأثير كلوريد الكادميوم على المعايير السمية والمناعية في الفئران البالغة البيضاء

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أجريت الدراسة على عدد (٤٠) من ذكور الفئران البالغة البيضاء يتراوح أوزانها بين ١٠٠جم و ١٤٠جم. تم استخدام كلوريد الكادميوم في معالجة ذكور الفئران البالغة بجرعات مختلفة , تعرضت الفئران لهذه الجرعات المختلفة من خلال مياه الشرب و لمدة تسعون يوما مدة إجراء البحث. قسمت الفئران إلى ٤ مجاميع كل مجموعة عشرة فئران: المجموعة الأولى: هي المجموعة الضابطة و التي تجرعت الماء المقطر فقط. المجموعة الثانية : هي المجموعة التي تعرضت إلى جرعة من كلوريد الكادميوم تعادل (٥) أجزاء في المليون. المجموعة الثالثة: هي المجموعة التي تعرضت إلى جرعة من كلوريد الكادميوم تعادل (٥٠) جزء في المليون. المجموعة الرابعة: هي المجموعة التي تعرضت إلى جرعة من كلوريد الكادميوم تعادل (١٠٠) جزء في المليون. تم متابعة معدل النمو في الجسم من خلال وزن الفئران في اليوم الأول من التجربة ثم متابعة الوزن كل ثلاثون يوما حتى نهاية التجربة. في اليوم الأخير من التجربة تم أخذ عينات من الدم لاستخلاص السيرم لأجراء بعض القياسات البيولوجية lysozyme activity, bactericidal activity, nitric oxide and tumor necrosis factor-α تم ذبح الفئران في نهاية التجربة وأخذت بعض الأعضاء الداخلية (الكبد, الكلي) و تم وزنها و فحص أنسجتها لمعرفة مدى التأثير السمي لكلوريد الكادميوم بجرعاته المختلفة كما تم قياس مستوي الكادميوم و الزنك بها.

و قد أسفرت نتائج هذا البحث عن الأتي: كان هناك زيادة معنوية في معدل النمو في ذكور الفئران البالغة البيضاء خاصة التي لم تعالج بكلوريد الكادميوم و لكن المجموعات التي عولجت بجرعات (٥٠, ١٠٠) جزء في المليون قد تأثرت. كان هناك انخفاض معنوي في lysozyme and bactericidal activities, nitric oxide and tumor necrosis factor-α في المجموعات التي عولجت بجرعات (١٠٠،٥٠) جزء في المليون و لكن كان هناك ارتفاع في هذين الاختبارين في المجموعة التي عولجت بجرعة (٥) جزء في المليون من كلوريد الكادميوم.

كان هناك ارتفاع في مستوي الكادميوم و الزنك في أنسجة الكبد و الكلي في المجموعات التي عولجت بكلوريد الكادميوم مقارنة بالمجموعة الضابطة. أظهرت نتائج فحص أنسجة الكبد للفئران التي تعرضت للجرعة (٥٠) جزء في المليون أن الخلايا الكبدية عانت من ظهور فجوات داخل السيتوبلازم كما أظهرت بعض خلايا الكبد مراحل مختلفة من النخر الذي كان واضحا من قبل تكسير نواة الخلية, أما في الفئران التي تعرضت (١٠٠) جزء في المليون من كلوريد الكادميوم أظهرت اضطراب متعدد البؤر و لاسيما في الفصيصات الكبدية.

و الخلاصة ان كلوريد الكادميوم بالجرعات المستخدمة في البحث له تأثير علي الجهاز المناعي في ذكور الفئران البالغة البيضاء و ذلك بان الجرعات المنخفضة (٥) جزء في المليون تعزز بعض المؤشرات المناعية و في المقابل فان الجرعات العالية (٥٠, ١٠٠) جزء في المليون تثبط تلك المؤشرات المناعية.