

Cadmium Toxicity and some Target Organs: A Review

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Abstract

Cadmium is dangerous pollutant in environment because it is difficult to excrete out of the body. It causes disease in humans and animals. When the body absorbs large quantities of cadmium or when constantly exposed to small quantities, it is toxic to the body. Cadmium affects many parts of the body, the most important of which are the liver, kidneys, lungs, and testes. Both the liver and the kidney are considered organs to excrete toxins, such as heavy metals. Therefore, they are most influenced by cadmium. This study focuses on the toxicity of cadmium in the liver, kidneys, lungs and testes and its toxic effects on the histological, cellular, and functional level of each organ. We will discuss the mechanism through which cadmium causes damage to the organs of the body and the interaction that results from it.

Keywords: Cadmium, Kidney, Liver, Lung, Testes, and Toxicity.

سمية الكاديوم وبعض الأعضاء المستهدفة

الخلاصة

يعد الكاديوم من الملوثات البيئية الخطيرة لكونه من المعادن الثقيلة التي يصعب طرحها من الجسم ويسبب اضرار في صحة الانسان والحيوان عند دخوله الجسم. وعند امتصاصه من قبل الجسم خاصة بكميات كبيرة او عند التعرض المستمر بكميات صغيرة فانه يكون سام على الجسم. ويؤثر الكاديوم في العديد من أعضاء الجسم أهمها الكبد والكلية والرئة والخصية. وتعد كل من الكبد والكلية أعضاء ل طرح السموم كالمعادن الثقيلة لذلك فأنها الأكثر تضررا من الكاديوم عند التعرض له. وتركز هذه الدراسة على سمية الكاديوم في الكبد والكلية والرئة والخصية وتأثيراته السمية على المستوى النسيجي والخلوي والوظيفي لكل عضو. وسناقش الالية التي من خلالها يتسبب الكاديوم في احداث الاضرار في أعضاء الجسم وما هي تلك الاضرار التي تنتج عنه.

Introduction

Cadmium (Cd) is a heavy, soft metal that has silvery-white or bluish-white luster (1). There is 0.1–0.5 mg per kg of cadmium in the crust of earth (2). It is non-essential mineral for body metabolism and is toxic to all types of organisms (3). The source of cadmium pollution is produced by mining, industry and

such as weathering of rocks, volcanic eruptions, and forest fires or anthropogenic such as using plant fertilisers, burning coal, iron alloys, component of batteries, steel and cement dust (5). The body is exposed to cadmium from many sources, such as occupational exposure to workers in industries, through contaminated water and food, and smoking (6). Cadmium is absorbed

by the gastrointestinal tract or lungs and accumulates in various parts of the body, the most important of which are the liver and kidneys (7). Other organs are affected by the toxicity of cadmium, such as the lung and testes (8).

Since cadmium does not have any vital function and cannot be degraded by living organisms, it accumulates in cells and interacts with cellular components (9). Dose of cadmium in drinking water is 0.0005 mg per kg per day, while its dose in food is 0.001 mg per kg per day (1). Cadmium may cause several diseases in different organs such as cancer and may cause death. It can cause the transformation of normal cell into carcinogenic cell by inhibiting the biosynthesis of proteins (10). Cadmium generates oxidative free radicals that break down cell components, affect calcium levels in cells and stimulate the apoptosis system (11). Cadmium leads to a decrease in antioxidant enzymes (12 and 13). Oxidized free radicals cause infections that are directly proportional to the amount of cadmium dose exposed (14). Cadmium oxidizes lipids and adds the carbonyl group to proteins, so both proteins and lipids lose their functions (15). Cadmium folds proteins in the endoplasmic reticulum, alters protein properties, and denatures protein (16). The amount of cadmium can be estimated in blood, urine, saliva, hair and nails (17). It causes a decrease in body weight, an increase in the weight of the liver compared to body weight, less drinking water, and less urine (18).

Cadmium has dangerous effects on the body's immunity and inhibits the humoral and cellular immune response in immune cells, and accumulates in the spleen (19). The number of neutrophils in wounds decreased due to a lack of chemical response caused by cadmium. Genes that encode to neutrophil response and that encode for inflammation are inhibited by exposure to cadmium (20). Cadmium causes severe damage to the endocrine glands, which negatively changes hormone concentrations in the body, which may cause metabolic effects (21).

Cadmium toxicity in liver

Exposure of the body to cadmium leads to a significant accumulation in the liver (22). Cadmium is more accumulated in the liver, after which the kidneys (23). It causes abnormalities in the tissue and cells of the liver, represented by an increase in the volume of cells, the amount of glycogen, necrosis, infiltration of cells, and causing inflammation (24). It also causes congestion around the hepatic portal vein, the expansion of the hepatic sinuses and a change in the regulation of hepatic plates (25). Cadmium increases the expansion of the central vein in the lobule, destroys its walls and increases the size of glycogen granules and fat droplets within the hepatic cell (26). It cause Infiltration of lymphocytes and neutralized cells in hepatic lobes (27). The liver exposed to cadmium undergoes vesicular fatty degeneration in the hepatic lobules and the shape of the hepatocytes transforms into a ring-like (28). Cadmium inside the hepatocytes causes swelling in both the rough endoplasmic reticulum and mitochondria, the cristae lose, nuclear chromatin presses, the fat drops increase, the liver cells disassociate with each other, and the production of metallic protein (Metallothionein) in the hepatic cells increases (29). The number of lysosomes increases, the endoplasmic reticulum is broken, the nucleus is damaged (30) the cell membrane thickens and the nuclear membrane is destroyed by cadmium (31). Cadmium toxicity damages liver cells, increases secretion of liver enzymes, and decreases concentration of antioxidant enzymes (32). It inhibits the enablers that activate the genes responsible for producing antioxidant enzymes (33). The Superoxide dismutase is one of the most important antioxidant enzymes that are affected by cadmium toxicity in liver tissue (34). Copper, iron, and zinc are replaced with cadmium and accumulated in the liver (35). Cadmium affects liver function in concentrations of glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (ALP), lipid, bilirubin, and total protein in

serum (36 and 37). The amount of proteins in serum such as albumin and globulin is reduced (38). Concentration of γ -glutamyl transferase (GGT) decreases and the expression of genes that encode inflammation increases (39). Cadmium induces apoptosis in the liver and consequently hepatic cell death (40). The sensitivity of the liver to cadmium is possibly due to the liver's ability to synthesize the metallothionein that is cadmium-inducible protein protecting the cells by binding the cadmium ions. The free oxidizing radicals induced by cadmium may be responsible for several liver diseases (41).

Cadmium toxicity in kidneys

The kidney is the target organ of cadmium toxicity and exposure to it causes tissue damage represented by the destruction of the tubules, the appearance of gaps between them, the destruction of the glomeruli, the fibrosis of the region, the infiltration of the monocyte, bleeding, fluid collection and necrosis in the kidney tissue (42). Glycogen is deposited in the kidney cells and wrinkles glomeruli, which disrupts their work (43). The epithelial cells in the glomeruli of the renal glomeruli and the absence of urinary space in the Bowman capsule enlarge due to the large capillary expansion (31). The glomeruli swell, the renal tubules narrow, the epithelial cells in the renal tubules die, accumulate in the cavities, infiltration of inflammatory cells and edema (18). Congestion and inflammation around the blood vessels, fibrosis of the tissue and condensed nuclei in the cells of the renal tubules (28). Capillaries in the renal glomeruli and peritubular blood capillaries are congested (38).

Cadmium causes cellular changes, as the mitochondria swell, the cristae lose, the nuclear chromatin is compressed, the number of ribosomes increases, the number of microvilli on the surface of the renal tubule cells decreases, and the production of

metallothionein in the kidney cells increases (29). The pores of the fenestrated capillaries in the renal glomeruli close, the nuclear membrane is disturbed, the number of lysosome increases, and finally the cells die (31).

Cadmium has several effects on kidney function as it increases urea and creatinine in the serum (36 and 44). Cadmium disturbs proximal convoluted tubules, raises blood pressure, reduces glomerular filtration, and the most important treatment is to avoid Cadmium disturbs proximal convoluted tubules, raises blood pressure, reduces glomerular filtration, and the most important treatment is to avoid cadmium exposure (45). It stimulates the programmed death system of cells by stimulating the P53 gene to build a protein that stimulates apoptosis in proximal convoluted tubules in the kidney (46). The damage caused by cadmium in the kidney is affected according to gender, age and cigarette smoking (47). The kidneys are affected greatly by the toxicity of cadmium. In one of the cities in Japan, its residents were exposed to cadmium pollution in a river, which caused a disease called Itai-Itai disease, as it causes a dysfunction in the proximal convoluted tubules, which leads to the excretion of amino acids, glucose and phosphorous in urine (48). The ability to excrete nitrogenous wastes such as urea is lost in the body because of the accumulation of cadmium in the epithelial cells lining the proximal convoluted tubules (49). The kidneys are the target for the toxicity of heavy elements and have the ability to filter, reabsorb and concentrate the two-ion elements. Damage of the kidneys depends on the exposure dose and the duration of the exposure (50). It affects the mineral elements such as zinc, iron and copper in the kidneys, replaces them and accumulates in the kidneys (35). Cadmium, is accumulated in

cells of proximal tubule, produces a different toxic effects resulting in the death of renal epithelial cells via necrosis or apoptosis. However, the initial stages of cadmium-induced proximal tubule damage may include many specific changes in cellular signaling pathway, cellular adhesions, and autophagy that happen before the onset of necrotic or apoptotic mechanisms (49). Cadmium may cause renal damage according to the method of giving, which may be ascribed to the disordered absorption of iron ions, disruption of oxidative stress and apoptosis in the kidney (18).

Cadmium toxicity in lungs

Cigarettes are one of the most important sources of cadmium that enters the lung through smoking (51). A study in Iran on smoking people showed that cadmium increases in the blood of smokers (52). Cadmium has toxic effects on the lungs and causes pathological changes in lung tissue (8). It causes infiltration, inflammation and fibrosis around the blood vessels in the alveolar septa, and chronic infections and destruction of type I lung cells and hyperplasia in type II lung cells (53). A study indicated that exposure to cadmium mixture with silica leads to the destruction of the alveoli and the formation of granules and exfoliation of epithelial cells in the bronchi (54).

The mechanism of the effect of cadmium in the lung through activation in a group of genes in the epithelial cells of the bronchial cells that stimulate inflammation and cause lung diseases (55). The lung immunity decreases when exposure to cadmium and changes in the ratios of cytokines, some interleukins, anti-oxidant enzymes, tumor necrosis factor, and interferons (56). It inhibits the action of phagocytic cells by affecting the cytokines secreted by them (activate other immune cells) and thus reduce or inhibit the immunity of the lung (57). Cadmium may

induce lung diseases, possibly through redox imbalance and by disrupting macrophages (58). It causes lung cancer, increases the resistance of cancer cells to treatment, and increases the rate of division (59).

Cadmium toxicity in testes

The testes are sensitive to cadmium and cause an enlarged testicle size, epididymis and seminal ducts (60). Histopathological changes occur in the testes of rats exposed to cadmium chloride (32). The oxidative stress in the testes increases and causes necrosis of the seminal tubules and the surrounding tissue. The seminal tubules become wrinkled, the cells lining them die and gaps are formed in the Sertoli cells (the supporting cells) and Ledge cells (61). It causes an increase in the area surrounding the seminal tubules and reduces the thickness of the germinated layer (62). The testes are severely damaged and bleeding occurs. The cavities of the seminal tubules expand, the germ cells necrosis, the process of sperm production and the spermatogenesis stages are discouraged (60). The germinated cells are elongated, cadmium is deposited in them, and the nucleus is transformed into a crescent shape. This shape is a characteristic of the apoptosis with large cavity in the cells. The shape and size of the mitochondria change, the mitochondrial membrane decomposes, and the endoplasmic reticulum expands (63). The seminiferous tubules break down, the cells' adhesion disintegrates and the testosterone concentration decreases (64). The low concentration of the male hormone due to the effect of cadmium on the cellular receptors that receive the hormone regulator to produce male hormones in the testes (65).

There is a relationship between the amount of cadmium in the body and male infertility. This relationship was represented by changes in hormones and seminal fluid (66).

Cadmium is a very toxic substance on the reproductive system. It kills male sperms, deforms their shape, reduces male sperm activity, and reduces numbers (67 and 68). The seminal fluid alkalinity decreases (69). Seminal fluid volume and concentration decrease (60). A deformed sperm loses its head, and the tail and body of the sperm curves (70). The number and movement of sperms in the epididymis decrease (62). The weight of the testis decreases, the lipid peroxidation increases, and the concentration of antioxidant enzymes such as catalase and superoxide dismutase decreases (71 and 72).

Conclusions

Cadmium is a heavy metal that is difficult to put outside the body and when accumulated causes serious damage to various parts of the body. It causes serious damage to the liver, kidney, lung and testis tissues, and the damage may be irreparable. It affects various body functions, especially in the liver, kidneys, lungs, and testes, such as a change in the concentrations of enzymes, hormones, and other functions.

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