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RESEARCH ARTICLE

HISTOPATHOLOGICAL EFFECTS OF CADMIUM ON LIVER, KIDNEYS AND TESTIS

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ABSTRACT

Cadmium (Cd) is an important toxic metal which causes on organs such as liver, kidneys and testes of both humans and animals. This paper, therefore, reviewed the histopathological effects of Cd on liver, kidney and testis in experimental animal models: rat and mice. The effects of Cd showed that functional and histological damages by an imbalance of redox status which leads to oxidative stress in liver, kidneys and testes tissues.

INTRODUCTION

Cadmium (Cd) is an important environmental pollutant ranked eighth in the top 20 hazardous substances which is seriously affects some organs in humans and animals, including the liver, kidneys, testis, lungs, and pancreas (Arroyo *et al*., 2012) It has an extremely long half-life (20-30 years), and acts as a cumulative poison causing disorders in the respiratory, renal, liver, skeletal, and vascular systems (Warren *et al*., 2000). Human acute and chronic Cd exposures occur through food, air, water, and smoking and occupational exposure (Duruibe *et al*., 2007). Cd in its elemental form is a soft, silver-white metal. It is a metallic element belonging to group II B of the Periodic Table with atomic number 48, and relative atomic mass 112.41. It's melting and boiling point is 320.9 °C and 765 °C at 100 kPa, respectively. Furthermore, it has a density of 8.64 g/cm3 and soluble in dilute nitric acid and concentrated sulfuric acids (WHO, 2011). The principal uses of Cd are nickel– cadmium (Ni–Cd) batteries, 83%; pigments, 8%; coatings and plating, 7%; stabilizers for plastics, 1.2%; and others, 0.8% (USGS, 2008). Basically there are three possible ways of Cd absorption: Gastrointestinal, pulmonary and dermal.

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The uptake of Cd is depending on the exact dose and nutritional composition and is influenced by the type of diet and the person's nutritional (Jin *et al*., 2002). Cd is not essential for biological function in humans. The first description of the health effects of Cd referred to lung damage after acute inhalation in the 1930's. In the organisms which are exposed to Cd, the highest levels of Cd have been detected in liver and kidney cortex (Kocak, 2006). Therefore, this paper has reviewed by reading different published journals and books: mainly from browsing different journal catalogs on internet like PubMed, Medline, Hinnary and Google scholar to identify relevant articles that has been published related to histopathological effects of Cd on the liver, kidney and testes.

Histopathological Effects of Cd on Liver, Kidneys and Testis: The liver is one of the most important organs in the body, performing a fundamental role in the regulation of diverse processes, among which the metabolism, secretion, storage, and detoxification of endogenous and exogenous substances are prominent (Adewusi, 2010). As the liver, the kidney is the primary organ of drug and xenobiotic execration. Toxic effects of chemicals usually appear primarily in the liver and kidney; and then in testes and other tissues (Abdel-Daim *et al*., 2013). Cd is one of the most toxic environmental and industrial pollutants known to deplete glutathione and protein-bound sulfhydryl groups, which results in enhanced production

of reactive oxygen species (ROS) such as superoxide ion, hydroxyl radicals and hydrogen peroxide (Liu *et al*., 2001). These ROS result in increased lipid peroxidation. Also, Cd exerts its toxic effects via oxidative damage to cellular organelles by inducing the generation of (ROS). Reactions of these ROS with cellular biomolecules have been shown to lead to lipid peroxidation, membrane protein damage, altered anti-oxidant system, DNA damage, altered gene expression and apoptosis (Stohs *et al*., 2000).

Effects of Cd on Liver: Liver is a target organ for the accumulation of Cd and toxicants (Yannai, 1993). Several studies show that Cd cause hepatotoxicity. The hepatotoxicity of this metal is manifested by the disturbance in the activity of some plasmatic enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and lactate dehydrogenase. Several morphological changes in hepatic tissue were noted also after intoxication with Cd (Koyu *et al*., 2006). In addition, the mechanisms of Cd associated hepatotoxicity are mediated by the up regulation of ROS (hydroxyl groups, superoxides and hydrogen peroxides) which cause oxidative damage to lipid contents of membranes.

Accordingly, Table 1 below indicated that the liver weight and body weight show significantly decrease with increasing of Cd doses. The metal treatment caused marked changes in liver such as swelling and massive fatty degeneration in hepatocytes and large vacuoles in cytoplasm. Cytoplasm of hepatocytes showed vacuoles and nuclei with pycontic and staining affinity of nucleus was comparatively poor, due to damage of the hepatic cells after treatment with Cd. There was observed that the damage of hepatic cells increase with increase of dose. Apoptosis was also seen at 10 mg/kg body weight of Cd administration (Gathwan *et al*., 2012). This result was in lined with (Brzoska *et al*., 2003) who reported liver weight of Wistar rats reduced by 8% ($P < 0.05$) following Cd administration. According to (Mohapatra *et al*., 2013) the histopathological alterations in the liver tissue of Cd treated mice manifested by disruption of hepatocytic plates, disintegration of hepatocytes marked by rupture of cell membrane, cytoplasmic vacuolization and pycnosis of nuclei (Figures. 6a and 6b). These results agreed with that of (El-Refaiy, 2013) who showed severe hepatic necrosis, fatty changes, degeneration signs and inflammatory cell infiltrations of Cd administrated rats. The histopathological changes of the liver treated with Cd might be due to the formation of highly reactive radicals and subsequent lipid peroxidation. The accumulated hydroperoxidase can cause hepatoxicity, which is associated with the peroxidation of membrane phospholipids by lipid hydroperoxidase, the basis of hepatocellular damage (Renugadevi, 2010). The results reported by (Jihen *et al*., 2008) also suggested that Cd inhibits protein synthesis and glycogen metabolism in liver of Cd contaminated rats. Some results also shows cellular infiltration and hemorrhagic spots of Cd treated rat liver also found in agreement with acute and chronic effects of Cd documented by (Mohapatra *et al*., 2013). The relatively hemorrhage in Cd treated liver may be due to the congestion of the blood vessels and blood sinusoids through which blood has escaped. Moreover, some scholars reported that a considerable number of Kupffer cells are observed in the sinusoid walls. Proliferation and increased number of Kupffer cells could be indicates there is defense mechanism against Cd treated rats (Omar, 2013) and (El-Refaiy, 2013). It was also observed that the severity of pathological effects in Cd treated rats dependent on the dose and duration of post treatment period (El-Refaiy, 2013). This result was found in agreement with that of (Singh *et al*., 2007) who revealed low dose of Cd (1 mg/kg/day) for 30 days compared to that of Cd administration at a large dose given as 25 mg/kg/day for 20 days and 200 mg/kg/day for 5 days resulted in severe chromosomal damage. The result as well in lined with (Sarojni, 2011) which showed variable intensities of empty spaces (increased intercellular spaces) after one week of Cd treatment (5 mg/kg body weight day) in the albino rats.

Effects of Cd on Kidneys: Once Cd is absorbed into the liver from the digestive tract, it stimulates the synthesis of metallothionein (MT) in the organs and forms MT bound Cd (MT-Cd). The MT-Cd transfers to the kidneys via the blood stream. When MT-Cd reaches the kidney, it is filtered through the glomerular membrane and is reabsorbed in the tubular cells especially in the proximal convoluted tubules (Nordberg, 1984). MT-Cd shows strong nephrotoxicity after pinocytosis and accumulation in the proximal tubular cells. This is found to be in agreement with a large number of studies who noted similar pronounced changes in the renal tissues under Cd effect (Jihen *et al*., 2008). (Mahran, 2011) Indicated that significant Cd Pathological changes on the kidney structure in rat kidney which are obtained after 6 weeks of administration of 50 mg Cd/l. After 12 weeks, they revealed signs of tubular necrosis and fibrosis, swelling renal glomeruli and decreases of the glomerular space with some capsular fibrosis after eight weeks of exposure to Cd when compared to control groups which shows normal structure of renal glomeruli, the proximal and with distal convoluted tubules. In addition, the kidney section showed that narrowing of the capillary lumen and swelling of the capillary endothelium of the glomeruli, injured brush border microvilli and swollen mitochondria in the proximal convoluted tubular cells.

These results were in agreement with that of (Omar, 2013). Following Cd intoxication in rat results narrowing of capillary lumina which is contributes to the hypertension. Hypertension may result from Cd induced changes in vasculature, the rennin-angiotensin system, or renal ion transport process (Puri, 2003). The author also stated that the effects of Cd on proximal cell were loss of brush border, nuclear membrane damage, chromatin condensation, swelling of the mitochondria with regression of mitochondrial crestae, degranulation and disintegration of protein synthesizing structures such as rough endoplasmic reticulum, increased number of lysosomes and ultimately cell death. These changes were attributed to the reduction of the surface density of microvillus membrane per unit cell volume to Cd contaminated rats. Cd also inhibits the vacuolar hydrogen ion-ATPase and endocytosis in proximal tubule brush border of rat kidney and this may inhibit endocytosis of filtered proteins and impair vesicle mediated recycling of some membrane (Herak-Kramberger *et al*., 1998). The histoarchitectural changes observed in the above result was found in agreement with the report of (Mohapatra *et al*., 2013) that showed lesions in the cortex and medulla of kidney of Cd treated albino rats. The effect of Cd in this study showed that cuboidal epitheliums of proximal and distal convoluted tubules were affected loss of cellular integrity. In addition, there was significant distortion of Bowman's capsules with disorganized glomeruli with cellular infiltration and hemorrhagic spots (Figure. 1a).

Table 1. Effect of Cd on body weight of male mice (Source: (Gathwan *et al*., 2012))

Group	Initial Body Weight (gm)	Final Body Weight (gm)	Percentage Change
Control	31±2.1	34.36±3.08	8.34
Low dose	32±3.3	30.84±2.8*	-3.62
Moderate dose	32.4±2.2	29.6±2.19**	-8.64
High dose	31.6±3.07	28.6±2.06***	-9.49

Value represents mean ± S.D., n=5 in each group
The P-value was calculated between the test group and control group
* Non-significant different from the control value p>0.05
** Significant different from the control value p<0.05
*** Highly significant different from the control value p<0.001

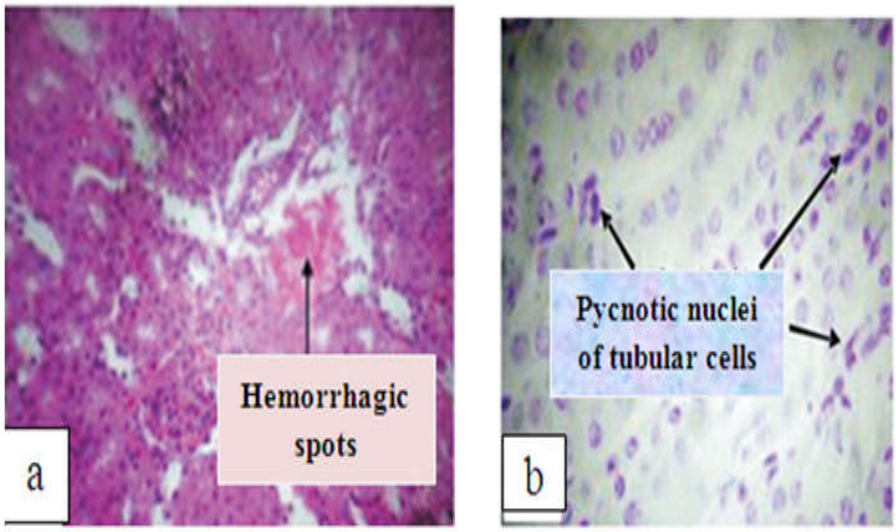

Figure 1. Photomicrographs showing albino rats kidney section exposed to Cd with x400 magnification (a) Hemorrhagic spots; and (b) Pycnotic nuclei of tubular cells (Adopted from (Mohapatra *et al*., 2013))

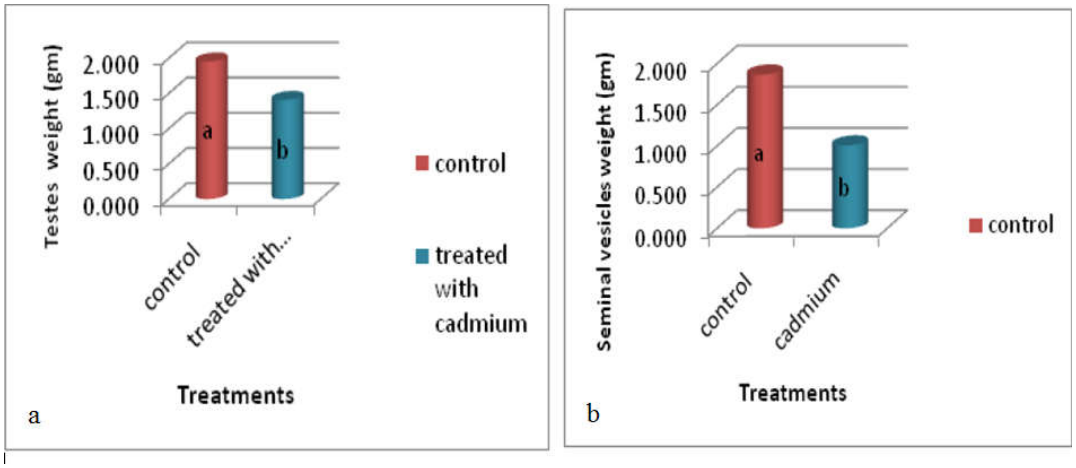

Figure 2. Bar graph showing effects of administration of CdCl2 on the weight of the reproductive organs of the male rats (a) testes (gm) and (b) Seminal vesicles (gm) (Source: (Saeed, 2013)).

Table 2. Effect of administration with 20 ml CdCl2 (200 mg/1L body weight) during the 4 weeks period of the experiment on certain sperm parameter of the male rats (Source: (Saeed, 2013))

Treatments sperm parameters	control (distill water for 4 weeks	CdCl2 (200mg/1L body weight)
sperm concentration (millions/ml)	96.750±5.218 a	42.500±4.233 b
Progressive sperm motility (%)	40.750±2.175 a	8.500±1.688 c
Non-progressive sperm motility (%)	32.750±1.109 a	21.667±2.929 b
Immotile sperm (%)	34.000±7.246 b	69.833±4.254 a
Sperm morphology (%)	54.500±3.329 b	1.667±1.667 c

Differences a, b, c are significant (p<0.05) to compression rows.

Majority of the cells had paler cytoplasm due to vacuolization and disrupted nuclei which was indicated by the presence of scanty chromatin. It was observed that the severity of the histopathological effects dependent on the duration of post treatment period. The result also showed light pink staining of the nuclei in the tubular cells and collecting ducts of treated mice after Feulgen's reaction indicated the possibility of DNA damage by Cd (Figure. 1b). Similar results have been reported by (Garba *et al*., 2007) who noticed histopathological lesions which ranged from severe multifocal congestion, cystic dilation in the medulla, proteinaceous releasing within ducts, and interstitial mononuclear cellular infiltration with hemorrhage in the rat kidney. These degenerative changes in kidney may be due to alteration of metabolic activity or due to metal ion-renal tissue interaction.

Furthermore, (Omar, 2013) reported that related results that showed an enlargement of renal glomeruli and epithelial cells of the tubules; and desquamated to their lumen in the cortical part of the rat kidney. Mononuclear cell infiltrates were observed in some places of the medullary part of the kidney, and at these sites the inflowing cells blurred the tubular structure. Other studies of Cd treated albino rats showed destruction of some cells of the proximal and distal tubules, and the collecting tubules exhibited extensive degeneration and cytoplasmic vaculation (Hefny, 2004). In general, the nephrotoxicity of Cd mainly affects renal glomerulus and renal tubules. This result is supported by (Jemai *et al*., 2010) who found that Cd affected the glomerular capillaries in favour of Bowman's space, atrophy of some glomerulus. In addition, histopathological studies revealed that the toxicity of Cd in the kidney affects proximal tubular necrosis, apoptosis, and tubular degeneration. On its way through the kidney, mainly in the cortical region, Cd leads to loss of kidney function. These damages may be due to the accumulation of free radicals of MT-Cd or free Cd as the consequence of increased lipid peroxidation in renal tissues of animal models (Renugadevi, 2009).

Effects of Cd on Testis: Testis has high sensitive cellular composition of the spermatogenic epithelium and high rate of mitotic activity which makes it more vulnerable to environmental and occupational hazards than other tissue. It has also been suggested that the human male fertility is even more sensitive, as the output of human sperms is few times less than other mammals in terms of the number of sperms produced per gram of tissue. So, any factor identified in laboratory studies as a reproductive hazard is also expected to exert detrimental impacts on the human reproductive performance (Ige *et al*., 2012). Therefore, there are many studies goes to the effect of Cd exposure on testis of experimental models such as rats and mice. Results reported by (Saeed, 2013) were showed that the effects of Cd on sperm parameters, histological and hormonal changes in testes of mature rats. According to the investigator the following results have been justified. Exposure to Cd in figure 2a and 2b below showed that statistical significant ($P< 0.05$) decreasing of body weight in testis and seminal vesicle, respectively. In addition, the results of this study revealed that Cd administration for 4 weeks duration significantly decreased sperm concentration, sperm motility, and sperm morphology (Table2). The observation of this study was agreed with the report of (Ige *et al*., 2012) that showed administration of Cd impairs testicular and a significant decrease in the sperm count, sperm motility and increase in the fraction of morphologically abnormal sperms. The significant reduction in sperm concentration sperm motility and sperm morphology observed in this result following Cd administration may be associated to that of impairment of spermatogenesis (Pasqualotto *et al*., 2003). The results reported by (Saeed, 2013) also showed that there was a significant decrease in the level of testosterone hormone in the treated group, while highly significant ($p\leq0.01$) increase in the follicle stimulating hormone (FSH) in the treated group when compared to the level of the hormone in the control group. On the other hand, a significant ($P<0.05$) decrease in the level of luteinizing hormone (LH) in the treated group.

The above idea was also found in agreement with that of (Mohamed *et al*., 2014) who proved the testicular sections exposed to Cd showed that multiple shrunken tubules and have different shapes and diminished layers of germinal epithelium. Some tubules were also resting on an irregular basement membrane. In the administration of Cd wide lumina and wide interstitial spaces were noticed. The lumina of some tubules were filled with degenerated germ cells. In addition, the result is in agreement with that of testis exposed to Cd in the dose- and time range (0-40mg/kg) which causes a gradual damage to the histology of the testes. These damages were characterized by destruction of germ cells and STs, vascular congestion, focal necrosis of tissue, reduction of spermatocytes, pyknosis, destruction of nucleus, oedema in the STs and interstitial tissue (Obianime, 2009). Similar study carried out in Cd-treated Wistar rat was also showed total necrotic change in the STs with severely disorganized germinal epithelium. It also showed absence of clearly defined basement membrane and **e**xaggerated interstitial space with atrophied Leydig cells (Olufemi *et al*., 2014). Furthermore, observations presented in testes treated with Cd damage the sertoli cell communications with the developing germ cells which is the spermatocytes. In these places the cytoplasmatic membrane of both cells were extensively dilateted; thereby vacuolar spaces were present between these cells. Cd impact on Sertoli cell communication may be due to its effects on actin filaments in places where connection with germ cells. Furthermore, exposure to Cd in the above result also showed that a pronounced alteration of spermatogenic process with dramatically reductions of spermatozoa produced in the lumen of the STs sections and a decrease of the intratubular tissue volume. This result is in lined with that of (Mohapatra, 2013) who found significant histopathological abnormalities in testes. These abnormalities are distortion of the STs accompanied by disorganization of cells and devoid of sperms and cytoplasmic vacuolization, nuclear fragmentation and nuclear pycnosis in the spermatogonia, spermatocytes, spermatids and sertoli cells are more pronounced in Cd treated mice when compared to control groups which show normal spermatogonia, spermatocytes, spermatids, sperms and interstitial cells. Testicular damage in this regard may be attributed to compete of Cd with zinc in zinc containing enzymes and decreased activity of testis-specific enzymes which leads to detrimental effects on testicular function (Ekhoye, 2013).

Conclusion and Recommendation

The review concluded that Cd intoxication have shown histological impairments in the selected organs of experimental animal models: liver, kidneys and testes. The effects of Cd causes histological changes in the liver which are

characterized that disintegration of hepatocytes, rupture of hepatic cell membrane; vocalization of cytoplasm, pycnosis of nuclei and accumulation of kupffer cells. Moreover, the Cd also changed the activities of some antioxidative enzymes in the liver. As well, Cd intoxicated kidneys exhibited histopathological changes which was evidenced by tubular necrosis and fibrosis, shrinking of the glomeruli, pycnotic nuclei of tubular cells, and hemorrhaging. In testes, the review suggested that Cd administration induced damage which leads to impair the functions of sperm parameters and cause histological alterations such as widening of the central STs lumen, prominent germ cells necrosis, vacuoles within the tubules, abundant sertoli cells and narrow diameters of STs. The current paper recommended that researchers should address regarding the exact mechanism of Cd inducing in the tissues.

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