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NEPHROTOXIC EFFECTS OF CADMIUM

Suman Sharma and P.Vijaya*
Department of Zoology and Environmental Sciences, Punjabi University, Patiala-147 002, India.
*(Corresponding Author: E-Mail: pvijaya193@gmail.com)

ABSTRACT
Cadmium is a modern toxic metal and is a by-product of zinc and lead mining and smelting, which are important sources of environmental pollution. In humans, the kidney is recognized as the most critical organ affected by chronic exposure to cadmium. The present study was designed to explore the renotoxic effects of intraperitoneal acute administration of $CdCl_2$ (0.32 mg/kg b.w.) in albino mice. Cd administration led to significant ($P<0.001$) reduction in body weight and kidney weight. Cadmium treatment increased glycogen content but decreased cholesterol content and total proteins when compared with the control group. In parallel, serum urea and creatinine was also elevated in toxic group.

KEYWORDS: Cadmium (Cd), biochemical and kidney.

INTRODUCTION

Cadmium is well-known heavy metal present in the environment and causes serious environmental and occupational hazards to humans (Tarasub *et al*., 2011). Both acute and chronic exposure to cadmium can damage various organs including kidney, liver, testes, lungs and bone depending on the dose, route and duration of the exposure. Cadmium has a very strong ability to accumulate in kidneys and this can be dangerous (Karimi *et al.*, 2012). This metal may interfere with metabolic process via renal cortex resulting in renal dysfunction (Siddique, 2010). Long term exposure may lead to slow progressing physical, muscular and neurological degeneration processes and may even cause cancer (Newairy et al., 2007).The molecular mechanism for describing the toxic effect of cadmium is not well understood, but it is obvious that Cd itself is unable to generate damage and it has been shown that the relationship between Cd and free radicals is indirect (Murugraval and Pari, 2007). Recently it has been reported to be one of the major human carcinogens (Rekha et al., 2011). The extensive mutagenic and carcinogenic spectrum of the metal has warrented the humanity to restrict undesired abuse of the metal so as to save the planet from its dangerous clutches (Acharya *et al.*, 2001). This study was designed to investigate renotoxic effects of cadmium in mice.

MATERIALS AND METHODS

Animals: Albino mice weighing were procured from GADVASU, Ludhiana. They were kept and acclimatized to the laboratory conditions for 15 days under optimal conditions of light and temperature and *ad libitum* access to tap water. The animals were handled with humane care in accordance with the guidelines of the Institutional Animal Ethical Committee.

Chemicals: Cadmium chloride ($CdCl_2$) was bought from S.D FINE CHEM LIMITED, Mumbai. It was dissolved in double distilled water and administered intraperitoneally (i.p.) to mice.

Experimental Design: The mice were divided into two groups. **Group I –** Control animals were given distilled water and kept as control. **Group II** – Mice were administered a single dose of 0.32 mg/kg body weight of cadmium (i.p.). Six mice were autopsied at the intervals of 1, 5 and 10 days post treatment. Kidneys were removed, blotted dry and weighted separately.

Biochemical Studies: Kidney homogenates were prepared with the help of tissue homogenizer in 3 ml of phosphate buffer and used for estimation of glycogen, cholesterol and protein by Montgomery, Zlatkis and Lowery method. On the day of autopsy, 1ml of blood was collected from each mouse under ether anesthesia. Blood was pooled in separate eppendrof tubes, centrifuged (3000 rpm at 2^oC for 15 minutes) and serum was collected in separate clean tubes. It was then used for various biochemical analyses. Serum urea and creatinine were determined by using appropriate kits provided by Reckon Diagnostics P. Ltd., Vadodara, India.

Statistical analysis: The data was analyzed by using Student's *t*-test and two way ANOVA.

RESULTS AND DISSCUSSION

A gradual increase in body weight was observed in control group. But in cadmium treated group, a gradual decrease in weight was observed which may be due to the oxidative stress of metal as suppression in food and water intake was observed. A reduction in kidney weight was also observed in mice treated with cadmium in comparison to control group (Fig.1). This reduction may be attributed to the damaging effects of cadmium on various tissues. Anderson et al. (1999) suggested that organ toxicity can be evaluated by considering the weight of the organs after exposure to toxicant in animal toxicity studies.

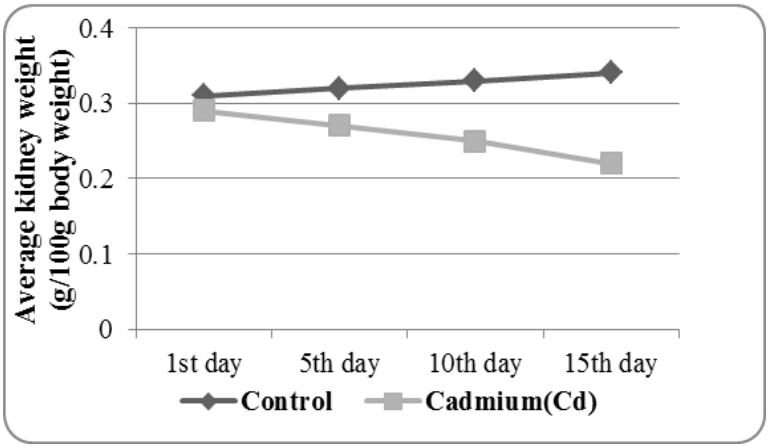

Fig. 1Average Kidney Weight in control and cadmium treated group.

A significant decrease ($p<0.0001$) in glycogen content was observed in kidney of treated group (Fig. 2). Ivanova-Chemishanska (1982) suggested the changes in the levels of glycogen to be either due to increased catabolism of the biomolecules to meet the enhanced energy demand of animals under stress or their reduced synthesis due to impaired tissue function.

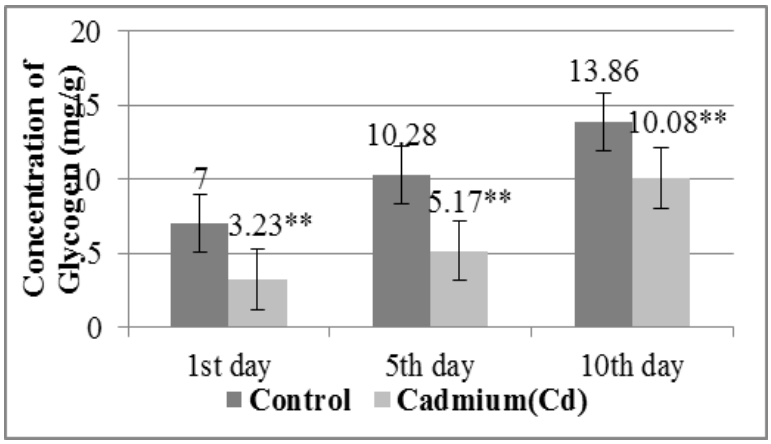

Fig. 2 Comparison of Kidney Glycogen in control and cadmium treated group.
**Highly Significant variations at $p<0.0001$ (Control vs Cd)

Cadmium exposure in the present study caused significant decrease ($p<0.05$) in kidney cholesterol (Fig. 3). These observations are in accordance with the findings of Khan (1980); Purohit *et al.* (1993).

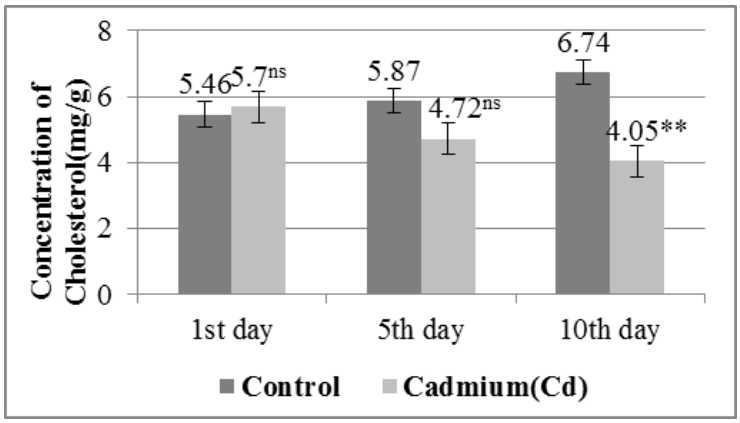

Fig. 3 Comparison of Kidney Cholesterol in control and cadmium treated group.
**Highly Significant variations at p<0.0001 (Control vs Cd)
ns Non Significant variations at p>0.05 (Control vs Cd)

A significant decrease (p<0.0001) in protein content was observed in kidneys of treated mice (Fig. 4) which indicated that the amount of total proteins is adversely affected by cadmium.

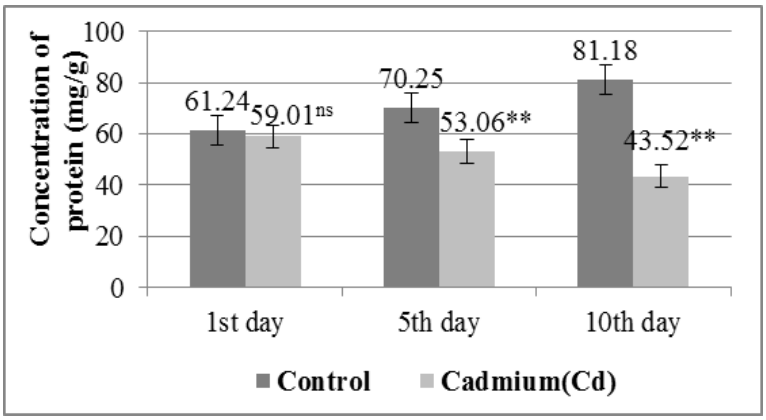

Fig. 4 Comparison of Kidney Protein in control and cadmium treated group.
**Highly Significant variations at p<0.0001 (Control vs Cd)
ns Non Significant variations at p>0.05 (Control vs Cd)

Omata et al. (1978) suggested that the decrease in protein synthesis can be correlated to direct toxic effects of heavy metals. They also believed that ribosomes can be intoxicated by heavy metals which led to their deterioration and reduction in protein synthesis. Swamy et al. (1992) suggested that decrease in total proteins and soluble proteins indicate their metabolic utilization. They also correlated the increase in proteases with decrease of soluble and total proteins. Hypoproteinuria with a simultaneous reduction in albumin is generally interpreted as a nonspecific indicator of toxicity and can be caused by several factors, including reduction in food intake, chronic liver function and renal protein loss (Jadhav et al., 2007).

The renal indices: serum urea and creatinine also reflect kidney function and renal structural integrity. A statistically significant increase (p<0.05) in serum urea and creatinine was observed in cadmium treated group (Fig. 5 and 6). These results are in confirmation with the results of Yiin et al. (1999). Further, heavy metals have been found to cause alterations in the blood biochemical attributes (Sidhu et al., 2005).

According to Gaurav et al. (2010) urea and creatinine levels are used to monitor renal function and their levels will not rise until at least half of the kidney nephrons are destroyed.

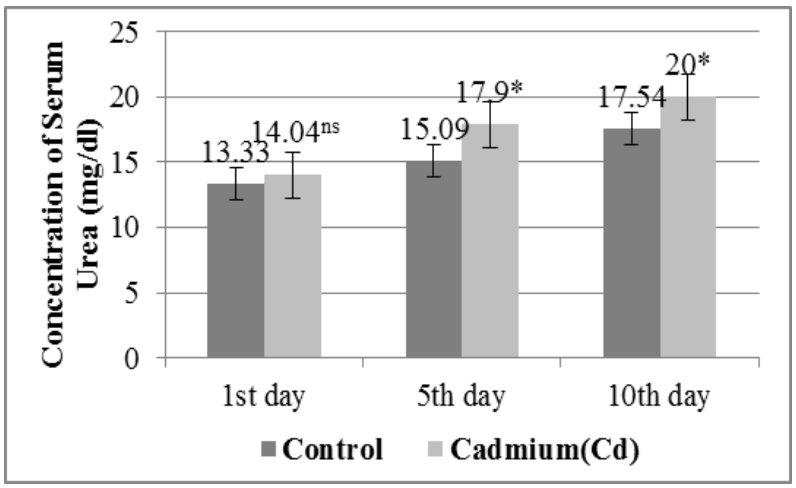

Fig. 5 Comparison of Serum Urea in control and cadmium treated group.
* Significant variations at p<0.0001 (Control vs Cd)
ns Non Significant variations at p>0.05 (Control vs Cd)

According to Lee et al. (2006) the nephrotoxic metal cadmium at micro molar concentrations induces apoptosis of proximal tubule cells within 3-6 hours of exposure which involves a complex and sensitive interplay of signaling cascades involving mitochondrial pro apoptotic factors, calpins and caspases, whose activation is determined by cadmium concentration and the duration of cadmium exposure.

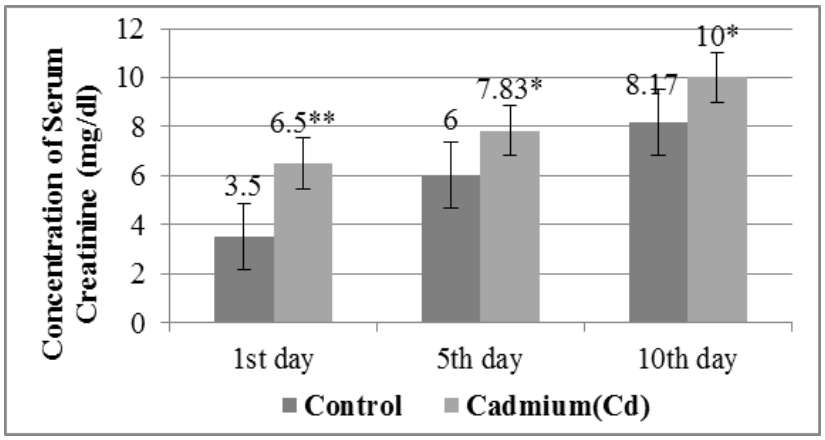

Fig. 7 Comparison of Serum Creatinine in control and cadmium treated group.
**Highly Significant variations at p<0.0001 (Control vs Cd)
* Significant variations at p<0.05 (Control vs Cd)

Also, non-protein nitrogenous (NPS) substances such as urea and creatinine are increased only when renal function is below 30% of its original capacity. Plasma urea appears to be most useful variable for detections of pre-renal causes of renal failure (Kaneko et al., 1997). Cadmium induced nephrotoxicity is thought to be mediated through cadmium metallothionein (Cd-MT) complex synthesized in the liver, released into circulation and taken up by renal proximal tubular cells (Dudley et al., 1985). In fact, when the synthesis of MT becomes insufficient for binding all Cd ions in the

liver, the free Cd ions, present in liver, produce hepatocyte injury and Cd-MT complex is released into the blood stream. The complex is then filtered through the glomeruli in the kidney and taken up by the proximal tubular cells (Sudo *et al.*, 1996). Thus, on its way through the kidney, Cd-MT complex causes injury to cortical region, reaches proximal tubules and causes gradual loss of organ's function (Thijssen *et al.*, 2007). The biochemical changes in the present work might be due to the formation of highly reactive radicals induced by Cd.

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