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Histopathological Changes in the Liver of Rats Exposed to Cadmium

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ABSTRACT

Cadmium (Cd) is a toxic heavy metal widely recognized for its detrimental effects on human and animal health. The liver, a primary organ for detoxification, is particularly susceptible to cadmium-induced damage. This study aimed to investigate the histopathological changes in the liver of rats exposed to cadmium. A total of 24 adult male Wistar rats were divided into four groups: a control group and three experimental groups exposed to 2.5 mg/kg, 5 mg/kg, and 10 mg/kg of cadmium chloride ($CdCl_2$) for 28 days. Histopathological analysis of liver tissues revealed dose-dependent alterations, including hepatocellular degeneration, necrosis, inflammatory cell infiltration, and fibrosis. Biochemical markers of liver function, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were significantly elevated in cadmium-exposed groups. The findings underscore the hepatotoxic potential of cadmium and provide insights into the mechanisms of cadmium-induced liver injury. This study highlights the need for stringent regulations on cadmium exposure to mitigate its adverse health effects.

1. INTRODUCTION

Cadmium is a pervasive environmental pollutant with significant human and animal health risks. It is widely used in industrial processes, including battery manufacturing, metal plating, and pigment production, leading to its widespread distribution in air, water, and soil (1). Cadmium exposure occurs primarily through inhalation of contaminated air, ingestion of contaminated food and water, and tobacco smoking (2). Due to its long biological half-life (10–30 years), cadmium accumulates in tissues, particularly the liver and kidneys, leading to chronic toxicity (3).

The liver is a critical organ for detoxification and metabolism, making it a primary target for cadmium-induced damage. Cadmium toxicity in the liver is mediated through multiple mechanisms, including oxidative stress, mitochondrial dysfunction, and disruption of calcium homeostasis (4). Oxidative stress, in particular, plays a central role in cadmium-induced hepatotoxicity, as cadmium depletes cellular antioxidants such as glutathione and produces reactive oxygen species (ROS) (5). These ROS can damage cellular macromolecules, including lipids, proteins, and DNA, leading to cell death and tissue injury (6).

Histopathological examination is a valuable tool for assessing cadmium-induced liver damage. Previous studies have reported various histopathological changes in the liver following cadmium exposure, including hepatocellular degeneration, necrosis, inflammatory cell infiltration, and fibrosis (7). However, the dose-response relationship and the progression of these changes over time remain poorly understood. Furthermore, the interplay between histopathological alterations and biochemical markers of liver function has not been fully elucidated (8).

This study aimed to investigate the histopathological changes in the liver of rats exposed to different doses of cadmium chloride ($CdCl_2$) and to correlate these changes with biochemical markers of liver injury. By providing a comprehensive analysis of cadmium-induced hepatotoxicity, this study contributes to a better understanding of the mechanisms underlying cadmium toxicity. It informs strategies for preventing and mitigating its adverse effects.

2. METHODOLOGY

Experimental Design

A total of 24 adult male Wistar rats (weighing 200–250 g) were used in this study. The rats were housed in polypropylene cages under controlled environmental conditions (temperature: 22 ± 2°C, humidity: 50 ± 10%, 12-hour light/dark cycle) and provided standard rodent chow and water ad libitum. After a one-week acclimatization period, the rats were randomly divided into four groups (n = 6 per group):

- **Group I (Control):** Received distilled water orally for 28 days.
- **Group II:** Received 2.5 mg/kg body weight of $CdCl_2$ orally for 28 days.
- **Group III:** Received 5 mg/kg body weight of $CdCl_2$ orally for 28 days.
- **Group IV:** Received 10 mg/kg body weight of $CdCl_2$ orally for 28 days.

Cadmium Chloride Preparation

Cadmium chloride ($CdCl_2$, Sigma-Aldrich) was dissolved in distilled water to prepare the required concentrations. The doses were selected based on previous studies demonstrating hepatotoxic effects in rats (9).

Sample Collection

At the end of the 28-day exposure period, the rats were anesthetized using ketamine (75 mg/kg) and xylazine (10 mg/kg). Blood samples were collected via cardiac puncture for biochemical analysis. The liver was excised, washed with ice-cold saline, and divided into two portions: one was fixed in 10% neutral buffered formalin for histopathological examination and stored at -80°C for further analysis.

Biochemical Analysis

Serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using commercial kits (Randox Laboratories) following the manufacturer's instructions. These enzymes are markers of hepatocellular damage.

Histopathological Examination

Liver tissues were processed using standard histological techniques. Briefly, tissues were dehydrated in graded ethanol, cleared in xylene, and embedded in paraffin. Sections (5 µm thick) were cut using a microtome, stained with hematoxylin and eosin (H&E), and examined under a light microscope. Histopathological changes were scored semi-quantitatively as follows:

- **0:** No changes
- **1:** Mild changes (<25% of tissue affected)
- **2:** Moderate changes (25–50% of tissue affected)
- **3:** Severe changes (>50% of tissue affected)

Statistical Analysis

Data were analyzed using SPSS software (version 25). One-way ANOVA followed by Tukey's post hoc test was used to compare group differences. A p-value < 0.05 was considered statistically significant.

3. RESULTS

Biochemical Findings

Table 1 summarizes ALT and AST serum levels in control and cadmium-exposed groups. A dose-dependent increase in ALT and AST levels was observed, with significant differences ($p < 0.05$) between the control and cadmium-exposed groups.

Group	ALT (U/L)	AST (U/L)
Control	35.2 ± 3.1	40.5 ± 4.2
2.5 mg/kg	78.6 ± 5.4*	85.3 ± 6.1*
5 mg/kg	120.4 ± 8.7*	132.6 ± 9.3*
10 mg/kg	185.7 ± 10.2*	198.4 ± 11.5*

*Significantly different from control ($p < 0.05$).

Histopathological Findings

Table 2 summarizes the histopathological changes in the liver of control and cadmium-exposed rats. Dose-dependent increases in hepatocellular degeneration, necrosis, inflammatory cell infiltration, and fibrosis were observed (Fig. 1,2,3).

Group	Degeneration	Necrosis	Inflammation	Fibrosis
Control	0	0	0	0
2.5 mg/kg	1.2 ± 0.3*	0.8 ± 0.2*	1.0 ± 0.3*	0.5 ± 0.1*
5 mg/kg	2.1 ± 0.4*	1.5 ± 0.3*	1.8 ± 0.4*	1.2 ± 0.3*
10 mg/kg	3.0 ± 0.5*	2.7 ± 0.5*	2.9 ± 0.6*	2.5 ± 0.4*

*Significantly different from control ($p < 0.05$).

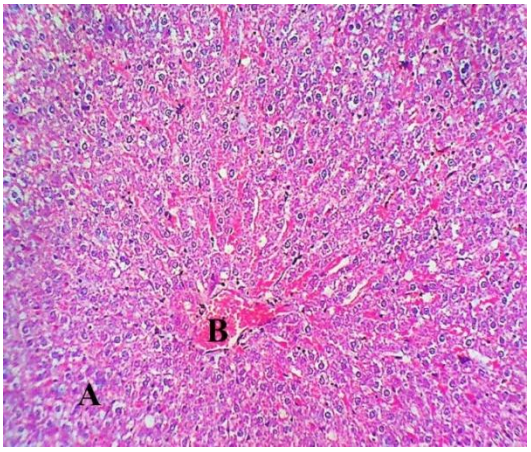

Figure 1. severe vacuolar degeneration (A), and severe congestion of central vein and sinusoid(B) and inflammation. H&E stain (100X).

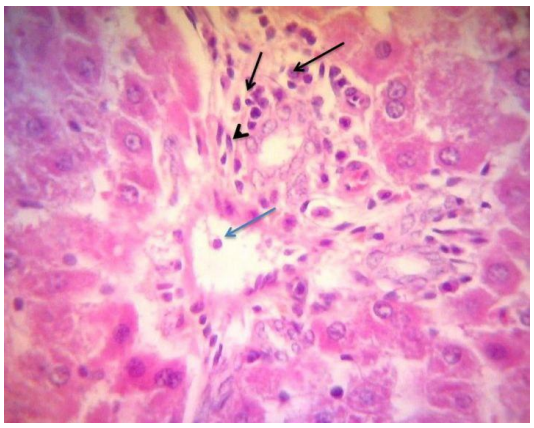

Figure 2. Presence of fibroblast and some fibrosis area. H&E stain (400X).

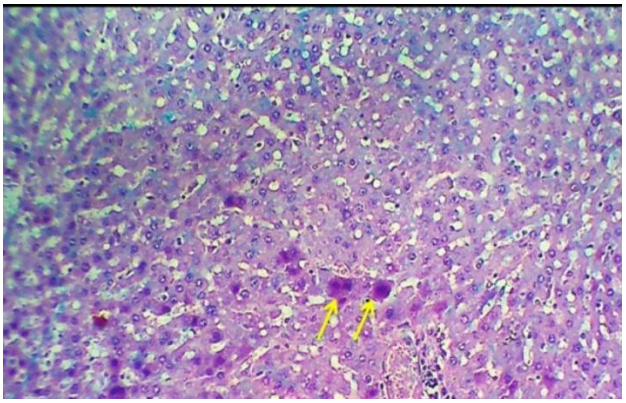

Figure 3. Area of necrosis and apoptotic cells. H&E stain (400X).

4. DISCUSSION

The results of this study demonstrate that cadmium exposure induces significant histopathological and biochemical changes in the liver of rats, highlighting its potent hepatotoxic effects. The dose-dependent increase in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) is a clear indicator of hepatocellular damage. These enzymes are released into the bloodstream upon liver cell injury, and their elevated levels are consistent with previous studies reporting cadmium-induced hepatotoxicity (10-12). The histopathological findings corroborate these biochemical changes, revealing dose-dependent alterations such as hepatocellular degeneration, necrosis, inflammatory cell infiltration, and fibrosis.

Cadmium exerts its toxic effects through multiple mechanisms, with oxidative stress playing a central role. Cadmium disrupts the balance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, leading to oxidative damage (13). Depleting cellular antioxidants, such as glutathione, exacerbates this imbalance, resulting in lipid peroxidation, protein oxidation, and DNA damage (14). As observed in the histopathological analysis, these molecular alterations contribute to cell death and tissue injury.

Mitochondrial dysfunction is another critical mechanism underlying cadmium-induced hepatotoxicity. Cadmium disrupts calcium homeostasis, leading to mitochondrial membrane depolarization and the release of pro-apoptotic factors (15). This mitochondrial pathway of apoptosis is characterized by cytochrome c release, caspase activation, and DNA fragmentation, ultimately resulting in hepatocellular necrosis (16). The necrotic changes observed in this study are consistent with this mechanism.

In addition to direct cellular damage, cadmium triggers an inflammatory response in the liver. The infiltration of inflammatory cells, such as neutrophils and macrophages, is a hallmark of cadmium-induced liver injury (17). These inflammatory cells release pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which exacerbate tissue damage and promote fibrosis (18). The fibrotic changes observed in this study, characterized by increased collagen deposition, are indicative of chronic liver injury and may progress to cirrhosis if exposure continues.

This study's key finding is the dose-dependent nature of cadmium-induced hepatotoxicity. Higher doses of cadmium chloride ($CdCl_2$) resulted in more severe histopathological changes and greater elevations in ALT and AST levels. This dose-response relationship underscores the cumulative nature of cadmium toxicity and its potential to cause progressive liver damage over time. The findings are consistent with previous studies demonstrating that chronic low-level cadmium exposure can lead to significant tissue accumulation and toxicity (19).

The hepatotoxic effects of cadmium observed in this study have significant implications for human health. Cadmium is a widespread environmental pollutant, and human exposure occurs through contaminated food, water, air, and tobacco smoke (20). Occupational exposure, particularly in battery manufacturing and metal plating industries, poses an additional risk (21). The liver is a primary target organ for cadmium accumulation, and chronic exposure can lead to liver dysfunction, fibrosis, and even hepatocellular carcinoma (22).

The findings of this study highlight the need for stringent regulations on cadmium emissions and improved protective measures to reduce exposure. Public health interventions, such as monitoring cadmium levels in food and water, implementing occupational safety standards, and promoting smoking cessation, are essential to mitigate the adverse health effects of cadmium. Further research is needed to explore therapeutic strategies for cadmium-induced liver injury, such as antioxidants and chelating agents.

5. CONCLUSION

This study provides compelling evidence of cadmium-induced hepatotoxicity in rats, characterized by dose-dependent histopathological changes and elevated biochemical markers of liver injury. The findings underscore the importance of addressing cadmium pollution to protect human and animal health. Future research should focus on elucidating the molecular mechanisms of cadmium toxicity and developing effective therapeutic interventions.

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