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Histomorphological and ultrastructural renal toxic effects of environmentally relevant concentration of cadmium in rabbit

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Abstract

Objective: The present work aimed to study the histological and ultrastructural effects of cadmium (Cd) on the kidney of rabbit. Materials and Methods: 2 groups of Egyptian adult rabbits were used for this study (4-5 rabbits for each). One group was used as a control and the other group (experimental) was exposed to cadmium intake in a dose of 100mg $Cdcl_2$/L in drinking water for 24 weeks. The animals were killed by cervical dislocation and kidney specimens were taken, fixed and processed for light and electron microscopic examination. Results: The cadmium had adverse effects on the kidney especially the proximal convoluted tubules and the glomerulus. The distal convoluted tubules showed no effects. The proximal tubules showed loss of the basal infoldings, the mitochondria appeared swollen with damaged transverse cristae and some appeared vacuolated. Abundant amount of lysosomes was seen in

the cytoplasm. The nucleus appeared irregular in shape and pyknotic in some cells. The apical border of the cells showed disordered and less extensive microvilli. The juxtaglomerular cells in the wall of the afferent glomerular arterioles were loaded with abundant amount of renin granules. The podocytes in the glomerulus appeared disorganized with pyknotic nuclei and degeneration in their pedicles. Conclusion: Cadmium has adverse effects on the kidney even at low concentration. These effects are exclusive on the proximal part of the nephron and present structural changes. Extreme attention must be taken to prevent the release of cadmium to the environment.

Keywords: Cadmium, Kidney, Histology, Ultrastructure.

Introduction

Cadmium (Cd) is a relatively rare element that occurs naturally in rocks together with other heavy metals or emitted into the air through the process of volcanic emissions. It became commercial in the 20th century due to agricultural and industrial applications [1]. Cadmium together with other heavy metals has been considered a main thread of human health [1, 2]. Most of the available epide -miological information obtained from occupationally exposed populations in highly contaminated areas has established that excessive Cd exposure produces adverse health effects including nephrotoxicity [3, 4]. Meanwhile, not only occupationally exposed workers but also environmentally exposed population can experience moderate to severe health problems due to Cd toxicity and a mild glomerular and tubular kidney dysfunction results [4, 5]. Cadmium is released into the environment mainly through industrial activities including non-ferrous metal production, waste incineration and fertilizer production. Dietary Cd intake mainly through consumption of rice from Cd contaminated environment contributed to the high level of blood Cd [6]. With the chronic low level patterns of exposure that are common in human, the primary target of toxicity is the kidney where Cd causes a generalized dysfunction of the proximal

tubules [7]. The Cd is excreted slowly and the biological half-life is estimated to be 16-38 years [8]. Excessive renal accumulation of Cd causes well defined morphological and ultrastructural pathological changes resulting in functional changes such as proteinurea, glycosuria, polyuria and hypercalciuria [7, 9]. Most of the previous studies were going towards the functions of the kidney after Cd intoxication and the use of reliable biomarkers to assess Cd nephrotoxicity [10, 11, 12, 13, 14, 15]. Little is known about the effect of long term low-level Cd exposure on the ultrastructure of the kidney [16]. So, the present work aimed to study the effect of environmentally relevant dose of Cd on the histology and ultrastructure of the kidney in rabbit.

Materials and Methods

Two groups of Egyptian adult rabbits (the weight ranged from 1.5-2kg) were used for this study (4-5 rabbits for each group). One group (experimental) was exposed to Cd intake in the form of cadmium chloride ($Cdcl_2$). As ingestion is the most important route of human exposure [17], the exposure via the drinking water was chosen. The dose of 100mg $Cdcl_2$/L drinking water was chosen according to average human intake data, soil cadmium concentrations from contaminated sites [1, 18, 19]. To be environmentally relevant concentration of Cd, the animals were exposed for 24 weeks [17]. So, the kidneys of the rabbits were exposed for 24 weeks to 100mg $Cdcl_2$/L in the drinking water.

The other group of animals was used as a control and taken drinking water without cadmium. The rabbits were housed and provided with access to standard rabbit chow and tap water. The animals were killed by cervical dislocation.

A midline abdominal incision was performed and the kidneys were dissected out and processed for light and electron microscopic examination. For light microscopic examination, the kidneys were fixed in 10% neutral formol-saline for 24 hours and were processed to prepare 5-micron thick paraffin sections. Paraffin sections were stained with periodic-acid Schiff (PAS) which stains basal lamina and the brush

border of the proximal convoluted tubules and also positive for the granules of the juxtaglomerular cells [16, 20] and the cytoplasmic lysosome-protein bodies of the endocytic process in the proximal convoluted tubules [21]. Also, the sections were stained with Masson trichrome which stains the brush border (green) [22].

For electron microscopic examination, the cortex was cut into small pieces and immediately fixed in 2.5% glutaraldehyde buffered with 0.1M phosphate buffer at PH 7.4 for 2 hours at 4C° and then washed with the phosphate buffer, post fixed in 1% osmium tetroxides in the same buffer for one hour at 4 C°. After washing in phosphate buffer, specimens were dehydrated with ascending grades of ethanol and then were put in propylene oxide for 30 minutes at room temperature, impregnated in a mixture of propylene oxide and resin (1:1) for 24 hours and in a pure resin for another 24 hours. Then, the specimens were embedded in Embed-812 resin in BEEM capsules at 60C° for 24 hours [23, 24]. Semi-thin sections of about one micron thick were obtained by glass knives and stained with 1% toluidine blue and examined by light microscopy. Ultrathin sections of about 50-70nm thick were cut using diamond knives and mounted on a copper grids, stained with uranyle acetate and lead citrate [23, 24] and examined using a JEOL JEM 1010 transmission electron microscope in Electron Microscope Research Laboratory (EMRL) of Histology Department, Faculty of Medicine, Zagazig University.

Results

In control animals the renal cortex examined by the light microscopy showed the renal corpuscle, the proximal and distal convoluted tubules. The proximal tubules have large cuboidal cells with large round nuclei and prominent nucleoli. The lumen is filled with the brush border formed by the microvilli. The distal tubules have a wide lumen due to absence of the brush border (Fig.1, 2 &3).

By electron microscopic examination, the cells of the proximal convoluted tubules showed numerous basal infoldings which extend into the cytoplasm with intervening

mitochondria. The mitochondria were found numerous, elongated and distributed all over the cytoplasm, mostly at the base. A small amount of lysosomes was seen and some pinocytotic vesicles were observed. The nucleus was found large, oval and central. The apical border showed an extensive amount of microvilli which were found to close the lumen of the tubule (Fig. 4). The distal convoluted tubules showed their cells with basal infoldings and many elongated mitochondria. The lumen showed scanty or no microvilli. The nucleus was large and oval (Fig.5). The afferent glomerular arteriole showed its lumen with endothelial lining. Within the wall of the arteriole, the juxtaglomerular cells were observed and were found to contain electron dense renin granules (Fig.6). The renal corpuscles were observed and showed the parietal layer of Bowman's capsule, urinary space and glomerular capillaries. The capillaries showed the lumen containing red blood cells and lined by endothelial cells. A podocyte was found near the capillary with its processes (pedicles) grasping the capillary (Fig.7).

In animals exposed to Cd intake by light microscopic examination, the renal cortex showed the renal corpuscles, the proximal and distal convoluted tubules. Near the renal corpuscles there were afferent arterioles with many juxtaglomerular cells in their walls and these cells were found to contain abundant amount of granules (Fig. 8, 9). The proximal convoluted tubules showed many small dark granules representing the lysosomes. The nuclei were found irregular in shape and some were pyknotic. The cells showed disordered brush border of microvilli (Figs. 8-10).

By electron microscopic examination, the cells of the proximal convoluted tubules showed loss of the basal infoldings with decrease in the number of mitochondria. The mitochondria appeared swollen with damaged transverse cristae and some appeared vacuolated. In some cells damaged mitochondria appeared among normal mitochondria. Abundant amount of electron-dense lysosomes was seen in the cytoplasm. The nucleus appeared irregular in shape and in some cells, the nucleus

appeared pyknotic. The apical border of the cells showed disordered and less extensive microvilli (Fig. 11-14). The distal convoluted tubules showed no changes. The cells showed basal infoldings and many elongated mitochondria. The apical border of the cells showed scanty microvilli (Fig. 15). The afferent arterioles were found to be lined with endothelial cells and contained many juxtaglomerular renin secreting cells in their walls. These cells were loaded with abundant amount of electron-dense granules (Fig. 16). The glomerulus showed one of the capillaries containing red blood cells. Some of the podocytes appeared disorganized with pyknotic nuclei and degeneration in their pedicles (Fig. 17).

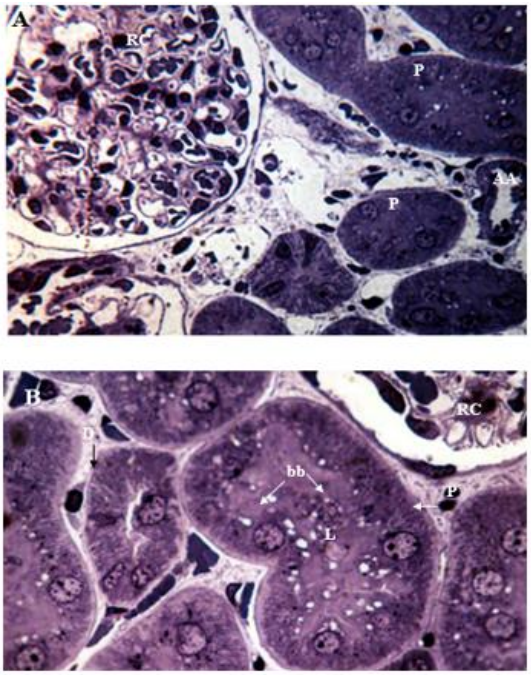

Fig. (1): Two photomicrographs of semi-thin sections in the renal cortex of control rabbit: (A) It shows the renal corpuscle (RC) afferent arteriole (AA) and proximal convoluted tubules (P). (X800) (B) It shows part of the renal corpuscle (RC), proximal (P) and distal (D) convoluted tubules with a higher magnification. The proximal tubules have large cuboidal cells with large round nuclei and prominent nucleoli. The lumen (L) is filled with the brush border (bb) formed by the microvilli. The distal convoluted tubule has a wide lumen due to absence of brush border. (X 2000) (Toluidine blue).

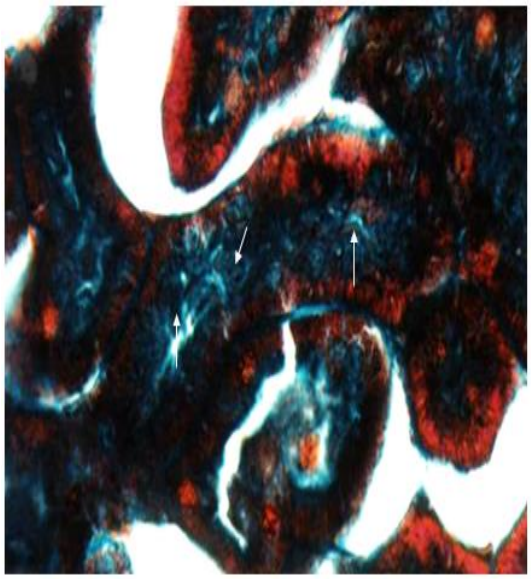

Fig. (2): A photomicrograph of sections in the renal cortex of control rabbit showing the proximal convoluted tubules with their basal lamina (arrow heads) and the brush border (arrows). (PASX2000)

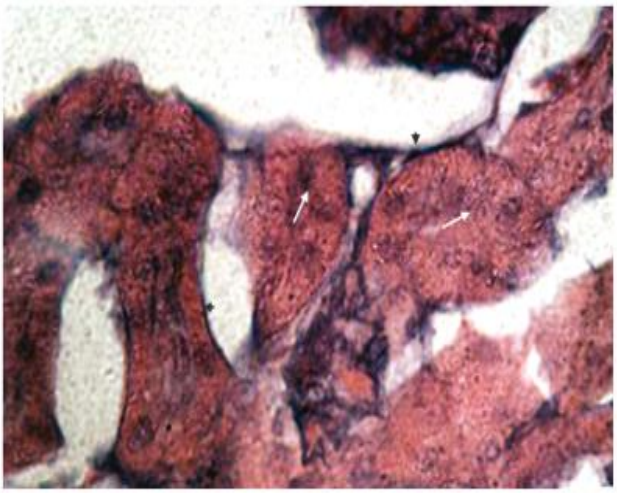

Fig. (3): A photomicrograph of sections in the renal cortex of control rabbit showing the proximal convoluted tubules with their epithelial cells are covered with a brush border of dense microvilli (arrows), (stained green). (Masson trichrome X2000).

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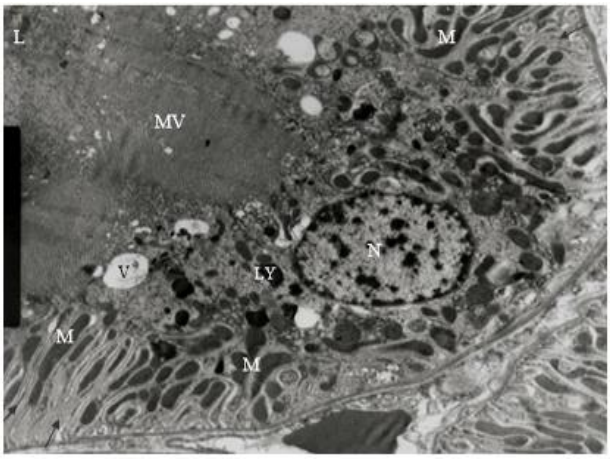

Fig. (4): An electron photomicrograph of ultrathin section in the renal cortex of control rabbit showing part of the proximal convoluted tubule. The cell of the tubule shows numerous basal infoldings (arrows) which extend into the cytoplasm with intervening mitochondria (M). The mitochondria are numerous, elongated and distributed all over the cytoplasm, mostly at the base. Small amount of lysosomes (LY) are seen. Some pinocytotic vesicles (V) are seen near the apex. The nucleus (N) is large, oval and central. The apical border shows extensive amount of microvilli (MV) which nearly close the lumen (L) of the tubule. (X9000)

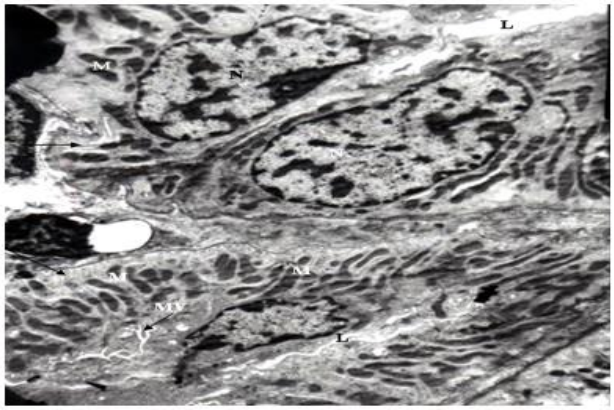

Fig. (5): An electron photomicrograph of ultrathin section in the renal cortex of control rabbit showing two portions of distal convoluted tubules in a transverse section. The cells lining the tubules show basal infoldings (arrows) with many elongated mitochondria (M) in between. The lumen (L) shows scany or no microvilli (MV). The nucleus (N) is large and oval. (X 9000)

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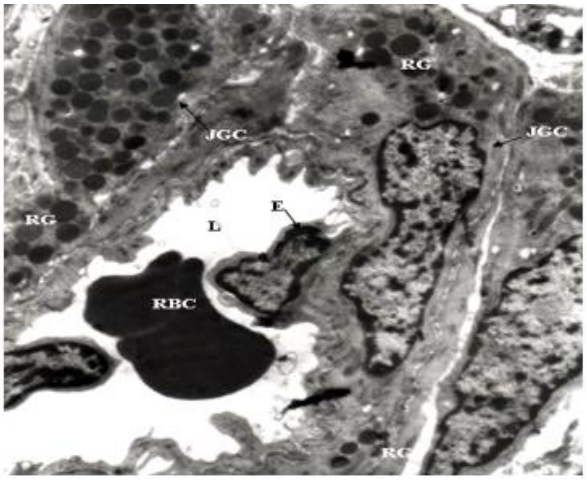

Fig. (6): An electron photomicrograph of ultrathin section in the renal cortex of control rabbit showing the afferent glomerular arteriole. The lumen (L) of the arteriole shows red blood cells (RBC) and endothelial cell lining (E). Within the wall of the arteriole, there are juxtaglomerular cells (JGC) containing electron-dense renin granules (RG). (X9000).

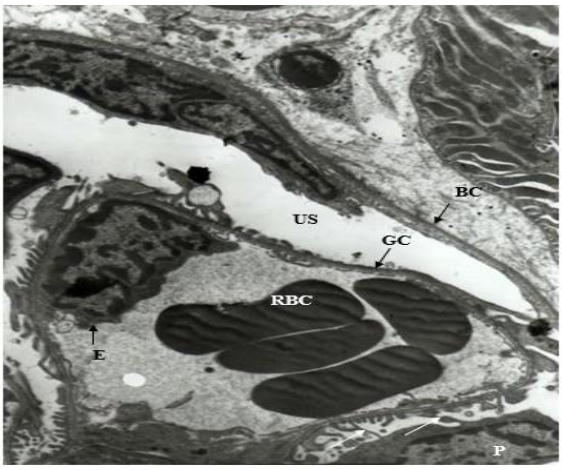

Fig. (7): An electron photomicrograph of ultrathin section in the renal cortex of control rabbit showing part of the renal corpuscle including the parietal layer of Bowman's capsule (BC), urinary space (US) and glomerular capillary (GC). The capillary shows its lumen containing red blood cells (RBC) and lined by endothelial cells (E). A podocyte (P) is seen near the capillary with its processes (pedicles) grasping the capillary (arrows). (X 9000)

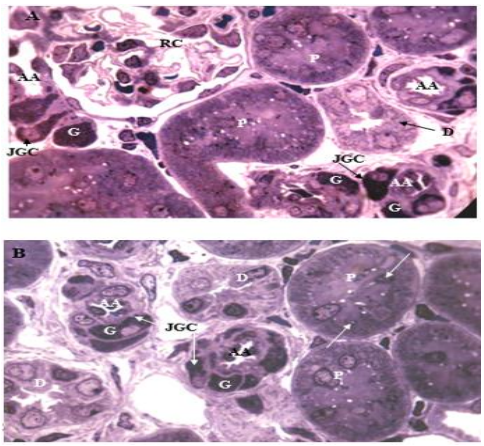

Fig. (8): Two photomicrographs of semi-thin sections in the renal cortex of rabbit exposed to cadmium intake: (A) this section shows part of the renal corpuscle (RC), proximal (P) and distal (D) convoluted tubules. Near the renal corpuscle there are afferent arterioles (AA) with many juxtaglomerular cells in their walls and contain abundant amount of granules (G). (B) This section shows 2 afferent arterioles with many juxtaglomerular cells containing granules (G). In the proximal tubules (P) the nuclei are irregular in shape and some are pyknotic (arrows). (Toluidine blue X 2000)

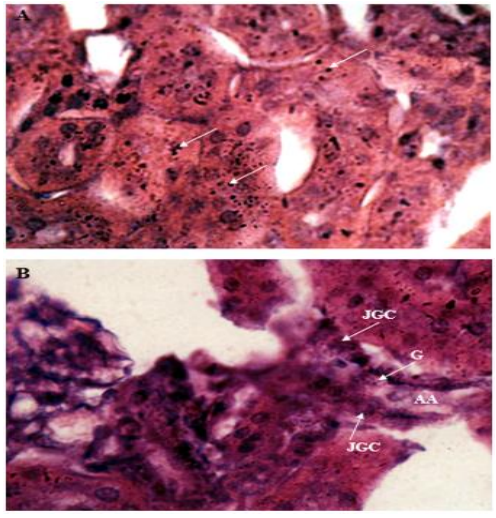

Fig. (9): Two photomicrographs of sections in the renal cortex of rabbit exposed to Cd intake: (A) This section shows the proximal convoluted tubules with many small dark granules representing the lysosomes (arrows). (B) This section shows the afferent arteriole (AA) with juxtaglomerular cells (JGC) in its wall and contain granules (G). (PAS X 2000)

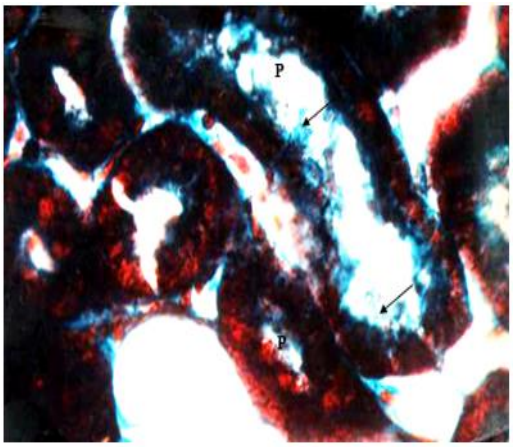

Fig. (10): A photomicrograph of sections in the renal cortex of rabbit exposed to Cd intake showing the proximal convoluted tubules (P) with disordered brush border of microvilli (stained green), (arrows). (Masson trichrome X 2000)

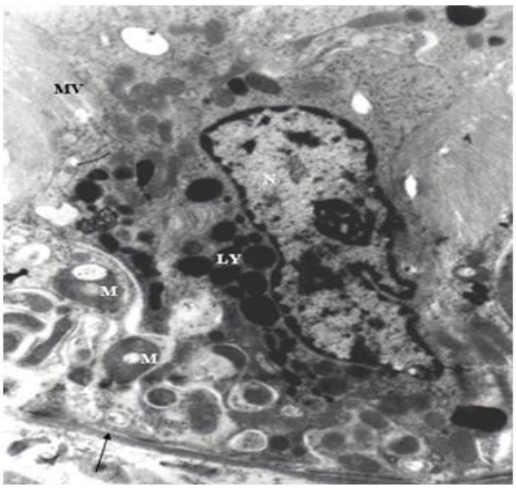

Fig. (11): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing one of the epithelial cells of the proximal convoluted tubule. The cell shows loss of the basal infoldings (arrow) with decrease in the number of mitochondria. The mitochondria (M) appear swollen with damaged transverse cristae. Some of the mitochondria appear vacuolated. Abundant amount of electron-dense lysosomes (Ly) are seen in the cytoplasm. The nucleus (N) appears irregular in shape. The apex of the cell shows less extensive microvilli (MV). (X 13000)

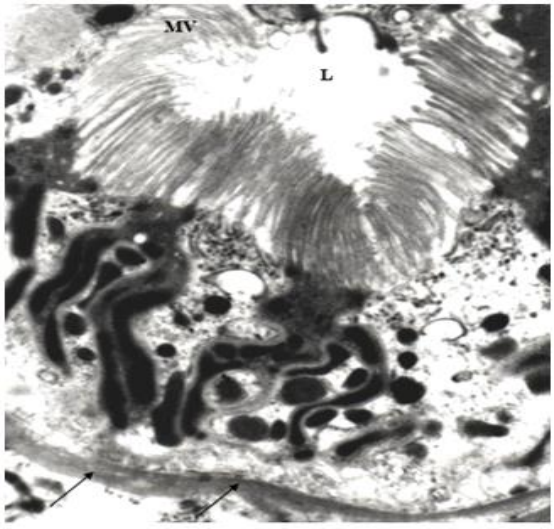

Fig. (12): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing the cells of the proximal convoluted tubule surrounding the lumen (L). The apical border of the cells shows disordered and less extensive microvilli (MV). Also the cells show loss of the basal infoldings (arrows). (X 13000)

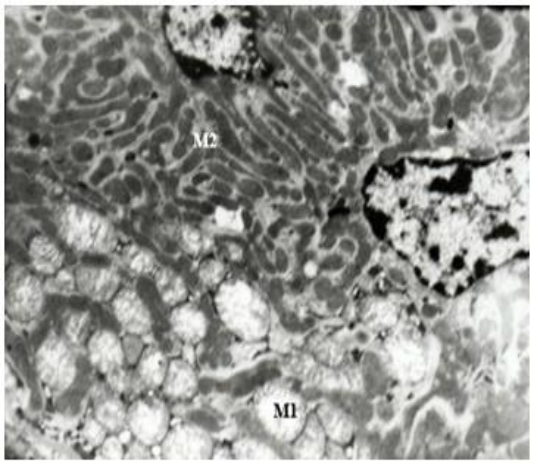

Fig. (13): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing cells of the proximal convoluted tubule with damaged mitochondria (M1) among normal mitochondria (M2). The damaged mitochondria are swollen with loss of transverse cristae and even some appear vacuolated. (X 12000)

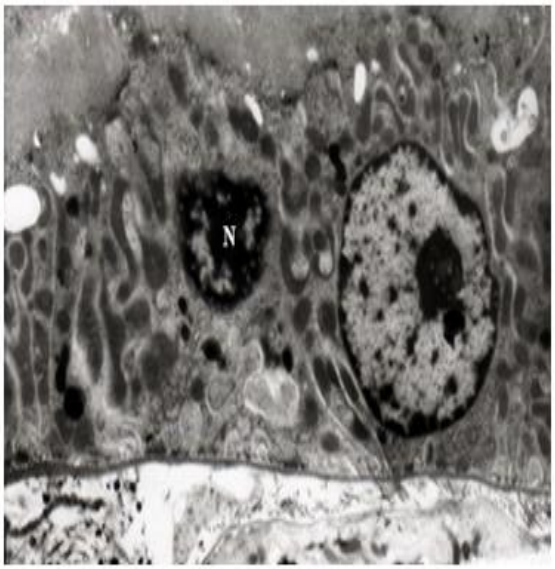

Fig. (14): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing 2 cells of the proximal convoluted tubule. One of the cells shows pyknotic nucleus (N) in addition to lack of the basal infoldings. (X 9000).

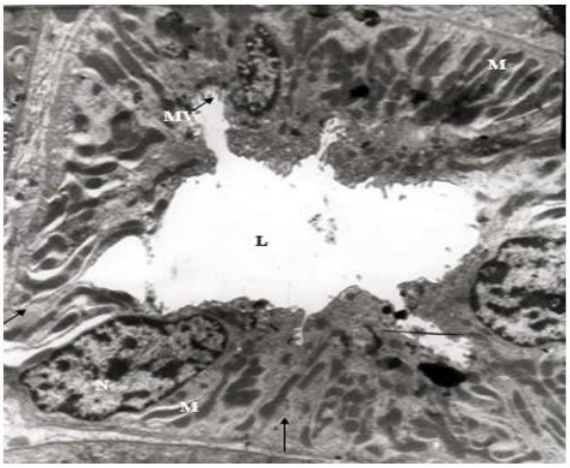

Fig. (15): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing the distal convoluted tubule in a transverse section with its lining cells surrounding the lumen (L). The cells have basal infoldings (arrows) and many elongated mitochondria (M). The nucleus (N) is large and oval. The apical border of the cells shows scanty microvilli (MV). (X 9000).

Fig. (16): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing afferent glomerular arteriole in a transverse section showing the lumen (L). The arteriole is lined by endothelial cells (E) and contains many juxtaglomerular renin secreting cells (JGC) in its wall. These cells are loaded with abundant amount of electron-dense renin granules (RG). (X 7000)

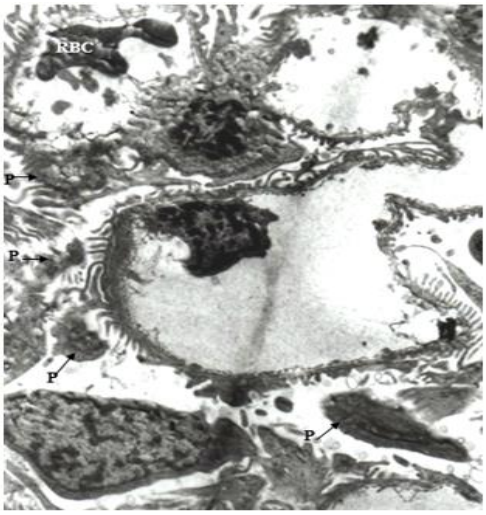

Fig. (17): An electron photomicrograph of ultrathin section in the renal cortex of rabbit exposed to Cd intake showing the glomerulus. One of the capillaries contains red blood cells (RBC). Some of the podocytes (P) appear disorganized with pyknotic nuclei and degeneration in their pedicles. (X 9000)

Discussion

In the present study, exposure to cadmium (Cd) intake even on its environmental relevant dose (100 mg $Cdcl_2$/L) had adverse effects on the renal cortex especially the proximal part of the nephron including the glomerulus and the proximal convoluted tubules. The distal convoluted tubules showed no effects on Cd exposure.

The proximal tubules showed loss of the basal infoldings. This is in accordance with Wu etal. [25] Who found that the basement membrane became significantly thinner than that of the control and the infoldings of the plasma membrane were not well developed. In the present study, the mitochondria of the proximal tubules were decreased in number and appeared swollen with damaged transverse cristae and some appeared vacuolated. This is similar to that found by Kanglei etal. [26] Who observed vacuolated mitochondria and damaged inner membrane and Liu etal. [27] Who observed swelling of the mitochondria on chronic Cd administration. Cheville [28] added that, the mitochondrial swelling may reflect the entry of solutes and water into the mitochondrial matrix. In some cells of the present study the damaged mitochondria appeared among the normal mitochondria and this may indicate that on chronic Cd exposure, not all the mitochondria are damaged at the same time but there is gradual increase in the number of damaged mitochondria.

Also, abundant amount of electron-dense lysosomes were observed in the cells of the proximal convoluted tubules. This is in agreement with Wu et al. [25] who found numerous small and large concretion spherites with highly electron-dense material in the cytoplasm of many cells. Most of the Cd in plasma is bound to protein including albumen, metallothionein and other high or low molecular weight proteins [29]. Cadmium-metallothionein complex is filtered through the glomerular membrane and transported to renal tubular cells from blood. [30] The filtered cadmium-metallothionein is rapidly and completely re-absorbed and accumulated in the kidney, particularly in the proximal renal tubule in the cortex. [31] In renal cells,

cadmium-metallothionein enters the lysosomes, which release the cadmium into the cytosol and degrade the metallothionein into amino acids. Cd not bound to metallothionein can injure the renal tubules [29]. So, the lysosomes are important for breaking down cadmium-metallothionein that entered the proximal tubular cells. When more Cd enters the cells, more lysosomes are needed to deal with it [16].

In the present study the nucleus appeared irregular in shape and some cells had pyknotic nuclei. This is in accordance with Hamada et al. [32] who found that, Cd absorbed by proximal tubular cells rapidly reaches to the nuclei and affects nuclear as well as cytoplasmic metabolism. Liu et al. [27] Tanimoto et al. [33] and Kaur et al. [34] observed atrophic and pyknotic nuclei of the proximal tubules upon Cd administration. In the present study the apical borders of the proximal tubular cells showed disordered and less extensive microvilli. This is in agreement with Thophon et al. [35] and Wu et al. [25] who found disorganization of the brush border and the number of microvilli adjacent to the microvillus region are decreased. This is explained by Foulkes and Blank [36] who found that, one of the target sites of Cd in the proximal tubular cells is at the brush border and Herak-Kramberger and Sabolic [37] who found that, the Cd has a direct damage to the integrity of the proximal tubular cell plasma membrane and this may cause shortening and loss of microvilli. Shortening and focal loss of the brush border of microvilli in the proximal tubular cells indicates reduction of the reabsorptive surface due to damaged integrity of brush border membrane and may contribute to the reabsorptive and secretory defects [38, 39].

The afferent arterioles in Cd exposed animals of the present study were found to contain many juxtaglomerular renin secreting cells. These cells were loaded with abundant and larger amount of renin granules in comparison with that of the control animals. Janqueira and Carneiro [40] mentioned that once renin enzyme becomes liberated into the blood stream, it acts on the plasma globulin, angiotensinogen and converts it into a decapeptide called angiotensin I. This peptide is inactive and as a

result of a converting enzyme, it becomes an active octapeptide, angiotensin II that causes arteriolar vasoconstriction and thereby raises the blood pressure. In the present study continuous secretion of abundant amount of renin enzyme especially on chronic cadmium exposure may cause sustained hypertension. This is in agreement with Perry and Elanger [41] who found that, the potential mechanism for the hypertension in Cd exposed rats involves the increased activity of the renin-angiotensin system. This is supported by Perry et al. [42] who found that, a long term high level Cd exposure has been shown to increase blood pressure and Thun et al. [43] who noticed that, in occupational studies a positive effect on blood pressure was found among Cd workers. Also, Eum et al. [44] found that, at the current level of Cd exposure, Cd may have increased the blood pressure. On the other hand Satarug et al. [45] related the increased risk of high blood pressure to the renal tubular damage and dysfunction caused by environmental Cd exposure.

In the present study, the podocytes surrounding the glomerular capillaries appeared disorganized with pyknotic nuclei and degeneration in their pedicles. This is in accordance with Xichen et al [46] and Uriu et al. [47] who found that, during plasma ultrafiltration, the glomerular structures are important target in Cd induced nephrotoxicity. Also, Templeton and Chaitu [49] and Roels et al. [48] found that, in cadmium-induced urinary excretion of high molecular weight proteins evidenced glomerular filter damage with cellular damage.

It could be concluded that, the Cd has adverse effects on the kidney even at low concentration. These effects are exclusive on the proximal part of the nephron (the glomerulus and the proximal convoluted tubules) and present structural changes reflecting functional impairment with increased probability for development of hypertension. Extreme attention must be taken to prevent the release of cadmium to the environment.

References

1. World Health Organization (WHO): Cadmium: Air Quality Guidelines, 2nd ed., World Health Organization, Copenhagen, Denmark, 2000.
2. Thévenod, F.; Lee, W.K: Toxicology of cadmium and its damage to mammalian organs. Met. Ions Life Sci. 2013, 11, 415–490.
3. Bernard A and Lauwerys R: Effects of cadmium exposure in man. In: Foulkes EC: Cadmium Toxicology, Hand Book Exp. Pharm. Vol. 80, Springer, Berlin, 1986; pp: 136-177.
4. Buchet J, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, Deplaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint-Remy A and Nick L: Renal effect of cadmium on body burden of general population. Lancet, 1990; 336: 699-702.
5. Bernard A, Roels H, Buchet JP, Cardenas A and Lauwerys R: Cadmium and Health: The Belgian experience. IARC. Sci. Publ., 1992; pp: 15-33.
6. Moon CS, Paik JM, Choi CS, Kim DH and Ikeda M: Lead and cadmium levels in daily foods, blood and urine in children and their mothers in Korea. Int. Arch.Occup. Environ. Health, 2003; 76: 282-288.
7. Jarup L, Berglund M, Elinder CG, Nordberg G and Vahter M: Health effects of cadmium exposure a review of the literature and a risk estimate. Scan. J. Work Environ. Health, 1998; 24: 1-51.
8. Nomiyama K: The chronic toxicity of cadmium influence of environmental and other variables. Cadmium. In: E.C. Foulkes (ed.), Hand Book of Experimental Pharmacology, Springer, Verlag, Berlin, 1986; pp: 101-133.
9. Gonic HC, Indraprasit S, Rosen VJ, Newstein H, VanDerbavalde R and Raghavan SVR: Experimental Fanconi syndrome III. Effect of cadmium on tubular function. The Na-K ATPase transport system and renal tubular ultrastructure. Miner. Electr. Metab., 1980; 3: 21.
10. Shaukat A, Sidra H, Rida K, Shumaila M, Nasra A, Saiqa A, Hafiz A S, Hafiz Mu T, M, Khalil A and Mazhar U: Renal toxicity of heavy metals (cadmium and mercury) and their amelioration with ascorbic acid in rabbits. Environmental Science and Pollution Research 2019; 26:3909–3920 https://doi.org/10.1007/s11356-018-3819-8

11. Prozialeck WC, Lamar PC and Lynch SM: Cadmium alters the localization of N-cadherin, E-cadherin and beta-catenin in the proximal tubule epithelium. Toxicol. Appl. Pharmacol.; 2003; 189: 180-195.
12. Bernard A: Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals. 2004; 17: 519-523.
13. Prozialeck WC, Vaidya VS, Liu J, Waalkes MP, Edwards JR, Lamar PC, Bernard AM, Dumont X and Bonventre JV: Kidney injury molecule-1 (Kim-1) as an early biomarker of cadmium nephrotoxicity. Kidney Int., 2007; 72: 985-993.
14. Vaidya VS, Ferguson MA and Bonventre JV: Biomarkers of acute kidney injury. Ann. Rev. Pharmacol. Toxicol., 2008; 48: 463-493.
15. Prozialeck WC, Edwards JR, Lamar PC, Liu J, Vaidya VS and Bonventre JV: Expression of kidney injury molecule-1 (Kim-1) in relation to necrosis and apoptosis during the early stages of Cd-induced proximal tubule injury. Toxicol. Appl. Pharmacol., 2009; 238: 306-314.
16. Thijssen S, Lambrichts I, Maringwa J and Vankerkhove E: Changes in expression of fibrotic markers and histopathological alternation in kidneys of mice chronically exposed to low and high Cd doses. Toxicol., 2007a; 238: 200-210.
17. Thijssen S, Maringwa J, Faes C, Lambrichts I and Kerkhove EV: Chronic exposure of mice to environmentally relevant low doses of cadmium leads to early renal damage not predicted by blood or urine cadmium levels. Toxicol., 2007b; 229: 145-156.
18. Blanusa M, Mrkovic-Milic R and Durbesic P: Lead and cadmium in soil and Isopoda woodlice in Croatia. Ecotoxicol. Environ. Saf., 2002; 52: 198-202.
19. Satarug S and Moore MR: Adverse health effects of chronic exposure to low-level cadmium in food stuffs and cigarette smoke. Environ. Health Perspect., 2004; 112: 1099-1103.
20. Gartner PL and Hiatt J: Color Atlas of Histology, 3rd ed., Lippincott Williams and Wilkins, London, Sydney and Tokyo, 2000; pp: 327.
21. Bancroft DJ and Gamble M: Theory and Practice of Histological Techniques 5th ed., Churchill Livingstone, New York, London, Philadelphia, 2002.
22. Kuehnel W: Color Atlas of Cytology, Histology and Microscopic Anatomy, 4th ed., Thieme Flexibook, Stuttgard, New York, 2002, pp: 364 & 368.

23. Bozzola JJ and Russell LD: Electron microscopy principles and techniques for biologists. Jones and Bartlett publisher, Boston, 1995.

24. Glauert AM and Lewis PR: Biological specimen preparation for transmission electron microscopy. Vol 17, Portland press, London, 1998.

25. Wu G, Gao X, Ye G, Li K, Hu C and Cheng J: Ultrastructural alternation in midgut and Malpighian tubules of Boettcherisca peregrine exposure to cadmium and copper. Ecotoxicol. Environ. Saf., 2009; 72: 1137-1147.

26. Kanglei Z, Mengfei L, W. D, Jiahui L, Xueru W, Wenjing L, Qing H, Yuyu P, Hui Z, Ruilong S, Gang L, Di R and Zongping L: CadmiumInduces Kidney Iron Deficiency and Chronic Kidney Injury by Interfering with the Iron Metabolism in Rats. Int. J. Mol. Sci. 2024, 25, 763. https://doi.org/10.3390/ijms25020763.

27. Liu J, Liu Y, Habeebu SM, Waalkes MP and Klaassen CD: Chronic combined exposure to cadmium and arsenic exacerbates nephrotoxicity, particularly in metallothionein- I/II null mice. Toxicol., 2000; 147: 157-166.

28. Cheville NF: Ultrastructure pathology: an introduction to interpretation, 1st ed., Lowa state university press, 1994, pp: 67-68 in Wu et al., 2009.

29. Nordbergy M: General aspects of cadmium: transport, uptake and metabolism by the kidney. Environ. Health. Perspect., 1984; 54: 13-20.

30. Johnson DR and Foulkes EC: On the proposed role of metallothionein in the transport of cadmium. Environ. Res., 1980; 21: 360-365.

31. World Health Organization (WHO): Cadmium. Environmental health criteria, vol. 134. Geneva: WHO, 1992.

32. Hamada T, Tanimoto A, Iwai S, Fujiwara H and Sasaguri Y: Cytopathological changes induced by cadmium exposure in canine proximal tubular cells: a cytochemical and ultrastructural study. Nephron, 1994; 68(1): 104-111.

33. Tanimoto A, Hamada T, Higashi K and Sasaguri Y: Distribution of cadmium and metallothionein in Cdcl2- exposed rat kidney: relationship with apoptosis and regeneration. Path. Int., 1999; 49: 125-132.

34. Kaur J, Sharma N, Attri S, Gogia L and Prasad R: Kinetic characterization of zinc transport process and its inhibition by cadmium in isolated rat renal basolateral membrane vesicles: in vitro and in vivo studies. Mol. Cell. Biochem., 2006; 282: 169-179.

35. Thophon S, Kruatrachue M, Upatham ES, Pokethitiyook P, Sahaphong S and Jaritkhuan S: Histopathological alternations of white seabass, lates calcarifer, in acute and subchronic cadmium exposure. Environ. Pollut., 2003; 121: 307-320.

36. Foulkes EC and Blank S: Acute cadmium uptake by rabbit kidneys. Mechanism and effects. Toxicol. Appl. Pharmacol., 1990; 102: 464.

37. Herak-Kramberger CM and Sabolic I: The integrity of renal cortical brush border and basolateral membrane vesicles is damaged in vitro by nephrotoxic heavy metals. Toxicol., 2001; 156: 139-147.

38. Condron RJ, Schroen CJ and Marshall AT: Morphometric analysis of renal proximal tubules in cadmium treated rats. J. Submicrosc. Cytol. Pathol., 1994; 26: 51-58.

39. Prasad R and Nath R: Cadmium-induced nephrotoxicity in rhesus monkeys (Macaca mulatta) in relation to protein caloric malnutrition. Toxicol., 1995; 100: 89-100.

40. Janqueira LC and Carneiro J: Basic Histology, Text and Atlas, 11th ed., Mc-Graw-Hill Medical Pubilishing Division, New York, London, Sydney, Toronto, 2005, pp: 373-391.

41. Perry JRHM and Erlanger MW: Elevated circulating renin activity in rats following doses of cadmium known to induce hypertension. J. Lab. Clin. Med., 1973; 82: 399-405.

42. Perry JRHM, Erlanger MW and Perry EF: Elevated systolic pressure following chronic low level cadmium feeding. Am.J. Physiol., 1977; 232: 114-121.

43. Thun MJ, Osorio AM, Schobers, Hannon WH, Lewis B and Halperin W: Nephropathy in cadmium workers: assessment of risk from airborne occupational exposure to cadmium. Br. J. Ind. Med., 1989; 46: 689-697.

44. Eum K, Lee M and Paek D: Cadmium in blood and hypertension. Sci. Total Environ., 2008; 407: 147-153.

45. Satarug S, Nishijo M, Ujjin P, Vanavanitkun Y and Moore MR: Cadmium induced nephropathy in the development of high blood pressure. Toxicology Letters, 2005; 157: 57-68.

46. Xichen W, Zelong X, Jin O, Hui L, Chengguan C, Ting L, Shiqun Y, Li M, and Shaoxin U: Histomorphological and ultrastructural cadmium-induced kidney injuries and precancerous lesions in rats and screening for biomarkers. Bioscience Reports (2022) 42 BSR20212516 https://doi.org/10.1042/BSR20212516

47. Uriu K, Kaizu K, Komine N, Ikeda M, Qie YL, Hashimoto O, Matsuoka A and Eto S: Renal hemodynamics in rats with cadmium-induced nephropathy. Toxicol. Appl. Pharmacol., 1998; 150: 76-85.

48. Roels HA, Lauwerys RR, Bernard AM, Buchet JP and Oversteyns M: Assessment of the filtration reserve capacity of the kidney in workers exposed to cadmium. Br. J. Ind. Med., 1991; 48: 365-374.

49. Templeton DM and Chaitu N: Effects of divalent metals on the isolated rat glomerulus. Toxicol., 1990; 61: 119-133.