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IJPBS |Volume 2| Issue 4 |OCT-DEC |2012|235-246

Review Article
Biological Sciences

CADMIUM TOXICITY- A HEALTH HAZARD AND A SERIOUS ENVIRONMENTAL PROBLEM -AN OVERVIEW

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ABSTRACT

Cd^{2+} a heavy metal accumulates in the body and has a very long biological half-life (10–30 years) in humans. Environmental cadmium contamination occurs through industries related to batteries, coatings, electroplating, alloys, plastics, glasses, ceramics, enamels and artists' colors, zinc, copper, lead, and iron ores treatment, coal and oil burning power plants, weathering of parent rocks etc. This review is mainly focused on general characteristics of cadmium, effect on human health in relation to different organs such as kidneys, liver, lungs, reproductive system etc. and mechanism of toxicity. Renal toxicity, hepatotoxicity and carcinogenicity are the major effects of cadmium induced toxicity. Production of reactive oxygen species, free radical induced cell damage, interference with calcium and vitamin-D metabolism (major mechanism involved in cadmium induced bone damage), oxidative DNA damage, glutathione depletion, accumulation as metallothionein complex (Renal toxicity), CFTR (Cystic fibrosis transmembrane conductance regulator) dysfunction (lung toxicity), chromosomal aberrations, modification of transcription factors, altering the antioxidant defense system are the observed mechanisms involved in cadmium induced cytotoxicity. Exogenous supplementation of glutathione (GSH) and metallothionein (MT) will play protective roles against cadmium toxicity. Reducing the use of cadmium in industries or avoiding of Cadmium exposure and recycling the cadmium products prevent the cadmium induced cytotoxicity to some extent.

KEYWORDS

Cadmium, Cytotoxicity, Genotoxicity, Environmental pollution, Kidney, Liver.

INTRODUCTION

Cadmium (Cd^{2+}) is one of the most common nonessential elements, relatively accessible heavy metal in our environment causing wide range of toxic effects. Cd^{2+} accumulates in the body and has a very long biological half-life (10–30 years) in humans [1-3]. The most common forms of cadmium found in the environment exist in combinations with other elements such as cadmium oxide, cadmium chloride and cadmium sulfide etc. Inhalation and accumulation of cadmium disturbs various metabolic functions and there by affects the human health. Effect of cadmium on various organs of the human body has been studied earlier and several mechanisms have been proposed. In this review all those mechanisms have been scrutinized to some extent and propose some pathways for cadmium induced toxicity on various organs of the human body.

Toxic effects of Cadmium:

Impact of Cadmium on Human health

Exposure to cadmium through food is typical for most people but is not a major health concern. This is because the cadmium present in the body from our diet is about 0.0004mg/kg/day. This figure is about ten times lower than the level of

cadmium that causes kidney damage from eating contaminated food (**Table.1**).

Table.1 Cadmium levels in Environment

Natural cadmium levels in the environment	
Atmosphere	0.1 to 5 ng/m^3*
Earth's crust	0.1 to 0.5 µg/g**
Marine sediment	~1 µg/g
Sea-water	~0.1 µg/l***

***ng/m3 = nanograms (10E-9 g) per cubic meter.**
**** µg/g = micrograms (10E-6 g) per gram.**
***** µg/l = micrograms (10E-6 g) per liter.**

Cadmium exposure may be implicated in some humans disorders related to hyper activity and increased aggressiveness [4]. Cadmium can enter to body by inhalation and other routes and accumulates mainly in the kidneys. At high levels, it can reach a critical threshold and can lead to serious kidney failure. Cadmium can enter through ingestion, intraperitoneal, subcutaneous, intramuscular and intravenous routes Vahter et al[5] that Cd^{2+} retention is generally higher in women than in men. "Ouch-ouch" or *itai-itai* is mainly a women disease. This disease is caused by long-term exposure of the inhabitants of Tayoma in Japan to Cd^{2+} intoxication. Clinical features of this disease include renal tubular dysfunction, osteomalacia, amino-aciduria, glycosuria and anemia which include decreased Hb, iron deficiency and low serum erythropoietin levels [6]in the human Hotz et al[7] shown that kidney effects may be reversible at low exposures once cadmium exposure is reduced or removed.

Cadmium – Carcinogenesis:

Cadmium affects cell proliferation, differentiation, apoptosis and other cellular activities and can cause numerous molecular lesions' that would be relevant to carcinogenesis. For a long time cadmium has been considered as a non-genotoxic carcinogen, as it is only weakly mutagenic in bacterial and mammalian cell test systems. Recently, it was evidenced that when assayed in a test system, in which both intragenic and multilocus mutations can be detected, cadmium acts as a strong mutagen which induces predominantly multilocus deletions. It was proposed that two mechanisms might play an important role in cadmium induced mutagenicity. They were 1.Induction of reactive oxygen species (ROS); and 2.Inhibition of DNA repair (**Figure.1**). Experimental evidence suggests that cadmium at relevant concentrations induces mutations by oxidative DNA damage and that it decreases genetic stability by inhibiting the repair of endogenous and exogenous DNA lesions, which in turn increase the probability of mutations and consequently cancer initiation by this metal. However, cadmium at nontoxic doses interferes with DNA repair processes and enhances the genotoxicity of directly acting mutagens.

Carcinogenic effect of cadmium in humans and in experiments with rats was discussed and concluded that, in rats induction of cancer in different organs by cadmium exposure was conformed but whereas in humans yet further studies are needed to conform the carcinogenic effect[8]. The rat testis may also develop tumors if cadmium is given peritoneal at high doses. Subsequent to testicular hemorrhagic necrosis, there will be loss of testosterone production and hyperplasia and neoplasia of testicular interstitial

cells, thought to be a response to trophic hormone release from the pituitary.

Regarding the apparent discrepancy between the results of human studies and those of laboratory animal studies, it should be clarified whether common mechanisms for the occurrence of carcinogenicity exist, and the apparent discrepancy should be explained at the molecular and cellular levels. Which means "The agent is probably carcinogenic to humans" based on the existing evidence proving it as causative for carcinogenesis.

Fig. 1: Showing Mechanisms involved in cadmium induced mutagenicity.

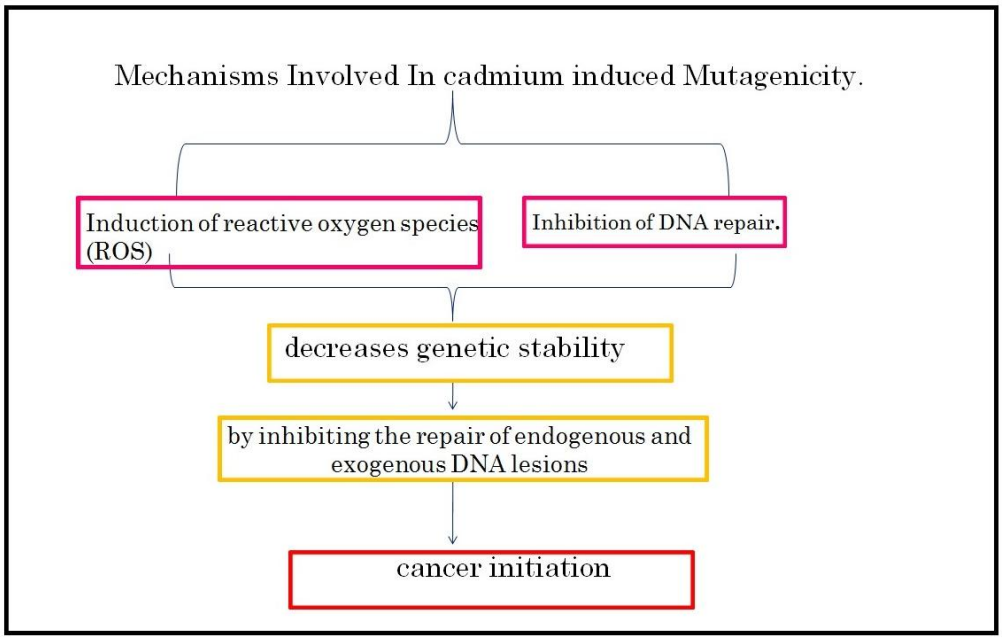
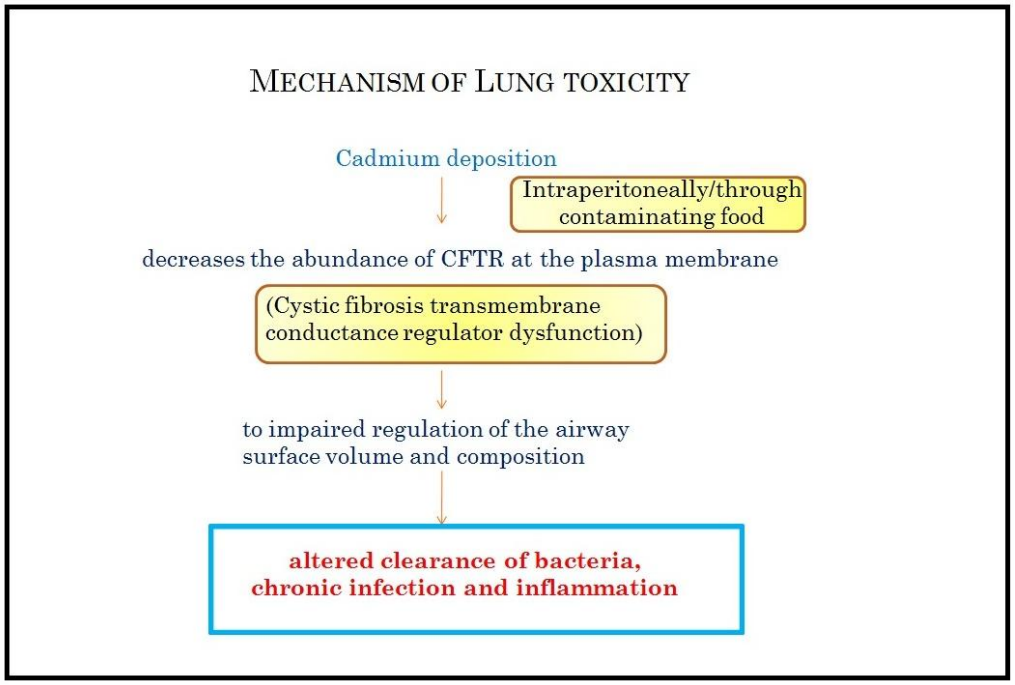


Fig. 2: Showing mechanism involved in cadmium induced Lung toxicity.



Genotoxic effect of Cadmium

Cadmium exposure has been established to induce cancer in various tissues of laboratory animals. Contrary to early findings of the lack of genotoxicity by cadmium, recent findings of mammalian cell culture studies have revealed genotoxic effects. Furthermore, cadmium exposure at relatively low doses induces circulatory diseases in laboratory animals. Despite such results of various cadmium toxicities in animal studies, data from human studies are lacking and insufficient to support the cause-effect relationship.

Non-genotoxic mechanisms upregulating intracellular signaling pathways leading to increased mitogenesis are discussed as major mechanisms for the interpretation of the carcinogenic activity by chronic cadmium exposure. About 1 µM cadmium stimulates DNA synthesis and cell proliferation in various cell lines, whereas more elevated concentrations are inhibitory. It stimulates the expression of immediate early genes (c-fos, c-jun, and c-myc), of the tumor suppressor gene p53, and of genes coding for the syntheses of protective molecules, including metallothioneins, glutathione, and stress (heat shock) proteins. The mechanisms underlying the modulation of gene activity by cadmium are discussed in terms of interference with cellular signaling at the levels of cell surface receptors, cellular calcium and zinc homeostasis, protein phosphorylation, and modification of transcription factors. In considering the available evidence, the carcinogenic properties of cadmium were interpreted using a multifactorial approach involving indirect genotoxicity (interference with DNA repair) and the up regulation of mitogenic signaling pathways.

Impact of cadmium on cell signaling pathways and in the induction of apoptosis:

The effect of Cd in altering the different signaling pathways and in induction of apoptosis[9, 10], Showed Cd induced apoptosis in different cell lines of different organisms including humans and reported that unlike Fenton-type metals Cd cannot produce reactive oxygen species directly; the apoptotic effects of cadmium at least in part are mediated via induction of oxidative stress. In C6 rat glioma cells, cadmium caused externalization of phosphatidylserine, break down of the mitochondrial membrane potential, and activation of caspase-9; inter nucleosomal DNA fragmentation, chromatin condensation and nuclear fragmentation. Cadmium as similar to H_2O_2 is a potent inducer of apoptosis in C6 cells[11]. Cd-induced apoptosis is partly caused by caspase-9 activation triggered by Cyt*c*[12]. Cadmium caused the PTP opening possibly through its binding to thiol groups of ANT. Furthermore, the mechanism of the PTP opening induced by cadmium was probably distinct from that of the calcium-induced PTP opening [13].The apoptotic effects of cadmium at least in part are mediated via induction of oxidative stress [11].

A rapid and transient ROS generation by Cd triggers apoptosis via caspase-dependent pathway and subsequent mitochondrial pathway. $CdCl_4$ treatment significantly increased the levels of apoptotic proteins such as caspases-3, PARP, Bax, Bid and cytochrome C and also increased the levels of inflammatory mediator'siNos and Cox-2 [14].

Cadmium – Cardiovascular dysfunction:

The incidence of cardiovascular disease has increased in the general population, and cardiac damage is indicated as one important cause of mortality. Recent investigation has established that free radicals may be important contributors to cardiac dysfunction and myocardial damage [15]. In our laboratory [16]reported that the cadmium toxicity could have induced oxidative damage in both liver and kidney by enhancing peroxidation of membrane lipids due to inhibition of the antioxidant enzymes,[17] has been carried some

investigations in our laboratory and reported cadmium toxicity induced alterations in heart and muscle tissues of rabbit leading to changes in blood constituents, abnormalities in heart and muscle function altering glycolysis, citric acid cycle, phosphotase metabolism, transamination reactions and induction of free radical stress.

The cardiovascular effect of cadmium was discussed by [9]and analyzed that renal tubular dysfunction by cadmium was associated with regulation of blood pressure.

Since both cadmium exposure and the incidence of cardiac damage have increased in recent years, Cadmium exposure could initiate some series of events that occur in the heart and result in the production of free radicals. If so, free radicals might contribute to the alterations processes in heart which result in further injury. Cd induced atherosclerosis was reported in rabbit [18]. According to [19] pretreatment with zinc produces tolerance to several cadmium toxic effects. They also reported that zinc-induced protection against the cytotoxicity of cadmium in stellate cells may be related to the maintenance of normal redox balance inside the cell. Thus the free radical induced damage was found to be major mechanism of cadmium induced cardiovascular diseases.

Cadmium – Lung damage:

The lungs absorb cadmiummore efficiently than the gastrointestinal tract[20,] Takenaka et al[21] that inhaled ultrafine Cd^{2+} oxide particles cloud cause lung injury in rats. An association between cadmium exposure and an increased risk of pulmonary diseases such as lung cancer and chronic obstructive pulmonary disease has been reported in humans and animals [22]. Cd induced CFTR (Cystic fibrosis transmembrane conductance regulator) dysfunction leads to impaired regulation of the airway surface volume and composition resulting in altered clearance of bacteria and chronic infection and inflammation [23]. Cadmium decreases the abundance of CFTR at the plasma membrane resulting in a decrease in chloride transport in epithelial cells present in the lung [24]. Minute amount of cadmium deposit in lungs if administered intraperitoneal or through contaminating food, it can still induces inflammation and proliferation due to persistent presence in lung cells but these two events may occur independently [25]. Thus the toxic effect of cadmium on lungs was mainly due to CFTR dysfunction, which results in altered bacterial clearance, there by infection and inflammation (**Figure.2**).

Cadmium – Hepatotoxicity:

The liver is the primary target organ following acute systemic Cd exposure. Approximately half of Cd absorbed systemically is rapidly accumulated in the liver, which results in the reduced availability of Cd to such organs as the kidneys and testes, which are more sensitive to its toxic actions [26]. Productions of reactive oxygen species and oxidative tissue damage due to Cd have been associated with hepatotoxicity.

It has been demonstrated that Cd produces both dose- and time-dependent increases in intracellular glutathione concentration during chronic environmental or occupational exposure at low doses. However, with high level acute Cd exposure, significant glutathione depletion occurs. Moreover, Cd is known to cause a reduction in glutathione content in isolated hepatocytes [27]. Liver injury due to acute Cd exposure is dominated by apoptosis and necrosis. Apoptosis seems to play a major role in eliminating damaged cells and its participation is profound in nonparenchymal liver cells where it represents the major type of cell death [28].

Histological evaluation of liver injury reveals that acute toxicity comprises hepatocellular swelling, sinusoidal congestion, pyknosis, and karyorrhexis[29]. Cd induced hepatotoxicity has

been shown to cause early cellular changes in the rough endoplasmic reticulum and nucleus [30]. Later alterations include mitochondrial swelling and the appearance of fibrillar material within the cytoplasm [31].

Several reports have addressed the direct mechanism of Cd-induced hepatotoxicity at the sub-cellular and molecular level. Sub-cellular localization of Cd demonstrates that Cd is distributed to the nucleus mitochondria and endoplasmic reticulum, which localizes Cd in target organelles[32]. Furthermore, Cd administration may also bring about DNA damage [33]. CdCl4 significantly increased the levels of lipid peroxides, oxidized glutathione and decreased the levels of reduced glutathione, SOD (Superoxide dismutase) and CAT (catalase) [14.] Production of reactive oxygen species, oxidative tissue damage, apoptosis, glutathione depletion were found to be the major mechanisms attributed for cadmium induced liver injury.

Renal toxic Effects:

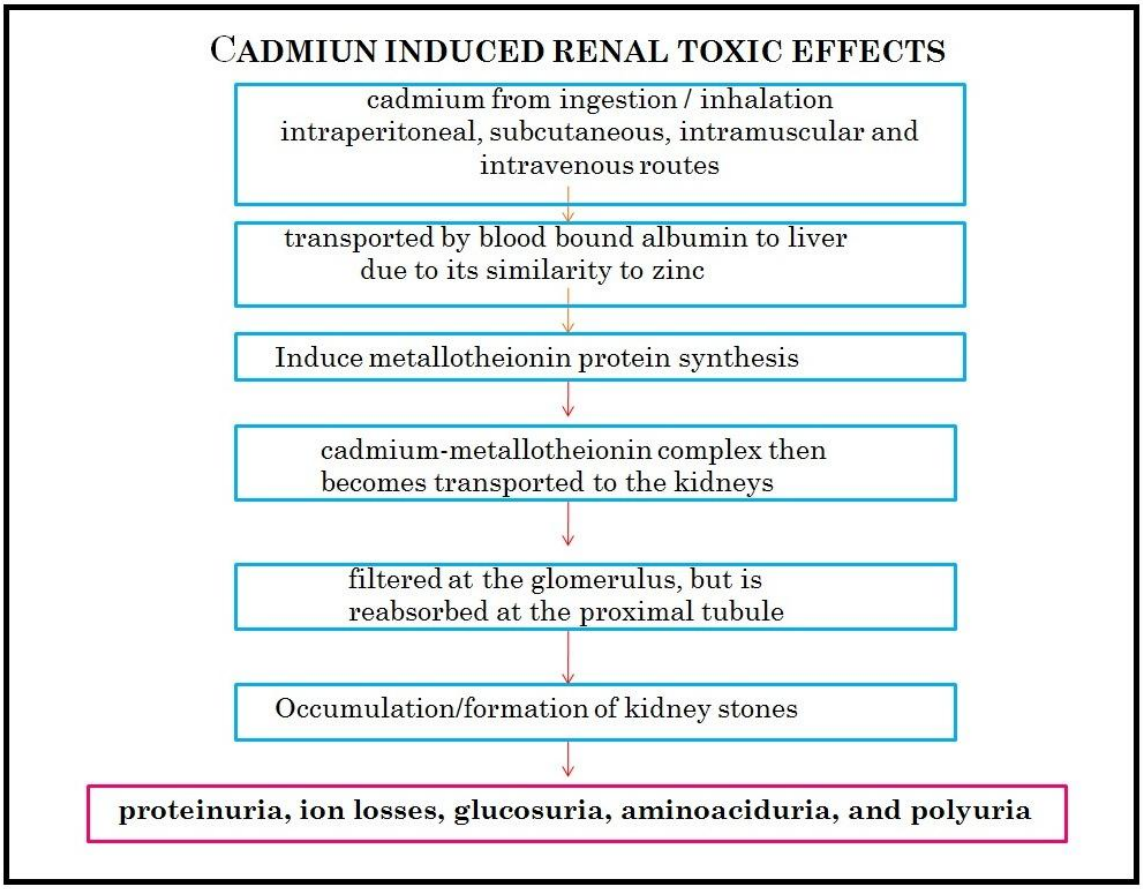
Cadmium can enter to body by inhalation and other routes and accumulates mainly in the kidneys. At high levels, it can reach a critical threshold and can lead to serious kidney failure. Cadmium can enter through ingestion, intraperitoneal, subcutaneous, intramuscular and intravenous routes. Expression of the ZIP8 metal ion transporter (*Slc39a8* gene) appears to be a key factor contributing to the selective toxicity of Cd in the endothelial cells of organs such as the testes and kidneys [34-35]**.** Cadmium and lead as chronic kidney disease risk factors in the general population and provide novel evidence of risk with environmental exposure to both metalsSeverity of renal toxicity increases with Cd accumulation in the kidney, which depends on the level and duration of exposure. A very important finding of this study is that Cd affects the kidney, especially the main tubules, even at relatively low accumulation levels in this organ.

The lower and long-term exposure to cadmium through air or through diet can cause kidney damage. Although the damage is not life-threatening, it can lead to the formation of kidney stones and affect the skeleton, which can be painful and debilitating. Humans have a daily intake of cadmium from ingestion and inhalation which is around 20 to 40 µg per day, but only 5 to 10% of this is absorbed. After absorption, cadmium is transported into the blood bound albumin. It is taken up by the liver and due to its similarity to zinc, causes this organ to induce the synthesis of the protein metallotheionin (MT) to which it binds. The cadmium-metallotheionin complex then becomes transported to the kidneys, and it is filtered at the glomerulus, but is reabsorbed at the proximal tubulewhere it remains stored therefore; the kidney is one of the main target organs for cadmium induced toxicity [36]. Within the renal tubular cells, the cadmium-MT complex becomes degraded by digestive enzymes, which releases the cadmium. Renal tubular cells deal with the release of this toxic substance by synthesizing MT to neutralize it, but eventually the kidneys lose their synthetic capacity for MT. At this point, the cadmium has accumulated to a high level in the renal tubular cells, and irreversible cell damage occurs (**Figure.3**)[37].

The renal toxicity of cadmium in humans and in various experimental animal studies from the previous studies and concluded that induction of renal dysfunction may be partly dependent upon the biosynthesized amounts of metallothioneins in the kidney[9]. Several mechanisms have been proposed to explain the toxic effect of Cd^{2+} on renal cells. Cd may cause nephrotoxicity by generating free radicals [38-39]. Interestingly, a protective effect of zinc (Zn^{2+}) has been reported in vitro against the cellular toxicity due to Cd^{2}.

Zn^{2+}protection is probably due to an action on oxidative stress and apoptosis [40]while Cd^{2+} induces cytochrome C release from mitochondria, leading to apoptosis via the activation of the caspase 3 and 9 cascade (**Figure.3**)[41].

Fig. 3: Showing cadmium induced renal toxicity



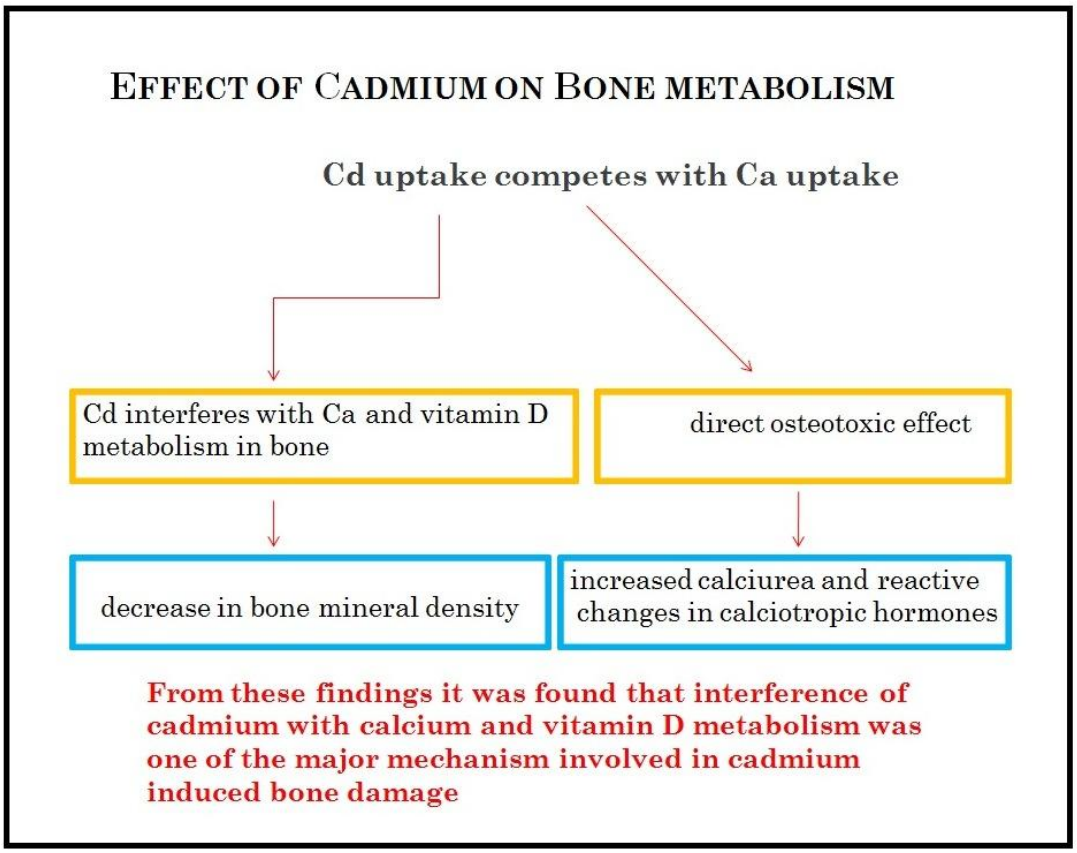
Cadmium – bone metabolism:

Bone density and biomarkers such as parathyroid hormone, calcitonin and bone specific alkaline phosphatase activity levels were studied on exposure to Cd in women population[42].

Renal dysfunction and bone metabolism disorder are known to be the representative adverse health effects of chronic Cd toxicity in humans and animals. Other effects of Cd exposure on humans and animals are also recognized as follows: cases of acute and chronic toxicity due to occupational and environmental exposure, such as anemia, respiratory disorder, hypertensive and cardiovascular effects, nervous system symptoms, cancer of the lung and prostate, toxic effects on the placenta and teratogenicity[43, 44]. Particularly, Cd interferes with Ca and vitamin-D metabolism in bone, kidney and intestine. The interaction between Cd and Ca in bone, intestine, and kidney may result in the disorder of bone metabolism. On the other hand, pregnancy and lactation are also important physiological factors affecting bone metabolism in the mother. Ca absorption is decreased by competition with Cd in the intestine, and more Ca is released from maternal bone and transferred to neonate by lactation. In

the intestine, Cd uptake competes with Ca uptake. Cd causes a marked decrease in bone density compared to the normal decrease in bone mineral density during lactation. Lactation is an important factor contributing to the decrease in bone mineral density and Cd has an additive effect of decreasing bone metabolism of mother animal, although the Cd intake level is relatively low (approximately 3-14µg Cd/kg/day). Environmental exposure to cadmium increases bone resorption in women, suggesting a direct osteotoxic effect with increased calciurea and reactive changes in calciotropic hormones [42]. Long-term dietary exposures in rats, at levels corresponding to environmental exposures in humans, result in increased skeletal fragility and decreased mineral density. Cadmium-induced demineralization begins soon after exposure, within 24 hours of an oral dose to mice. In bone culture systems, cadmium at low concentrations acts directly on bone cells to cause both decreases in bone formation and increases in bone resorption, independent of its effects on kidney, intestine, or circulating hormone concentrations[45]. Cd administration affects bone marrow, spleen and thymus (Figure.4)[46]. From these findings it was found that interference of cadmium with calcium and vitamin-D metabolism was one of the major mechanisms involved in cadmium induced bone damage.

Fig. 4: Showing mechanism involved in cadmium induced bone damage



Effect on reproduction:

Cd^{2+} has been shown to exert significant effects on ovarian and reproductive tract morphology, with extremely low dosages reported to simultaneous ovarian luteal progesterone biosynthesis and high dosages inhibiting it[47].

Survival of adult insect *Oncopeltus fasciatus* females was decreased at concentrations higher than 10 mg Cd/l, while males were only affected at 30 mg Cd/l or higher doses. Reproduction was the most affected parameter. Oviposition rate, fecundity and fertility of females exposed to 10 mg Cd/l were significantly lower than controls (73%, 58% and 55% relative to controls, respectively). Areduction in adult survival and no reproduction at the highest concentrations of Cd and Zn was observed in *Proisotomaminuta*Tullberg (Collembola) [48].

Cadmium is directly toxic to primary Leydig cells, and that the decreased percentage of normal cells and the increased level of DNA damage in cadmium-exposed Leydig cells may be responsible for decreased testosterone secretion in rats [49].

The combined exposure of lead and Cd^{2+} causes decreased glutathione status and SOD activities in rat ovarian granulose cells.[50] They reported that these toxic metals disturb membrane integrity of cells via reactive oxygen species (ROS) and thereby classifying mechanism for altered receptor binding, steroidogenesis, and hormone production[51], observed increased Cd^{2+} concentrations and shortened prothrombine time leads to a stage of hyper coagulation which in turn leads to a risk of thrombosis in rats. Significant positive association between the percentage of immotile sperms and seminal plasma levels of lead and cadmium was observed [52]. No association is indicated for blood cadmium from women and oocyte fertilization, adjusted for urine cadmium, however, an inverse adjusted association between blood cadmium from men and oocyte fertilization (relative risk=0.66, P=0.143) was observed [53].

In SPEED 98 (Strategic Programs on Environmental Endocrine Disruptors '*98*) declared that cadmium is one of the 70 susceptible elements found to have adverse effects on endocrine system. Production of Reactive oxygen species, necrosis, and inhibition of progesterone biosynthesis, decreased glutathione status and SOD activities in were the so far observed mechanisms of cadmium induced reproductive toxicity.

CONCLUSION

Finally it is concluded that, based on existing literature a significant association was observed between risk of pathogenicity and environmental exposure to cadmium. An attempt has been made first time to project such an association to our knowledge has been reported in relation to cadmium toxicity. These findings of information helps to understand the cadmium induced serious health hazard leading to necessitating the importance of preventive measure formulation and practice.

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