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The Effect of L-Carnitine on Cadmium Toxicity in Liver and Kidney Tissue in Prepubertal Female Rats

Efecto de la L-Carnitina sobre la Toxicidad del Cadmio en el Hígado y el Tejido Renal en Ratas Hembras Prepúberes

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SUMMARY: Cadmium (Cd) is a toxic element that accumulates in kidney and liver. L-carnitine(LC) is a natural compound that has been shown to exhibit antioxidant activity. Aim of this study was to investigate the effect of L-carnitine against cadmium-induced changes in liver and kidney tissues in prepubertal female rats. In this study 21-day-old female Wistar Albino rats were used. Control, cadmium (2 mg/kg cadmium intraperitoneally), L-carnitine (300 mg/kg orally) and cadmium+L-carnitine groups were formed. Liver and kidney tissue sections were stained with Hematoxylin-Eosin and Masson Trichrome. Histological scoring was performed in liver and kidney. In the liver tissue given Cd, bile duct proliferation, inflammation cells and connective tissue in the portal area were decreased in treatment group. In kidneys, cadmium group treated with L-carnitine, it was observed that the capillary congestion in the kidneys decreased,but tubular dilatation continued in some places. In fibrosis scoring of the liver groups,statistically significant decrease was observed in the Cd+LC group compared to group of cadmium. In the histological scoring results of the kidney groups, statistically significant decrease in congestion and tubular epithelial degeneration was observed in the group treated with L-carnitine compared to group with cadmium. In conclusion medium-dose cadmium has toxic effects in liver and kidney of prepubertal female rats in subacute period,these effects are alleviated with L-carnitine.

KEY WORDS: Cadmium; Kidney; L-carnitine; Liver.

INTRODUCTION

Cadmium is a heavy metal that mainly accumulates in the liver and kidneys and affects various other organs. It causes embryotoxic, mutagenic, epigenetic changes, and cancer (Genchi *et al*., 2020). The half-life in the human kidneys is between 6 to 38 years, and in the liver, it is defined as 4 to 19 years. The human body takes in the nickel-cadmium mixture through batteries, accumulators, exhaust, cigarettes, water, and food. The respiratory, digestive system, and skin absorb it largely. Therefore, it poses a significant public health concern (Mezynska & Brzóska, 2018). Rice (Itai-Itai disease) (Shi *et al*., 2020), fish, other shellfish, wheat, leafy greens, potatoes, carrots, and plants grown in contaminated soils and waters are high in cadmium. People who consume these foods for an extended period, experience chronic kidney diseases, liver disorders, cardiovascular and musculoskeletal system diseases (Genchi *et al*., 2020; Wang *et al*., 2021). Smoking is one of the significant sources of respiratory cadmium and causes cancer (group I of the International Agency for Research on Cancer Classification, IARC). Cadmium reduces lipid and lipoprotein production in the liver, causes endoplasmic reticulum stress, and increases cell death by raising reactive oxygen radicals (Zhu *et al*., 2020).

To mitigate the toxic effects of cadmium, it is recommended to consume foods rich in polyphenols. These compounds reduce apoptotic cell death caused by free oxygen radicals due to time, dose, and diet (Al-Gnami, 2014).

L-Carnitine is a vitamin-like substance and non-protein modified amino acid mainly produced in the liver and kidneys (Ferrari *et al*., 2004). L-Carnitine positively regulates energy and lipid metabolism and protects the antioxidant system, liver, and kidneys (Li *et al*., 2021).

The molecular mechanism behind the toxic effects of cadmium in the liver and kidney is still not fully understood. Cadmium is a known environmental pollutant

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commonly present in air, water, and food, making its effects on living organisms, particularly during growth and development, unavoidable. However, there is a dearth of research on this topic in the literature. The objective of this study is to investigate the potential preventative effects of carnitine in prepubertal female rats that have been exposed to cadmium by creating an experimental model and examining the liver and kidney tissues for toxicity.

MATERIAL AND METHOD

Chemicals. Cadmium and L-carnitine were purchased from Sigma-Aldrich Chemical Company (St Louis, MO, USA).

Animals and experimental design. Rats obtained from Near East University Experimental Animals Research Center (DEHAM) were used. Near East University Experimental Animals Local Ethics Committee Permission was obtained for the study (Ethics No 2021/126). Female Wistar albino rats weighing 65-70 g prepubertal were used. 21-day-old female rats weaned after birth were placed in separate cages, and were housed in a light and dark cycle for 12 hours at 220°C, without any feed and water restrictions. Randomly created 4 groups:

1. Control group (n=6), untreated group
2. CdCl2 group (n=6), cadmium chloride dissolved with distilled water (Merck-Germany) 2 mg/kg ip/day given group.
3. L-Carnitine group (n=6), Carnitine (Sigma-USA) 300 mg/kg/day given by oral gavage group.
4. CdCl2 + L-Carnitine group (n=6), the group given the same doses of cadmium and L-carnitine

Collection and preparation of blood and serum. At the end of this study, rats were anesthetized through intraperitoneal injection of 1:1 xylazine: ketamine combination (0.1 ml/100 gm. b.wt.) after weighting and dose calculations.

Immediately before anesthesia and decapitation, blood samples were collected from the intracardiac. After clotting, serum was obtained by centrifugation at 3000 for 15 min; serum samples were stored at – 80 °C until the biochemical analysis.

Kidney and liver function biomarkers. The indicators for liver damage such as serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were evaluated using commercial kits. The kidney function parameters such as serum urea and creatinine were measured by colorimetric kits following the manufacturer's protocol.

Histological examination. Liver and kidney tissue samples were fixed with 10 % neutral formalin. They were passed through graded alcohol series and xylol and then paraffin blocks were prepared. Sections taken from the tissues with a thickness of 4-5μm were stained with hematoxylin-eosin and Masson's trichrome. Histological changes in the liver were scored semiquantitatively in terms of inflammation, necrosis, fibrosis, and bile duct proliferation with X 40 objective magnification. Changes were evaluated as 0 (no change), 1 (mild changes < 25 %), 2 (moderate changes 25-50 %), and 3 (severe changes > 50 %) (de Lima EC *et al*. 2020). Histological changes in the kidney were scored with X40 objective magnification in terms of tubular necrosis, tubular epithelial cell vacuolization, congestion, and tubular dilatation. Changes were evaluated as 0 (normal), 1 (mild changes < 15 %), 2 (moderate changes 16-35 %), and 3 (severe changes >35 %) (Arab *et al*., 2022).

Statistical Analysis. Obtained values were evaluated statistically by one-way analysis of variance using GraphPad Prism version 9. $p<0,05$ were considered significant.

RESULTS

Biochemical results. Serum ALT (p:0,03), AST (p:0,02) and Urea (p:0,04) activities in the cadmium group were significantly higher compared to the control group. Also there was significant lower in ALT (p:0,02), AST (p:0,02) and urea (p:0,03) activities between the cadmium and Cd+LC group (Fig. 1).

Histological findings. The liver tissue of the Cd group exhibited bile duct proliferation, an increase in connective tissue around the portal area (Figs. 2C,D), an increase in inflammatory cells (Fig. 2E), and necrotic foci (Fig. 2F) compared to the control group (Figs. 2A,B). The treatment group showed a decrease in bile duct proliferation (Fig. 2G), inflammatory cells, and connective tissue in the portal area (Fig. 2H). In the kidneys of the Cd group, congestion in the intertubular capillaries and dilatation of the tubules (Figs. 3B,C) were observed compared to the control (Fig. 3A). In the Cd group treated with L-carnitine, capillary congestion in the kidneys decreased, but tubular dilatation persisted in some areas (Fig. 3D).

In the inflammatory cell scoring of the liver, a statistically significant increase was observed between Cd with control (p:0.009), Cd with LC (p:0.004), fibrosis scoring with control Cd (p:0.002), control with Cd+LC (p:0.03), with LC Cd (p:0.006), control for necrosis (p:0.001), LC and Cd (p:0.001), bile duct proliferation control and Cd (p:0.001), LC and Cd (p:0.02) groups. Renal histological scoring revealed that tubular dilatation (p:0.01), congestion

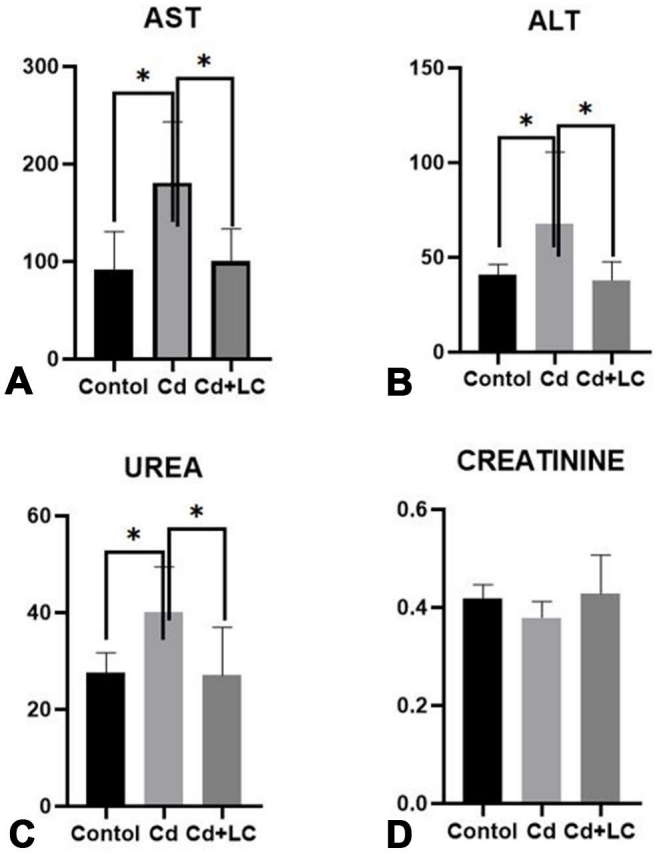

Fig. 1. Effect of cadmium and L-carnitine on liver and kidney serum parameters. (A) AST (B) ALT (C) Urea and (D) Creatinine concentration in experimental groups. (*$p < 0.05$, **$p < 0.01$).

(p:0.001), and tubule epithelial cell degeneration (p:0.03) showed statistically significant increases in the Cd group compared to the control group. The treatment group showed a statistically significant decrease in congestion (p:0.03) and tubule epithelial cell degeneration (p:0.01) compared to the Cd group (Table I).

DISCUSSION

In this study, the preventive/reducing effects of L-carnitine on the toxic changes induced by cadmium in the liver and kidneys of non-adolescent mice using both light microscopy and biochemical methods was investigated. Cadmium is a major environmental pollutant that causes dose- and time-dependent organ degeneration and poses a significant threat to the health of living organisms (Alves Peixoto & Jadán-Piedra, 2021). Chronic exposure to environmental Cd levels adversely affects the health of children and adults, as indicated by numerous health studies (Satarug *et al*., 2022).

Experimental models of cadmium exposure involve various administration methods, such as oral gavage, water consumption, subcutaneous (SC) and intraperitoneal (IP) injections. Orally administered doses tend to be higher than IP and SC administered doses, and the administered doses have different effects on the body and organ weights of the subjects. While low doses did not cause any decrease in weight, it was observed that weights decreased at medium and high doses (Liu *et al*., 2019; Zamani *et al*., 2021). In our experimental model, 2 mg/kg Cd was administered, which is considered a medium dose for IP applications, to the subjects, for 28 days. Statistically significant change was not observed in the body and organ weights of the subjects.

The liver, the body's primary site for xenobiotic metabolism and detoxification, is the second major organ to face damage caused by Cd exposure. Oxidative stress is recognized as one of the main mechanisms of cell damage caused by Cd toxicity. Cadmium increases proinflammatory cytokines such as IL-1, IL-6, and TNF-α from Kupffer cells in the liver, while L-carnitine reduces inflammation (Abu-El-Zahab *et al*., 2019). L-carnitine plays an important role in lipid metabolism and regulates energy metabolism, thus

Table I. Histological scoring in groups of liver and kidney tissues.

GROUPS	Tubuler dilatation	Necrosis	Congestion	Tubuler epithelial degeneration	Inflammatory Cell	Fibrosis	Necrosis	Bile duct proliferation
Control	0.00±0.00	0.00±0.00	0.00±0.00	0.16±0.40	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
LCarnitine (L-C)	0.16±0.41	0.00±0.00	0.17±0.41	0.17±0.41	0.16±0.41	0.17±0.41	0.00±0.00	0.33±0.52
Cadmium	1.16±0.75[a]*	0.00±0.00	2.00±0.00[a]**	1.50±0.84[a]*	2.00±0.63[a]*	1.83±0.41[a]*	1.67±0.52[a]*	1.67±0.52[a]*
L-C + Cadmium	0.50±0.55	0.00±0.00	0.83±0.40 [b]*	0.33±0.52 [b]*	1.17±0.41	1.33±0.52[b]*	0.83±0.41	0.66±0.52

Data. mean ± SD
a Statistical significance when compared to control
b Statistical significance when compared to cadmium
*p < 0.05. **p < 0.01 vs. control.

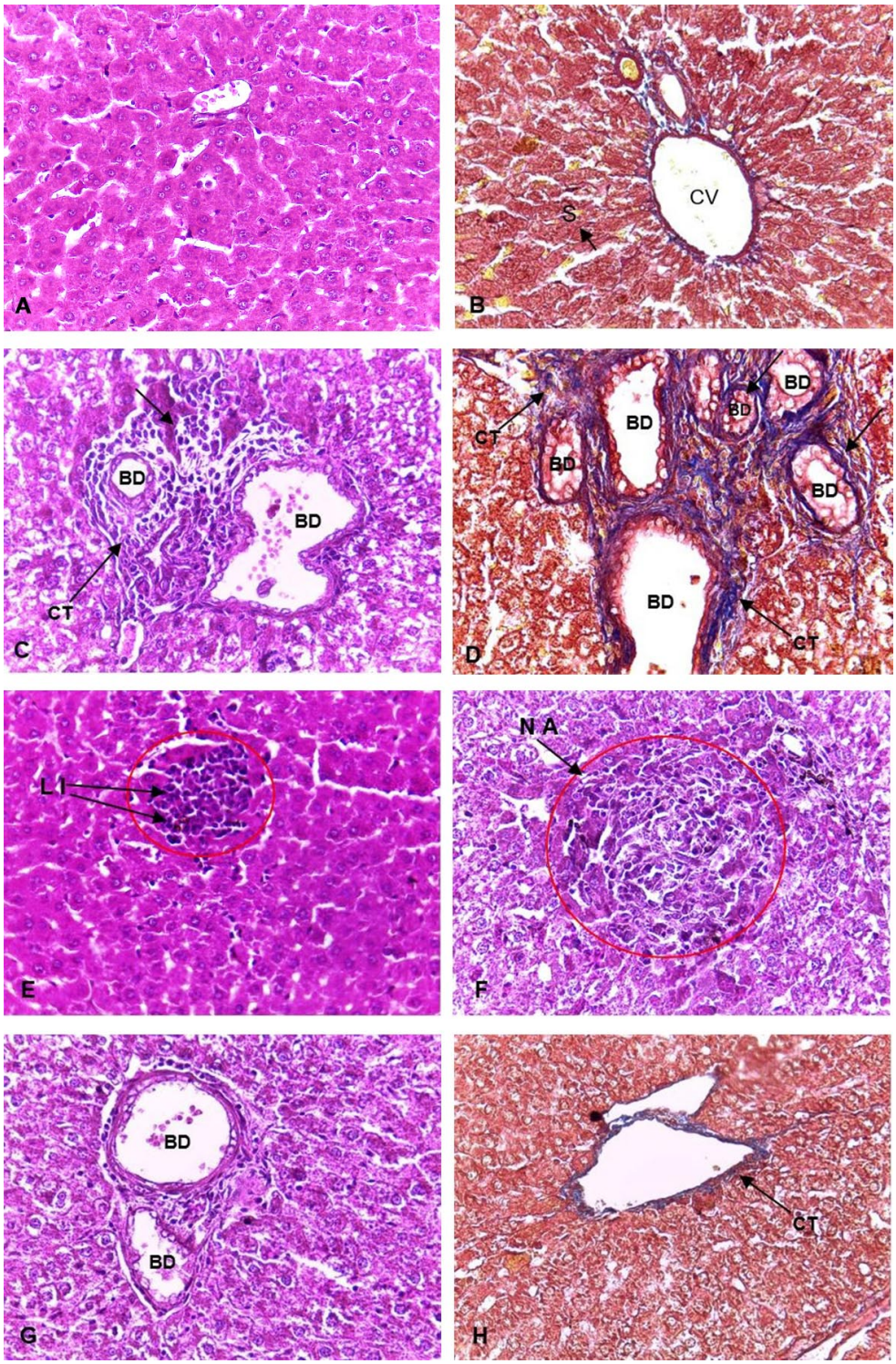

Fig. 2. Hematoxylin-Eosin (A, C, E, F, G) and Masson Trichrome (B, D, H) stainings showing histological damage in control and experimental groups. A and B Control liver section with normal contained normal hepatocyte (Hp) architecture with distinct hepatic strands, sinusoids (S), and central veins (CV). Rats treated with Cd with bile duct proliferation, increase in connective tissue around the portal area (arrow shows) (C and D) increase in inflammatory cells (LI) (E), necrotic area (NA) (F) were detected in the renal tissue. Treatment of LC reduced these histological changes in liver tissue. Bile duct proliferation, inflammation cells and connective tissue in the portal area were decreased (G and H).

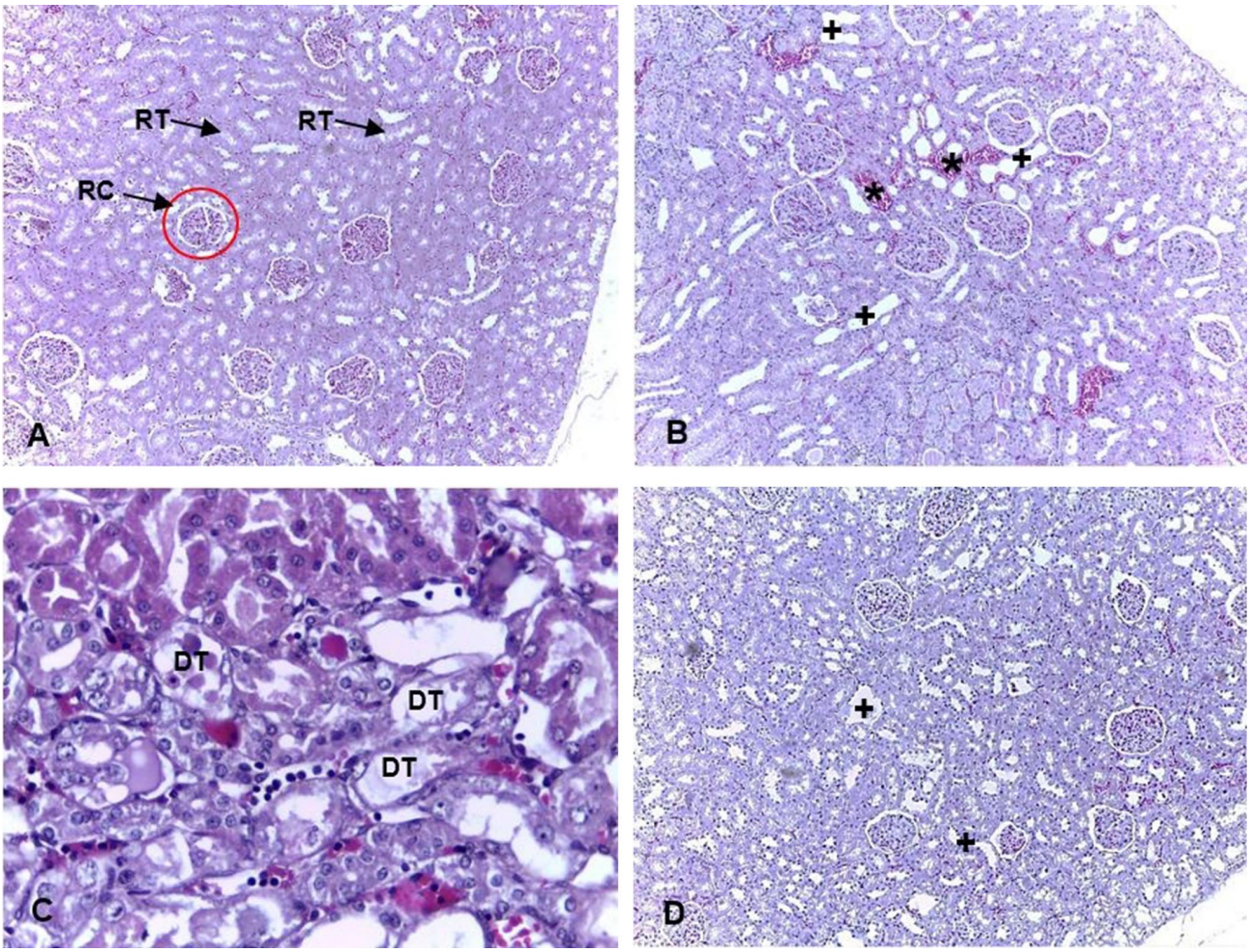

Fig. 3. Hematoxylin-Eosin staining showing histological damage in control and experimental groups. Control kidney section with normal renal corpuscle and renal tubules (A). Rats treated with Cd with degeneration of epithelia of the tubules (DT), congestion in the intertubular capillaries (*), dilatation in the tubules were detected in the renal tissue (+) (B and C). Treatment of LC reduced these histological changes in renal tissue. Capillary congestion in the kidneys decreased, but the tubular dilatation continued in some places (D).

protecting hepatocytes with the antioxidant system and reducing mitochondrial dysfunction. In liver tissue of adult subjects, there is an increase in stellate macrophages (Kupffer cells), hydropic degeneration, enlargement of sinusoids, lymphocyte and neutrophil infiltration in portal areas, an increase in hepatocytes with heterochromatic nuclei, irregularity in hepatic cell cords, vacuolization in hepatocytes, congestion, inflammation, lipid accumulation in hepatocytes, an increase in the number of binucleated hepatocytes, and coagulation necrosis, as reported in studies by Abu-El-Zahab *et al*. (2019) and Rana *et al*. (2021).

In another study, prepubertal rats were administered 5mg/kg cadmium through their drinking water, and the resulting liver and kidney changes were examined after 7 days. The researchers observed no changes in organ or subject weight, but did detect increased liver enzymes, as well as necrosis and inflammation in the liver (Owumi *et al*., 2019). The cadmium-exposed rats also had higher levels of serum AST and ALT, consistent with findings from other studies (Agır & Eraslan, 2019). While AST and ALT serum levels increased in the cadmium group, they decreased in the group that was also treated with L-carnitine.

Histological examination of liver tissue from the cadmium group revealed various abnormalities, including uncommon areas of necrosis, congestion, increased inflammatory cells (including stellate macrophages), bile duct proliferation, and fibrosis in the portal area. Bile duct proliferation had not been previously reported in these studies, so this is a new finding. Treatment with L-carnitine reduced the severity of these findings, with fewer necrotic foci, inflammatory cells, bile duct proliferation, and portal area fibrosis observed. The anti-inflammatory and

antifibrotic effects of L-carnitine likely contributed to these positive outcomes.

The increase in cadmium concentration in blood and urine affects the glomerular filtration rate, as reported by Jain *et al*. (2020). In addition to apoptosis and necrotic death, cadmium also induces cell death via ferroptosis in renal tubule epithelial cells. Dose-dependent tubular degeneration, enlargement of tubules, loss of striated edges, disruption of mitochondria as observed by transmission electron microscopy (TEM), endoplasmic reticulum stress, and increased autophagy have been detected in response to cadmium exposure (Kukner *et al*., 2007). In cadmium-treated kidneys, diffuse edema, tubular necrosis, dilatation, glomerular atrophy, and an increase in serum creatinine and urea levels were observed. Moderate inflammation and congestion were also present (Owumi *et al*., 2019; Huang *et al*., 2021). A low dose (3 mg/kg) of cadmium administered over an 8-week period resulted in the shedding of tubular epithelial cells, degeneration in tubule structures, an increase in inflammatory cells, and changes in a small number of glomeruli. However, at a high dose (6 mg/kg), these changes occurred in the 2nd week and degeneration increased over time (Wan *et al*., 2022).

Similar microscopic changes were observed in the kidneys of our study subjects. The cortex exhibited congestion in the intertubular capillaries, diffuse tubularenlargement, and shedding of tubular epithelial cells. However, edema, necrosis, inflammation, or glomerular degeneration was not observed in this study. The group exposed to cadmium showed an increase in serum levels of creatinine and urea, while treatment with L-carnitine decreased both levels, as well as tubular enlargement and congestion.

The impact of cadmium varies based on the dose and administration method, with high doses causing degenerative effects in the liver and kidneys. Exposure to pollution in air, water, and soil can cause negative effects on pre-pubescent living organisms. Minimizing or preventing environmental pollution and purifying food from heavy metals are crucial for reducing the toxic effects of cadmium. Antioxidants, anti-inflammatory substances, or foods can partially protect against cadmium's harmful effects at the cellular level. In this study, it has been identified that even low doses of cadmium caused structural changes in the liver and kidneys of prepubertal rats, but these changes were reduced by L-carnitine. Few studies have examined this topic, and results of this study can serve as a reference for future studies. Further studies are necessary to understand the molecular effects of L-carnitine.

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RESUMEN: El cadmio (Cd) es un elemento tóxico que se acumula en los riñones y el hígado. La L-carnitina (LC) es un compuesto natural que ha demostrado tener actividad antioxidante. El objetivo de este estudio fue investigar el efecto de la L-carnitina contra los cambios inducidos por el cadmio en los tejidos del hígado y el riñón en ratas hembra prepúberes. En este estudio se utilizaron ratas Wistar Albinas hembra de 21 días de edad. Se formaron grupos control, cadmio (2 mg/kg de cadmio por vía intraperitoneal), L-carnitina (300 mg/kg por vía oral) y cadmio + L-carnitina. Se tiñeron secciones de tejido de hígado y riñón con Hematoxilina-Eosina y tricrómico de Masson. La puntuación histológica se realizó en hígado y riñón. En el tejido hepático que recibió Cd, la proliferación de los conductos biliares, las células inflamatorias y el tejido conectivo en el área portal disminuyeron en el grupo con tratamiento. En los riñones, en el grupo de cadmio tratado con L-carnitina, se observó que la congestión capilar disminuyó, pero la dilatación tubular continuó en algunos sitios. En la puntuación de fibrosis de los grupos de hígado, se observó una disminución estadísticamente significativa en el grupo de Cd+LC en comparación con el grupo de cadmio. Los resultados de puntuación histológica de los grupos de riñón, arrojó una disminución estadísticamente significativa en la congestión y el epitelio tubular Se observó degeneración en el grupo tratado con L-carnitina en comparación con el grupo con cadmio. En conclusión, las dosis medias de cadmio tienen efectos tóxicos en el hígado y los riñones de ratas hembras prepúberes en el período subagudo; estos efectos se alivian con L-carnitina.

PALABRAS CLAVE: Cadmio; Riñón; L-carnitina; Hígado.

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