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Acute Effect of Cadmium on Testicular and Seminal Structures: A Morphometric and Index-Based Study in Hamster

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ABSTRACT

Cadmium (Cd) is a widespread environmental toxicant recognized for its harmful effects on the male reproductive system; nonetheless, its immediate effects on testicular and seminal morphology in hamsters remain insufficiently investigated. This study examines the morphometric and functional changes in the male reproductive organs of Syrian Golden Hamsters (*Mesocricetus auratus*) after acute exposure to cadmium chloride. Animals were categorized into four groups: a control group and three experimental groups subjected to 0.5, 1.0, and 2.0 mg $CdCl_2$ per kg of body weight. Quantitative analyses demonstrated a significant, dose-dependent reduction in body and organ weights. The high-dose group demonstrated a significant decrease in final body weight (80.0 ± 3.4 g) relative to the control group (140.0 ± 2.7 g), reflecting a change of $-32.86 \pm 5.9\%$. Testicular

and seminal vesicle weights were significantly reduced in cadmium-treated groups, with high-dose testes weighing 1.30 ± 0.28 g compared to 3.60 ± 0.21 g in controls. Morphometric analysis revealed a reduction in testicular area (left: 0.761 cm^2; right: 0.414 cm^2) and perimeter (left: 3.339 cm; right: 2.491 cm) in high-dose subjects compared to control values (left area: 1.179 cm^2; right: 1.580 cm^2; left perimeter: 4.081 cm; right: 4.707 cm). The Gonadosomatic Index (GSI), which indicates the ratio of testis weight to body weight, demonstrated a significant reduction: the GSI for testis decreased from 2.60 ± 0.18 (control) to 1.63 ± 0.40 (high dosage), while the seminal GSI diminished non-significantly from 0.96 ± 0.18 to 0.75 ± 0.33 in the corresponding groups. Gross morphological observations validated these findings, indicating testicular discolouration, haemorrhagic foci, and tissue fragility at elevated doses. These findings demonstrate that cadmium chloride has swift and significant detrimental effects on the structure and function of the male reproductive axis in hamsters, underscoring the importance of morphometric indices in toxicological evaluations of environmental pollutants.

Introduction

Cadmium (Cd) is a heavy metal and considered as a xenobiotic compound because it has no role in biological system of animals and plants (1). The major sources of Cd include mining, paints and gaze, batteries, digital equipment, dust from industry exhaust and tobacco consumption (2). The industrial revolution in the 12^{th} century led to the widespread environmental contaminations of heavy metals. The primary sources of Cd exposure for humans are food, inhalation, and smoking (3). Tobacco users are at most risk and exposed to Cd at very high rate (4,5). It is reported that groundwater is also being contaminated by heavy metals, like cadmium, due to leaching from contaminated soil (6).

The different routes (7) and time (8) of cadmium exposure cause different level of harm. Al-Karmalawy et al., 2024 found that Cd absorption is influenced by exposure route, with inhalation contributing up to 50%, ingestion 10%, and skin contact almost negligible. Also, both prolonged and low dose or acute and high dose exposure of cadmium are cause of cadmium toxicity(9).

Cd has a long half-life (about 20-40 years) which helps in prolonged survival in the biological system and hence persistent health hazard (10). The long half-life of cadmium in animals is attributed to its high binding capacity to a transport protein called metallothioneins (MT) which make it to persist in body for long time with very low excretion rate (2,11) .

The cadmium retention in the body and subsequently absorption to the various cells poses many diseases. After studying in many experimental animals, researchers have suggested that possible mechanism of cadmium toxicity is induction of oxidative stress (12), cellular disintegration (9), competitive binding with some metalloenzymes, inactivation of kinases (13), mitochondrial abnormalities (1), apoptosis and immunogenic phagocytosis (14), genetic and epigenetic changes to DNA and carcinogenicity (15,16).

Researchers have reported that Cd toxicity affects almost every system of the body and results into many health complexities. The famous disease *itai-itai,* is caused by high cadmium exposure. This is a skeletal disease of human, characterized by painful joints and duck-like walking (17).

Besides other systems, cadmium affects male reproductive system in very potent manner (18–20). Cadmium is documented to induce numerous adverse alterations in the testis, epididymis, and seminal vesicle. This encompasses adverse alterations in seminiferous tubules, Sertoli cells, spermatogonial cells, as well as the quality, quantity and performance of spermatozoa (5,12,16,21,22). It disrupts the normal development of Leydig cells and may possibly trigger cancers in these cells (23,24). Moreover, cadmium compromises the integrity of the blood–testis barrier (BTB) (20,25) and the vascular system (10,26) within the testis. Physiological functions of the seminal gland are also affected and all of these abnormalities, consequently, may lead to male subfertility or infertility (12).

The heavy metal toxicity is studies in bacteria, insects, fish, birds, various animals especially rodents (rat, mice, hamster) and, to some extents, human (27). Rodents are the preferred animals for research, and the majority of heavy metal toxicity studies are carried out using rats and mice. The hamster ranks as the third most commonly utilized laboratory animal, following the rat and mouse, however its use in toxicology is much restricted (28). Also, only a few research utilize hamsters to investigate the impact of heavy metals on the male reproductive system.

Since there is a dearth of information about cadmium toxicity in hamsters, this experiment is designed to study the effect of cadmium chloride on the male reproductive system using the Syrian Golden Hamster (*Mesocricetus auratus*) as an experimental model animal. The objective of this study is to evaluate the effect of cadmium chloride toxicity on morphological features of primary and secondary reproductive

organs. We use quantitative and morphological measurements and organ indices to assess the impact of the toxicity.

Material and method

All procedures were performed in accordance with the guidelines of the Committee for Control and Supervision of Experiments on Animals (CCSEA), Government of India, regarding animal welfare.

Experimental Animal and its maintenance

Male Syrian Golden Hamster (*Mesocricetus auratus*) was selected as the experimental subject and kept at a stable temperature of 25 ± 2 °C, with a light/dark cycle of 12.5 hours of light and 11.5 hours of darkness. All hamsters were 90-100 days old, 100-130g weight, accommodated in polypropylene cages and were given commercial rodent pellets and drinking water *ad libitum*.

Chemicals

Analytical grade Cadmium Chloride (98% pure $CdCl_2.H_2O$) powder (CAS Number: 35658-65-2) was purchased from Cynor Laboratories, Surat, Gujrat, India. Regular table salt was purchased from market for preparation of normal saline.

Selection and Preparation of Dose

Doses of cadmium chloride, treatment duration and frequency were selected based on earlier reports with some modifications (29,30). The three chosen doses were: 0.5 mg $CdCl_2$ kg-1 B.W, 1.00 mg $CdCl_2$ kg-1 B.W and 2.00 mg $CdCl_2$ kg-1 B.W of hamster (here, B.W. means initial body weight). Agarwal et al., 1997 had suggested that higher doses cause much damage even after only 24 hrs of treatment. Different doses were freshly prepared by calculating and weighing different amounts of $CdCl_2$ powder and dissolving in 0.9% normal saline (vehicle). Hamsters were injected 100µl of solution using insulin syringe.

Experimental Design

Adult male golden hamsters (90–100 days old) weighing between 100 and 130 g were randomly selected and divided into 4 experimental groups as mentioned bellow, each containing five animals (n = 5/ group).

Group I: Control : Vehicle treated
Group II: Low dose : 0.5 mg $CdCl_2$ kg-1 B.W.

Group III: Middle dose : 1.00 mg $CdCl_2$ kg-1 B.W

Group IV: High dose : 2.00 mg $CdCl_2$ kg-1 B.W

Single dose/day was given to hamsters of each group by intraperitoneal (I.P.) injection using insulin syringe. Control group was treated with vehicle, i.e. normal saline (100 µl). Treatments were given every day in evening at a fixed time for 10 days.

Data collection, Biometry and morphometry

Animals in each group were thoroughly watched for activity and alertness ever day before treatments. Hamsters were anesthetized and weighed 24 hours after the last treatment. The testes and seminal were immediately removed, blotted, weighed, and photographed. Testis weight excludes tunica albuginea, giving the organ's functional portion. Liver and kidney were also dissected, blotted dry, and weighed.

The gonadosomatic index (GSI) was expressed as percentage of the total body weight in relation to the testis weight, and calculated by formula: GSI = (weight of both testes / total body weight of hamster) x 100 (32). The hepatosomatic index (HSI) was calculated as: HSI = (weight of liver / total body weight of hamster) x 100, expressed in percentage (33,34). MS excel software was used for recording the final data. Photographs of testes and seminal were observed, measured, analysed to deduce morphological changes.

Data analysis Statistical analysis of the data and preparation of histograms were performed using **Graph Pad Prism 8 (Version: 8.0.2)** with **one-way (ANOVA)** followed by **Dunnette multiple comparison test**. This test was applied to test the difference between control group vs each treatment group (Control vs Low, Control vs Middle, Control vs High dose). The differences were considered statistically significant when $P < 0.05$ (95% confidence level). For measurements of area and perimeter from image of testis & seminal, ImageJ software (Version: 1.52a) was used (35).

Results

I. **Animal Activity and alertness:** After 6^{th} day onwards, in comparison to control group hamsters, Cd injected hamsters were showing progressive decrement in activeness (appeared lethargic) and alertness which become more prominent in Group IV (highest dose).

II. **Body weight:** The results are presented as mean ± SD as shown in Table 1. High-dose cadmium caused a marked mean body weight loss of -32.86 ± 5.9% (***$p < 0.001$), contrasting with

moderate weight gains in control (7.75 ± 2.4%) and lower dose groups (6.91 ± 5.1% and 5.34 ± 5.9%).

Table 1: ***Average initial and final body weights, and percentage change (mean ± SD) in male hamsters exposed to cadmium. Significant reduction at high dose compared to control (**p < 0.001, Dunnett's test).***

Group	Initial Weight (Mean ± SD)	Final Weight (Mean ± SD)	%Change in Weight (Mean ± SD)
Control	130.0 ± 4.7	140.0 ± 2.7	7.75 ± 2.4
Low dose	120.0 ± 7.4	128.0 ± 2.0	6.91 ± 5.1
Middle dose	100.0 ± 7.4	105.0 ± 2.3	5.34 ± 5.9
High dose	120.0 ± 12.7	80.0 ± 3.4	-32.86 ± 5.9***

Table 2. ***Average organ weights (mean ± SD) of male golden hamsters treated with three doses of cadmium chloride compared to vehicle-treated controls. Statistical significance as determined by Dunnett's test is indicated (*p < 0.05; ***p < 0.001; ***p < 0.0001).***

Parameters	Control (Vehicle treated)	Low dose (0.5 mg $CdCl_2$ kg-1 B.W.)	Middle dose (1 mg $CdCl_2$ kg-1 B.W.)	High dose (2 mg $CdCl_2$ kg-1 B.W.)
Testis weight (Mean ± SD)	3.60 ± 0.21	3.22 ± 0.30	2.80 ± 0.21***	1.30 ± 0.28****
Seminal weight (Mean ± SD)	1.35 ± 0.25	1.20 ± 0.20	0.84 ± 0.29*	0.60 ± 0.27***
Liver weight (Mean ± SD)	4.10 ± 0.20	3.98 ± 0.40	3.50 ± 0.51	2.60 ± 0.59***
Paired Kidney weight (Mean ± SD)	0.86 ± 0.11	0.80 ± 0.14	0.75 ± 0.14	0.60 ± 0.11*

Table 3. ***Gonadosomatic index (GSI) of testis and seminal vesicle, and hepatosomatic index (HSI) in cadmium-treated and control groups (mean ± SD). Statistical significance as determined by Dunnett's test is indicated (***p < 0.0001).***

Parameters	**Control (Vehicle treated)**	**Low dose (0.5 mg $CdCl_2$ kg-1 B.W.)**	**Middle dose (1 mg $CdCl_2$ kg-1 B.W.)**	**High dose (2 mg $CdCl_2$ kg-1 B.W.)**
GSI (Testis) (Mean ± SD)	2.60 ± 0.18	2.51 ± 0.24	2.67 ± 0.25	1.63 ± 0.40 ***
GSI (Seminal) (Mean ± SD)	0.96 ± 0.18	0.94 ± 0.15	0.80 ± 0.27	0.75 ± 0.33
HSI (Mean ± SD)	2.93 ± 0.18	3.13 ± 0.37	3.34 ± 0.56	3.26 ± 0.84

III. Organ weight: The results are presented as mean ± SD as shown in Table 2.

(a) ***Testis Weight:*** Cadmium caused a dose-dependent drop in testis weight: from 3.60 ± 0.21 g in controls to 2.80 ± 0.21 g (***p < 0.001) and 1.30 ± 0.28 g (****p < 0.0001) at middle and high doses, indicating marked atrophy.

(b) ***Seminal Vesicle Weight:*** Seminal weight declined significantly at the middle (0.84 ± 0.29 g; *p < 0.05) and high doses (0.60 ± 0.27 g; ***p < 0.001) compared to controls (1.35 ± 0.25 g).

(c) ***Kidney Weight:*** Kidney weight fell modestly, reaching significance only at the high dose (0.60 ± 0.11 g; *p < 0.05 vs. control 0.86 ± 0.11 g).

(d) ***Liver Weight:*** Liver weight dropped significantly only at the high dose (2.60 ± 0.59 g; ***p < 0.001) versus control (4.10 ± 0.20 g).

IV. Organ indices: The results are presented as mean ± SD as shown in Table 3.

(a) Gonadosomatic index:

i. ***GSI (Testis):*** The testicular gonadosomatic index remained stable across low and middle dose groups but fell significantly in the high dose group. Mean GSI dropped from 2.60 ± 0.18 in controls to 2.51 ± 0.24 (low dose), 2.67 ± 0.25 (middle dose), and 1.63 ± 0.40 in the high dose group (***p < 0.001).

ii. ***GSI (Seminal Vesicle)***: Seminal GSI showed only minor, non-significant reductions. Values shifted from 0.96 ± 0.18 in controls to 0.94 ± 0.15 (low dose), 0.80 ± 0.27 (middle dose), and 0.75 ± 0.33 (high dose).

(b) HSI (Hepatosomatic Index): The hepatosomatic index exhibited a slight, non-significant increase with cadmium exposure, from 2.93 ± 0.18 in controls to 3.13 ± 0.37 (low dose), 3.34 ± 0.56 (middle dose), and 3.26 ± 0.84 (high dose).

V. Organ morphology and morphometry: The results are presented figure 1 and table.

(a) **Testis:** Control group testes are healthy, oval-shaped with smooth surfaces and well-defined blood vessels. Testes of control and low dose group appear morphologically similar. In the middle dose group, one testis experienced discoloration with red-purple patches indicating testicular haemorrhage while the other diminished in size. Both of testes of the high dose group shrank, pale, irregular in shape and became (physically) very delicate.

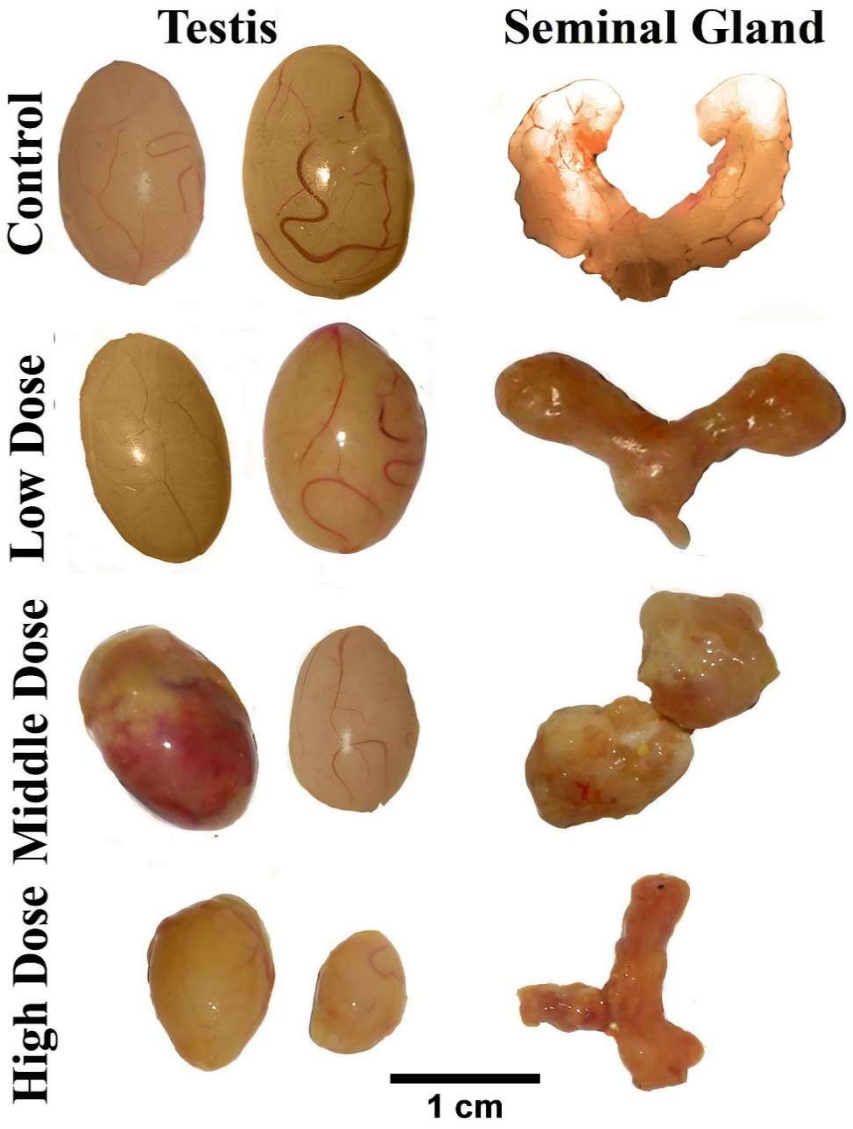

Figure 1. ***Gross morphological effects of cadmium exposure on testis and seminal gland in male golden hamsters. Representative photographs show dose-dependent atrophy, haemorrhage, discoloration, and structural alterations in testis (left column) and seminal gland (right column) across control, low dose, middle dose, and high dose cadmium-treated groups.***

a. **Seminal gland:** The seminal vesicles in the control group were crescent-shaped, translucent to white, and possessed a nodular surface (36). The low dose seminal appeared slightly thickened, altered shape and smoother surface. The middle dose seminal was highly swollen and very irregular in shape (malformed). Seminal of high dose group was highly distorted and reduced in size.

b. **Morphometric Analysis (Area & Perimeter)**: Morphometric assessment revealed dose-related shrinkage in testicular and seminal gland size. Left testis area decreased from 1.179 cm^2 in controls to 0.761 cm^2 in the high dose group; right testis area fell from 1.580 cm^2 to 0.414 cm^2. Similar trends were noted in perimeter measures and in seminal gland area (from 1.697 cm^2 in controls to 0.74 cm^2 in high dose). This seems aligned with morphological observations.

Table 4: ***Morphometric measurements of area (cm^2) and perimeter (cm) of left and right testes, and seminal gland in cadmium-treated and control hamsters, derived from digital images analysed using ImageJ software.***

Dose	Testis				Seminal gland	
	Area (cm^2)		Perimeter (cm)		Area(cm^2)	Perimeter(cm)
	Left	Right	Left	Right		
Control	1.179	1.580	4.081	4.707	1.697	8.232
Low Dose	1.203	1.281	4.196	4.246	1.373	6.858
Middle dose	1.181	0.863	4.101	3.551	1.418	5.881
igh Dose	0.761	0.414	3.339	2.491	0.74	5.281

Discussion

Cadmium exposure markedly affected the overall body weight of male golden hamsters, particularly at the highest dose (from 120.0 ± 12.7 g initially to 80.0 ± 3.4 g) which reflects systemic toxicity and general health deterioration at high cadmium exposure. The significant reduction in testis weight at

middle and high cadmium doses underscores cadmium's potent role in the testicular toxicity. This is consistent with other researcher's finding that cadmium induces oxidative stress and autophagy (36), damages seminiferous tubules, and impairs spermatogenesis, ultimately leading to atrophy (37). The decrease in seminal vesicle weight significantly at higher doses, suggests a functional compromise of accessory sex glands. This likely reflects reduced testosterone level, since seminal gland maintenance is testosterone-dependent (38). The impairment of seminal will cause reduction in quantity and quality of its secretion, consequently affecting sperm motility, viability and capacitation (39,40).

Standard morphometric indices like GSI and HSI standardize organ weight relative to body weight, revealing organ-specific effects independent of animal size. These are important in toxicological research when body weight changes. The significant decrease in testicular GSI at the high dose in our experiment highlights the gonadal effect of cadmium by indicating both proportional shrinkage in relation to body weight and absolute testis weight loss. However, the absence of significant changes in seminal GSI and HSI suggests cadmium's major effect was testicular rather than hepatic or seminal proportional mass, at least under these experimental conditions. The dose-dependent reductions in testis and seminal gland area and perimeter reinforce the anatomical atrophy observed grossly and quantitatively. It is obvious from the photographs that cadmium induces atrophy, haemorrhage, discoloration, and structural alterations in testis and seminal gland across all the cadmium-treated groups. These quantitative and qualitative findings demonstrate that cadmium's impact is not limited to weight but extends to morphological integrity.

Cadmium is a systemic toxicant that accumulates not only in gonads but also in organs like the kidney and liver (41), which play critical roles in hormone metabolism and detoxification. This corroborates cadmium's extensive toxicological profile, impacting other organs beyond the gonads (42). There is evidence that cadmium is nephrotoxic (43), which is demonstrated by a decrease in kidney weight. Low liver weight may indicate hepatocellular injury, which could impair testosterone production and metabolism. The liver produces carrier proteins like Sex Hormone Binding Globulin (SHBG) that regulate circulating androgen levels and remove excess hormones (44). Hepatotoxicity may disrupt this delicate hormonal balance, reducing androgen bioavailability needed for testes and accessory sex gland growth and function. this may lead to disruption of negative feedback mechanism of hypothalamic–pituitary–gonadal (HPG) axis. Thus, cadmium-induced hepatic damage may indirectly lead to testicular atrophy and reduction of the seminal glands at elevated dosages by undermining systemic endocrine function. It is important to note that the impact of cadmium on the liver and kidneys was less significant than on the gonads, indicating a major reproductive focus of cadmium exposure.

Conclusion

The current paper confirms that acute exposure of cadmium chloride has a definite pathogenic effect on testicular and seminal structures of the Syrian Golden Hamster. The decrease of body weight, organ mass, and gonadosomatic index, along with the apparent morphological and morphometric alteration, are clear signs of extensive gonadal damage at relatively brief exposure intervals. The morphological changes such as atrophy, haemorrhage and tissue disorganization indicate that cadmium disturbs the structural integrity and functional capability of male reproductive system. Although this also impacted several essential organs including the liver and kidneys, the most significant effect was on the gonads highlighting the effectiveness of cadmium in terms of reproduction toxicity. These results highlight the validity of morphometric and index-based parameters as useful instruments in the study and analysis of reproductive hazards that are formed by environmental toxicants.

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