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Cadmium toxicity and its effect – A Review

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Abstract
Cadmium is one of the most harmful nonessential heavy metals with lustrous properties**,** resulting from various anthropogenic activities industrial, mining, and agricultural activities, and the exhaust of automobiles. The exposure and uptake of Cadmium through various means may create serious health problems including damage to the lungs, and kidneys, liver and severe bone damage, itai-itai diseases, cancer, and reproductive delay in humans after the storage in the human body. However, certain measures to be taken to control exposure to heavy metals to maintain the health and well-being of the environment. In the future perspective, certain measures need to be taken to control the spread of heavy metals through bioremediation and microbial use.

Keywords: Cadmium, heavy metals, cadmium uptake, liver diseases, lung, kidney liver, itai-itai diseases, bioremediation

Introduction

Cadmium (Cd) is a naturally occurring nonessential heavy metal found in the earth's crust. The element cadmium is usually found as a mineral in combination with other elements such as oxygen, chlorine, or sulfur (Nriagu 1988) [38]. Over the past two centuries, anthropogenic and industrial activities have led to high emissions of cadmium into the environment leading to severe damages at concentrations significantly exceeding those originating from natural sources (Vangronsveld *et al.* 1995) [52]. Cadmium shows poisonous properties without being detectable in the environment with no taste or odor. In the environment, cadmium is released as a non-essential heavy metal pollutant resulting from various industrial, mining, and agricultural activities and the exhaust of automobiles (Foy *et al.* 1978) [12]. Cadmium is generally a divalent cation, paired with other elements (e.g.CdCl2) (Wedepohl 1995) [58]. Cadmium (CAS registry number 7440-43-9) is a naturally occurring element of relatively poor abundance (64th amongst elements) in the earth's crust with (0.1-0.5 ppm) as reported it is toxic, nonessential, and classified as a human carcinogen by the North Carolina National Toxicology Program 2000. Cadmium is a potentially toxic metal that is commercially used in lasers, batteries, and television screens with no physiological functions related to the human body (U.S. Geological Survey 2021). Agency for Toxic Substance and Disease Registry (ATDSR) submitted that cadmium holds the seventh position among the most hazardous heavy metals (Faroon *et al.* 2013) [11]. Cadmium is widely found in aquatic ecosystems due to its greater solubility in water (Lockwood 1976) [27]. Mainly, cadmium is used in industrial sectors to produce colorants, stabilizers of plastics and electroplating protective coatings, solders and alloys, and cadmium rods and is also used for the production of alkaline nickel-cadmium batteries, fireworks, and fluorescent paints (Martelli *et al.* 2006) [29]. The toxicity of Cadmium in the environment including animals and humans is a source of concern. One of the major organs Liver in the human body is primarily affected by the metal Cadmium (Cobb-Abdullah *et al.* 2019) [5]. Cadmium shows severe health effects in humans when it crosses its threshold concentration.

Epidemiology of cadmium

Despite the worldwide production through natural or anthropogenic activities, the consumption, and release of cadmium compounds in the environment there is no efficient recycling system for them. Human exposure to cadmium compounds through various means may create serious health problems including damage to the lungs, liver, reproductive parts, kidneys, and severe bone damage. Cadmium has been used in nickel-cadmium batteries for industrial purposes, as a pigment in paint production, and likewise, in electroplating and producing polyvinyl chloride plastic. Furthermore, cadmium is present in most foodstuffs, and depending on dietary habits, its level varies greatly. Cadmium considerably accumulates in the environment without proper recycling, as a result of human activities, such as the use of fossil fuels, metal ore combustion, and waste burning. Leaking sewage sludge to agricultural soil may cause the transfer of cadmium compounds to the field adsorbed by plants that may play a significant role in the food chain, and accumulate in various human organs reported (Munisamy *et al.* 2013) [34]. According to the report of FAO/WHO rules the permitted level of cadmium in rice is 0.2 mg/kg (Rahimzadeh *et al.* 2017) [41].

Cadmium uptake

Cadmium uptake takes place through food, inhalation, and smoking. The high rate of cadmium transport through the intracellular transport mechanism which cadmium can easily pass from soil to plant and transfer to the trophic level and enter the diet of human beings (McLaughlin *et al.*2006) [32]. Vessey (2010) reported that cadmium has similar chemical and physical properties to essential metals such as iron (Fe), zinc (Zn), or calcium (Ca), for which it can be transported through the cell membrane and taken up into the cells of mitochondria and other organs by a process referred to as "ionic and molecular mimicry". The Atmospheric deposition of airborne cadmium through certain activities

like mining and the use of cadmium-containing fertilizers in crop production leads to cadmium contamination and heavy metal accumulation of soils which increases cadmium uptake by crops and vegetables grown for human consumption (Elinder 1985) [6]. Heavy metals with toxic properties along with cadmium and its compounds enter the body primarily through the respiratory tract (10-40%) Cigarette smokers are at risk, 30- 64% of the inhaled cadmium is absorbed by the body (Sahmoun *et al*. 2005) [43]. An important source of cadmium accumulation in the human body and lung diseases is cigarette smoking, according to the reports, the mother's milk of smoking women may contain twice as much cadmium as the milk of non-smokers (Martelli *et al.* 2006) [29]. Van Assche *et al.* (1992) [50] have developed a model for cadmium exposure for human beings and allocated this exposure to various sources.

Storage of cadmium in the body

Klaassen *et al*. (1999) [24] reported that cadmium accumulates primarily in the liver cells after a single exposure to the organism. The presence of low molecular weight proteins called Metallothioneins (MT) in the liver cells forms a complex with Cadmium (CdMT complexes). After they are released from the liver into the bloodstream CdMT complexes exposure to low doses of cadmium results in their increased accumulation in the kidneys, especially in the cortical part of the kidney. The distribution of cadmium in the body depends on the chemical form of this element. Increased accumulation of Cd2+ ions in the liver, kidneys, or bones occurs after exposure to cadmium in the form of inorganic salts (e.g. CdCl2) than the cadmium present in conjunction with metallothionein (CdMT). CdCl2 accumulates mainly in the liver, whereas CdMT is in the kidney. Van Kerkhove *et al*. (2010) [51] reported that organs that store cadmium include the liver, kidney, testis, spleen, heart, lungs, thymus, salivary glands, epididymis, and prostate; however, approximately 50% of the Camiumd found in the body is stored in the liver and kidney due to their high MT concentration. Cadmium can also accumulate in the pancreas, lungs, central nervous system, and testes in men. Cadmium particles are transported along primary olfactory neurons to their terminations in the olfactory bulb. Some other metals, such as manganese, do migrate further into the brain, unlike cadmium which accumulates in the olfactory bulb (Nishijo *et al*.2017) [37]. Another site of cadmium accumulation after inhalation is the lungs, as observed with smokers for instance. Although the lung epithelium is an efficient barrier for toxic molecules and heavy metals, cadmium can pass through alveolar cells and get into the blood (Schauder *et al*. 2010) [44].

Mechanism of cadmium toxicity

The study of Cadmium demonstrates several tissues and organs related to injury to the human body through entering the human body affecting cell proliferation, apoptosis, and differentiation. Cadmium affects the DNA repair mechanism with intercalating properties involving cell division and induces apoptosis (Rani *et al*. 2014) [42]. Several epigenetic changes during chromosome separations are seen related to chromosomal aberrations (Wang *et al*. 2020) [57], and DNA disruption (Martinez-Zamudio and Ha, 2011) [30]. DNA protein crosslinks, and tissue injury related to reactive oxidative stress ROS (Matovic *et al*. 2012), cadmium inhibits several transport pathways in the cell by blocking particular motor proteins (Wan and Zhang, 2012) [56]. Due to cadmium depositions mineralization of bones in humans and animals has revealed skeletal damage (osteoporosis). An epidemic in Japan called itai-itai disease is due to cadmium contamination in the body (Nishijo *et al*. 2017) [37]. Cadmium shows disruption of heme group synthesis affecting blood circulation (Van Kerkhove *et al*.2010) [51]. By interacting with other toxic metals such as lead (Pb) and arsenic (As) the effects of Cadmium are magnified Nrf2 levels increase (Whittaker 2011) [59]. P53 the guardian of the cell introduces cell death by binding directly to the membrane-bound protein of mitochondria (Bcl-xl) (Wu *et al*.2012). Exposure to a huge number of cadmiums shows renal dysfunction (Jarup 2002). Several findings show Cadmium potentially affects the reproduction and development in several species of mammals, together with decreasing the density of volume and number of sperm count, and increasing the count of immature sperm in animals (Thompson and Bannigan, 2008) [48]. Cadmium toxicity shows hypertension related to cardiovascular diseases with sudden cardiac death (Pizent *et al*.2012) [40]. According to the findings of the International Agency for Research on Cancer (IARC), cadmium is a carcinogenic heavy metal related to lung, prostate, or renal cancer (Gallagher and Meliker,2010) [13]. The molecular mechanism of Cadmium as a carcinogenic compound activates protooncogenes and inactivates the tumor suppressor gene leading to DNA damage along with disruption of cell adhesion proteins (Menke *et al*. 2009) [33].

Overall health issues after the entry of cadmium

Cadmium affects the human body through progressing cell proliferation, cell differentiation, and apoptosis. These activities of the cadmium interact with DNA repair machinery, generating reaction oxygen species (ROS) and the induction of apoptosis (Rani *et al*. 2014) [42]. At very low concentrations the minute amount of cadmium can bind to the mitochondria and can inhibit both cellular respiration and oxidative phosphorylation at the cellular level (Patrick 2003) [39]. Cadmium deposition results in chromosomal aberrations, resulting in mismatched sister chromatid exchange, DNA strand breaks, and inhibiting DNA-protein crosslinks in cell lines, which results in mutations and chromosomal deletions (Joseph 2009) [21].

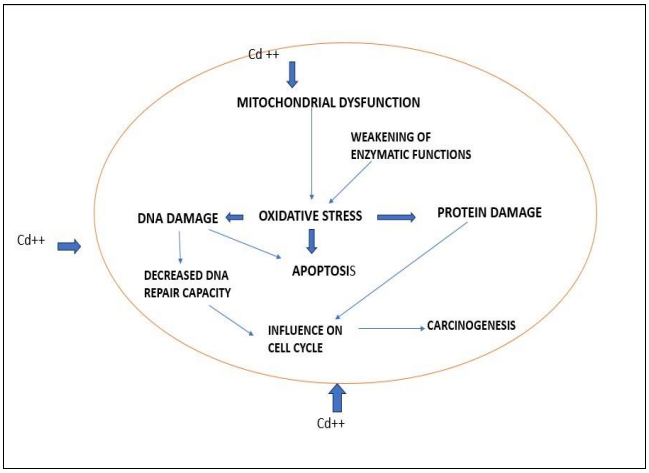

Fig 1: Showing cadmium acts on mitochondria disturbing the enzymatic and nonenzymatic dysfunction influencing the cell cycle and leading to cancer by halting various biological processes.

Cadmium toxicity and the depletion of certain enzymes

Cadmium toxicity reduces glutathione (GSH), binds sulfhydryl groups with protein, and enhances the production of reactive oxygen species (ROS) such as superoxide ion, hydrogen peroxide, and hydroxyl radicals generating free radicals in human beings. Cadmium also inhibits the activity of antioxidant enzymes, such as catalase, manganese superoxide dismutase, and copper/zinc dismutase (Filipic 2012). Metallothionein also can act as a free-radical scavenger, it is a zinc–zinc concentrating protein with 33% cysteine that scavenges hydroxyl and superoxide radicals (Liu *et al*. 2009) [26]. Generally, the cells that contain metallothionein's are resistant to cadmium toxicity. On the other hand, the cells that cannot synthesize metallothionein's are sensitive to cadmium intoxication (Han *et al*. 2015). The deposition of cadmium inside the cell can modulate the cellular level of Ca2+ and the activities of the caspases and nitrogen-activated protein kinases (MRPKs) in the cells, causing indirect apoptosis (Brama *et al*. 2012) [3]. P53 the guardian of the cell, causes cell death by directly binding to mitochondrial membrane proteins. The expression of B-cell lymphoma-extra-large (Bcl-xl), a transmembrane molecule present in the mitochondria, acts as a suppressor, suppresses mitochondrial-mediated apoptosis, and enhances the enlargement of the cancer cells (Rahimzadeh *et al*. 2015).

Cadmium toxicity and specific diseases

The effect of Cadmium deposition shows different forms and has different clinical manifestations and toxic effects that are explained in the present review.

Cadmium bone deposition and Itai-itai disease

Through previous studies it was mentioned, that cadmium can affect the skeletal system of the human body leading to skeletal demineralization, which directly interacts with bone cells, diminishes mineralization, also inhibits procollagen C-proteinases and collagen production where cadmium may interact with the metabolism of calcium, vitamin D3 and collagen. Therefore osteomalacia or osteoporosis could be observed in delayed manifestations of severe cadmium poisoning (Staessen *et al*.1999) [46]. The clinical findings of several researchers concluded that cadmium toxicity shows bone depletion with osteoporosis including pain, physical impairment, and decreased quality of human life along with decreased bone density imparts an increased risk for bone fractures. Osteoporotic fractures are most common in post-menopausal women with the age of 45 plus (Nawrot *et al*. 2010) [36]. The serum PTH levels in the bone decrease with higher cadmium exposure, this may induce the release of calcium from bone tissue (Schutte *et al*.2008) [45]. Itai-itai disease is the most severe form of chronic cadmium intoxication. The first recognition occurred in Jinzu River, Toyama Prefecture, Japan (Umemura and Wako, 2006) [49].

Renal damage in cadmium toxicity

The constant accumulation of cadmium in the cells of the kidney and liver shows early signs of renal damage, proteinuria, calcium loss, and tubular lesions that implicate renal dysfunction. They can be found in other tissues such as bone and placenta. (Jarup 2002). The urine analysis of the infected person may help to prove early signs of renal damage (Patrick 2003) [39]. Generally, the glomerular filtration rate (GFR) and reserve filtration capacity will be diminished first, and severe cadmium toxicity may induce nephrotoxicity with complications such as glucosuria, aminoaciduria, hyper phosphaturia, hypercalciuria, polyuria and decreased buffering capacity (Gonick 2008) [15]. The cellular damage and functional integrity in proximal tubules resulted in the loss of calcium, amino acids, and enzymes, and increased protein quantity in the urine. On the other hand, a decreased tubular reabsorption of a few molecular-weight proteins leads to tubular proteinuria. The most common proteins in the urine of the infected person are beta 2-microglobulin, retinol-binding protein, and alpha 1-microglobulin (Bernard 2004) [2].

Cadmium and the reproductive system

According to previous studies, it is found that cadmium has the potential to affect reproduction and development systems in several mammalian species, and recent studies have also confirmed these findings through various examples. In the female reproductive health, the function of the ovary is inhibited and the development of oocytes may be decreased. Steroidogenesis is reduced under Cadmium toxicity and ovarian hemorrhage and necrosis can co-occur (Thompson and Bannigan, 2008) [48]. In comparison to animal studies, it is claimed that cadmium decreases the mobility, density, volume, and number of sperm, and increases immature sperm forms in men. It has been reported that the rate of spontaneous abortion and time for fertility in women decreased, while pregnancy increased and the rate of live births decreased (Pizent *et al*. 2012) [40]. These problems are followed by a defect in the generation of sperm (spermatogenesis), sperm quality, and secretory functions of accessory glands. Besides, the presence of cadmium in males decreases libido, fertility, and serum testosterone levels (Chandel and Chand, 2014) [4].

Cadmium and cardiovascular system

Fagerberg *et al*. (2012) [9] have reported the involvement of cadmium in the cardiovascular system with endothelial dysfunction as well as carotid intima-media thickness (IMT) *In vitro* and the formation of atherosclerotic plaques *In vivo* studies. Everett and Frithsen (2008) [8] reported cadmium intoxication, endothelial dysfunction at starting of cardiovascular disease (CVD), loss of endothelial cell structure causing cell death, and thrombogenic events later. The results support the hypothesis of cadmium involvement in cardiovascular disease and myocardial infarction. Epidemiologic studies have shown the association of cadmium exposure with the risk of high blood pressure (systolic and diastolic blood pressure). Eum *et al*. (2008) [7] reported that cadmium may inhibit endothelial nitric oxide synthase and suppress acetylcholine-induced vascular relaxation resulting in hypertension. It may stimulate the production of cytokines and induce endothelial damage. Navas-Acien *et al*. (2004) [35] reported that cadmium toxicity may cause atherogenesis and long-term exposure may increase the incidence of peripheral arterial disease. Toxic exposure to cadmium may increase blood pressure and cardiovascular mortality in humans (Menke *et al*. 2009) [33].

Cadmium and other systems of the body

Ismail *et al*. (2015) [19] reported the acute central and peripheral neurotoxicity of cadmium. Cadmium may also induce cellular damage promoting cancer along with inhibiting the DNA repair system, and lipid peroxidation in

the brain. He further reported its effect on monoaminoxidase (MAO) is responsible for the oxidative deamination of monoamine neurotransmitters. The deposition of cadmium increases the production of free radicals in the central nervous system and decreases cellular defense against oxidation (Lopez *et al*. 2003) [28]. Kim *et al*. (2005) [23] reported the outcomes of this mechanism are olfactory dysfunction, neurobehavioral defects in attention, and disorders in psychomotor activity, and memory. Cadmium poisoning affecting the CNS may lead to neurodegenerative disorders, such as Parkinson's, Alzheimer's, and Huntington's diseases accompanied by loss of memory and behavioral changes. Recent study has shown a possible involvement of cadmium in pulmonary diseases such as chronic obstructive disease and emphysema (Lampe *et al*. 2008) [25]. He later showed through their studies that cadmium chloride can decrease lung vital capacity and increase the alveolar wall thickness. Inhalation of cadmium as vapor in the absence of antioxidants, and condition of oxidative stress, may result in pulmonary inflammation and emphysema. Cadmium is easily absorbed through the gastrointestinal tract (GIT) and the solubility and absorption are affected by gastric and/ or intestinal pH after that cadmium reacts with HCl and forms of cadmium chloride. It can induce the inflammation of GIT (Waisberg *et al*. 2005) [55]. Studies have shown cadmium can induce liver damage in the acute stage with high inflammation. Prolonged oral cadmium ingestion can cause Itai-itai disease in the chronic phase (Baba *et al*. 2013) [1]. Limited research studies in cadmium poisoning with skin manifestations showed hyperkeratosis and acanthosis, accompanied by occasional ulcerative change, and an increase in the mitotic index of the skin cells (Godt *et al*. 2006) [14].

Cadmium and carcinogenicity

Kellen *et al*. (2007) [22] reported that cadmium compounds were categorized as carcinogenic in humans by the International Agency for Research on Cancer (IARC) associated with bladder carcinogenesis. It may be considered a lung carcinogen, and also inducer of prostatic or renal cancers with renal dysfunction. The important point is that cadmium can disorder testosterone production and induce testicular interstitial cell hyperplasia (Goyer *et al*. 2004) [16]. Further, some of the reports suggested that cadmium may be involved with malignancies of the liver, hematopoietic system, bladder, and stomach. Furthermore, cadmium may be a potential risk factor for breast cancer. Another study from research suggested that cadmium exposure may be involved in pancreas cancer because of induces an increased risk for neoplasia (Waalkes 2003) [54]. The researcher in 2005 reported that the cellular and molecular mechanisms implicating cadmium carcinogenicity include the activation of protooncogenes, with inactivation of tumor suppressor genes, disruption of cell adhesion proteins, and inhibition of DNA repair (Il'yasovam *et al*. 2005) [18]. DNA strand damage or DNA-protein crosslinks disorder may completely inhibit cell growth. In summary, it is suggested that cadmium exposure can affect cell proliferation, differentiation, apoptosis, cell signaling, and other cellular activities. These activities could bear on carcinogenesis directly or indirectly resulting in cell death.

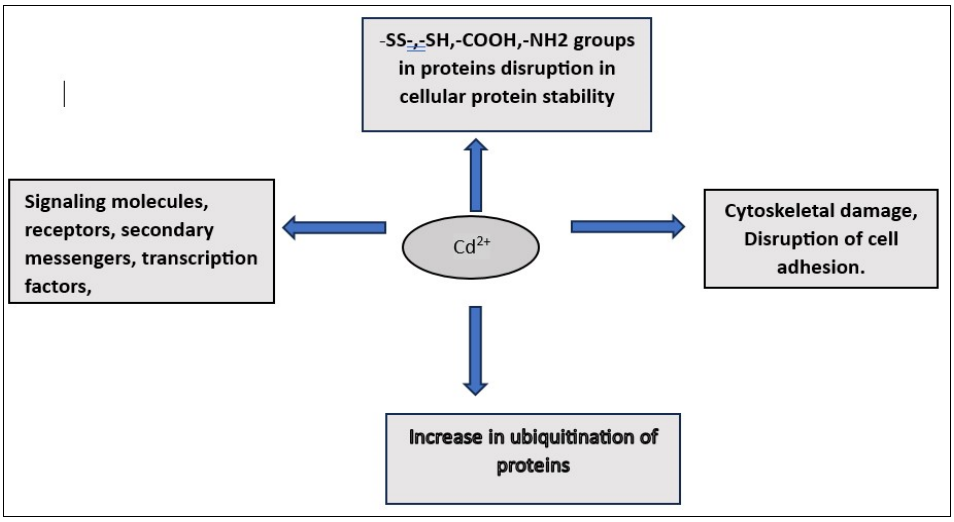

Fig 2: shows the overall effects of cadmium inside the cell interrupting various biological function.

Future perspective

The deposition of the compound cadmium and its uptake to the body through various means is dangerous to the organism causing certain death-threatening diseases to the human race along with certain animals. The overall uptake of cadmium to the body with little or more amount through anthropogenic activity must be controlled by eliminating the use of cadmium. Cadmium toxicity can be maintained through degradation, bioremediation, and certain ways. The compounds affecting the natural components must be eliminated in various ways, to save the human race from cadmium-associated diseases one must control the use of cadmium in industrial manufactures. Cadmium toxicity and its future perspective of the compound are recommended to identify the individual with high sensitivity, to cadmium exposure and, to ensure any contamination of agricultural soils, drinking water, and food chain. Necessary attention to be paid to the handling of cadmium compounds and it is then suggested to detect the contaminated sites and design education and awareness programs for the potential at-risk population to minimize overall cadmium toxicity. Recently, many microbial fermentation method has been developed to reduce cadmium levels in contaminated area. Studies regarding the removal of Cadmium from nature need further investigation to reduce the effects of this heavy metal's toxicity.

Conclusion

The present review concludes with the thought that cadmium is one of the most toxic elements that human beings can be exposed to at work or in the environment in various ways. Cadmium has no known important physiological role in humans. Exposure to Cadmium can occur through food, water, and the inhalation of cigarettes causing various life-threatening diseases. For which the utilization of cadmium must be reduced to control the toxicity of the compounds through future study and research and the investigation of alternate compounds which is environment-suitable.

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