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Review Article

Cadmium: An Environmental Heavy Metal with Nephrotoxic Potency, Especially in Diabetic Population

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Abstract

Our history began about 4.5 billion years ago when our solar system was formed and earth started to take a shape. We are being blessed with uncountable number of, known and unknown, natural resources. We are dependent on them as such that sometimes we cannot even notice their presence. Besides enormous beneficial impacts, the environment we live in is a huge reservoir of toxic metals. Our health is under constant risk due to increasing chronic exposure of such metals that adversely affect the quality of life of people. The deterioration of human health due to exposure to heavy metals has become a major issue of concern worldwide. Although adverse health effects caused by heavy metals have been known for a long time, exposure to heavy metals continues, and is even increasing in some parts of the world, particularly in developing countries. One such heavy metal with a high toxicity found in the earth's crust, associated with zinc, lead and copper ores is cadmium. Exposure to cadmium has long been recognized as a health hazard, both in industry and in general populations with high exposure. The parts of body that are potentially affected from exposures to cadmium mainly involve the kidney, liver, lung, heart and bone. There is also a positive association between cadmium exposure and increased nephrotoxicity in patients with diabetes mellitus. The objective of this paper is to review available information on possible toxicities specially nephrotoxicity of cadmium on human health in general and also in diabetic population.

Key words*: Cadmium toxicity; Environmental heavy metal toxicity; Diabetic nephropathy; Nephrotoxic heavy metal*

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1. Introduction

Natural resources occur naturally within environment in a natural form. Some of them are essential for our survival while most are used for satisfying our needs. A natural resource may exist as a separate entity such as fresh water, and air, as well as a living organism such as a fish, or it may exist in an alternative form which must be processed to obtain the resource such as metal ores, oil, and most forms of energy. We are dependent on them as such that sometimes we cannot even notice their presence. Besides their beneficial effects, our activities and ill intuitions have proved them to be potentially harmful when we use them irrationally. One of such element is cadmium.

1.1 Cadmium

Cadmium is a soft, bluish-white metallic element with the symbol Cd and atomic number 48. It was discovered in 1817 by two German scientists, Stromeyer and Hermann, as an impurity in zinc carbonate.[1,2] Naturally it is found in the earth's crusts. The most common forms found in the environment are in combination with other element, e.g., cadmium oxide, cadmium chloride, cadmium sulfide etc.[2]

1.2 Sources of human exposure to cadmium[3,4]

- Natural activities: Volcanic activity, weathering and

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erosion and river transport.

- Human activities: Tobacco smoking (both active and passive), tobacco leaf, food adulteration, mining, smelting and refining nonferrous metals, metal soldering, battery manufacturers, fossil fuel combustion, incineration of municipal waste, paint pigment, making polyvinyl chloride plastics, electroplating, manufacture of phosphate fertilizer and recycling of cadmium-plated steel scrap and electric and electronic waste.
- Remobilization of other sources: like remobilization of watercourses by drainage water from metal mines.

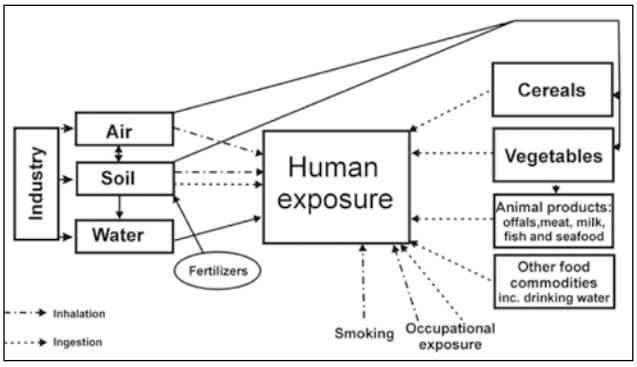

Fig 1. Sources of human exposure to cadmium[4]

1.3 Metabolism of cadmium in humans

Cadmium is more efficiently absorbed from the lungs (25−60%) than the gut (5−10%).[5-7] Absorption of Cd from both lungs and gut largely depends on solubility of the compound and size of the molecule. In our body Cd is bound to red blood cells or high molecular weight proteins in the plasma mainly. For this, it is widely distributed in our body. It accumulates in the liver and kidney and helps in producing metallothionein. Metallothionein (MT) is a low molecular weight intracellular protein, available in liver, kidney, intestine and pancreas. Much of the Cd in the kidney and in other tissues is bound to MT which is thought to sequester cadmium, prevent damage to cellular constituents, but which also retains cadmium in the cell.[5-12] When cadmium-metallothionein (Cd-MT) compound is released into the circulation it is filtered by kidney and reabsorbed by cells of proximal tubules. Cd thus accumulates in renal tubular cells, until the synthetic capacity for MT is exceeded.[10] For individuals who are chronically exposed to environmental levels of Cd either by diet or smoking, the highest concentrations of Cd are measured in the renal cortex.[6]

1.4 Safety level of cadmium for humans[3]

World Health Organization (WHO) cadmium guidelines
Provisional tolerable monthly intake (PTMI)
In 2010 the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable monthly intake for cadmium of 25 μg/kg body weight.
Drinking-water
3 μg/L
Air
5 ng/m^3 (annual average)

1.5 Health effects of cadmium[3,4,7, 8,13]

Though it is generally present in the environment at low level but human activity has greatly increased those levels. It is toxic for our kidneys, skeletal system and respiratory system and also carcinogenic.

- **High level of exposure**: If taken with food or water, it can severely irritate stomach and cause vomiting and diarrhea. But breathing high dose of cadmium can cause pneumonitis, pulmonary edema and also death.
- **Low level and long term exposure**: It can cause kidney damage, formation of kidney stone, softening of bones and osteoporosis, Itai-itai disease (osteomalacia, osteoporosis, painful bone fracture and kidney dysfunction), chronic obstructive pulmonary disease (COPD). There is also evidence that long-term low level exposure of Cd can cause lung cancer and also cancers of kidney and prostate.

1.6 Effect on kidney

The kidney is the critical target organ. Cadmium accumulates primarily in the kidneys and its biological half-life in humans is 10–35 years. Accumulation of cadmium in the kidney results in loss of tubular function, leading to tubular proteinuria evidenced by an increase in urinary excretion of β2-microglobulin, retinol binding protein and α1-microglobulin. Cd can cause irreversible damage to kidneys.[14,15]

2. Diabetes mellitus (DM), chronic kidney disease (CKD) and cadmium (Cd)

Most recent estimates of International Diabetes

Federation (IDF) indicate that worldwide 8.3% of adults (382 million people) have diabetes, and the number of people with the disease is set to rise beyond 592 million in less than 25 years. The alarming information is that 175 million people with diabetes are undiagnosed. Eighty percent of people with diabetes live in low and middle income countries. Diabetes caused 5.1 million deaths in 2013, which means in every six seconds a person died from diabetes. Kidney disease (nephropathy) is far more common in people with diabetes (50% of patients with DM of more than 20 years' duration develop diabetic nephropathy that is about 190 million people are at risk of DN) than in people without diabetes and diabetes is one of the leading causes of chronic kidney disease (DM is the cause of 30−40% of all ESKD in USA).[13,16]

Diabetes and diabetes-related kidney disease are serious health problems that are the causes of growing concern in many parts of the world. Diabetic nephropathy (DN) is associated with albuminuria, decreased creatinine clearance, altered glomerular morphology and tubular degeneration. Approximately 30−40% of type 2 diabetic patients will develop diabetic nephropathy, and it is now the most common cause of end stage renal failure in the Western world.[13,17] While DN is most commonly associated with the more severe and advanced stages of type 2 diabetes, there is increasing concern that even early stages of the disease, which are sometimes referred to as prediabetes, may be associated with increased risk of kidney disease.[13]

Type 2 diabetes and diabetic nephropathy are chronic progressive diseases that are associated with a combination of genetic, lifestyle and environmental factors. While many risk factors have been identified, it is most likely that there are also some unidentified environmental factors. The metabolism of Cd and effect of exposure to Cd on pancreas, liver, adrenal gland, kidney and adipose tissue suggests that Cd may play a role in the development and progression of diabetes and diabetes-related kidney disease (Fig 2)[13].

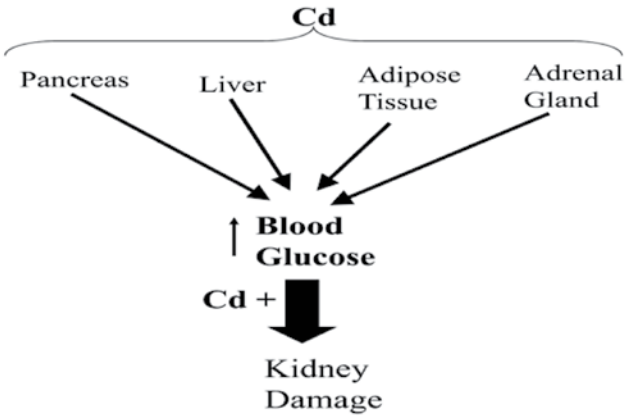

Fig 2. Schematic diagram summarizing potential mechanisms of Cd-induced elevation of blood glucose levels and subsequent renal damage[13]

Following Cd exposure, adipose, pancreatic, and liver tissues along with the adrenal gland, become injured leading to altered glucose metabolism and/or glucose uptake that ultimately results in increased blood glucose. Elevated blood glucose levels coupled with the direct effects of Cd on renal tissue eventually leads to kidney dysfunction and damage.[13]

3. Current status of cadmium exposure/toxicity

To avoid cadmium exposure and to make others aware, we should know about its current impact. Natural and anthropogenic sources are the major categorized sources of Cd emissions to the environments such as air, water and soil. Various human activities (such as mining, metal production, combustion of fossil fuels and other industrial processes) have resulted in elevated cadmium concentrations in the environment. Atmospheric deposition, phosphate fertilizers and sewage sludge appear to be the major contributors to cadmium levels in agricultural soils.[3-5,8] In a number of European countries, atmospheric deposition, animal manures, sewage sludge and the presence of cadmium in fertilizers are causing increase in the content of cadmium in topsoil. As cadmium is taken up by plants, increased soil concentrations can result in increased concentrations in food products.[8,18]

Food is an important source of Cd exposure. Rice, wheat and maize combinedly provides about 44% of worlds' dietary energy supply.[8] Nearly 90% of world's rice has been produced and consumed in Asian countries (China, India, Bangladesh, Sri Lanka,

Myanmar, Indonesia and others).[19] Scientists from all of these countries have reported in different studies about detection of high level of Cd in rice in different times.[8,20-23]

Different studies from Japan suggested high concentration of Cd in sea fish and algae. In 2012, European Food Safety Authority has named grain and grain products, vegetable and vegetable products, starchy roots and tubers as the dominating source of excessive Cd along with other foods like potatoes, bread and rolls, bakery wares, chocolate products, leafy vegetables and water molluscs.[24]

Occupational exposure to cadmium is mainly by inhalation; but it varies according to types of industry and duration of cadmium exposure. The National Institute of Occupational Safety and Health (NIOSH) estimated that in the United States 1500000 workers might be exposed to this metal.[8,9]

Cigarette smoking is another major source of cadmium exposure. It has been reported that the cigarette tobacco contains about 0.5 to 2.0 μg of cadmium and about 10% of the cadmium content is inhaled when cigarette is smoked (WHO 1992) and the non-smoker may passively inhale significant amount of cadmium as well. Even though the gastrointestinal absorption of cadmium is only a few percent, the absorption of cadmium in the lungs is 10–50%.[8,25] A study was carried out in Thailand to estimate the relative level of cadmium exposure from both diet and smoking in low exposure area (Bangkok) and high exposure area (Mae Sot). A comparison of observed urinary-Cd data from males and females who never smoked, in the 20 to 39-year old and 40 to 59-year old groups, in Mae Sot with respective counterparts in Bangkok indicated overall cadmium exposure levels in Mae Sot to be 3 to 3.8 times greater than in Bangkok.[26]

4. Further study on cadmium and diabetic nephropathy

Exposure to cadmium may cause kidney damage. Recent epidemiological studies suggest a positive association between exposure to Cd and the incidence and severity of diabetes.

In 2003, in a study on 8,722 U.S. citizens Schwartz et al[27] found a significant association between elevations in urinary Cd levels and increase in fasting blood glucose levels (110−126 mg/dL, N = 610) as well as the number of individuals diagnosed with type 2 diabetes (N = 1207).

In a cross sectional study among 229 Chinese type 2 DM patients, Chen et al[28] had proved that the presence of metallothionein antibody (MT-Ab) can potentiate tubular dysfunction among diabetic subjects and the patients with high MT-Ab levels are more prone to develop tubular damage.

In a study in Pakistan in 2009, Afridi et al[29] showed that diabetic males (N = 196) had significantly higher blood and urinary levels of Cd than non-diabetic males (N = 238). These differences were evident in both smokers (N = 209) and non-smokers (N = 225).

Haswell-Elkins et al[30] found a statistically significant correlation between urinary Cd levels and albuminuria in individuals with type 2 diabetes, but found no such correlation in non-diabetic individuals.

In another study in Belgium, Buchet et al[31] found a significant association between the urinary biomarkers of renal injury (NAG and β2-microglobulin), Cd exposure and diabetes as determined by a multivariate correlation analysis of data from a sampling of 1699 men and women aged 20−80. In a similar study on 820 Swedish women between 53 and 64 years, multiple linear regression analysis showed statistically significant associations between urinary α1-microglobulin, urinary Cd and diabetes.[32]

5. Recommendation by World Health Organization (WHO) to decrease Cd exposure[3]

To decrease global environmental cadmium releases and reduce occupational and environmental exposure to cadmium and associated health effects, the following actions are recommended by WHO.

- Prohibit smoking in public places.
- Reduce, as far as is practicable, emissions of cadmium ─ particularly on surface waters ─ from mining and smelting, waste incineration, application of sewage sludge to the land, and use of phosphate fertilizers and cadmium-containing manure. Develop techniques for the safe disposal of cadmium-containing wastes and effluents.
- Promote effective measures to increase recycling of cadmium and to restrict non-recyclable uses.
- Reduce cadmium exposure by, for instance,

improving working conditions in the non-ferrous smelting industry and disseminating information on the proper use of fertilizers (which sometimes contain high levels of cadmium).

- Raise global awareness on the importance of minimizing waste discharges of cadmium.

Conclusion

Cadmium is a toxic environmental pollutant and ranked the 7th toxicant in the Priority List of Hazardous Substances of the Agency for Toxic Substances and Disease Registry. It has the potency to enhance the progression of any nephropathy and can damage kidney irreversibly. Diabetes mellitus is a non-communicable disease which is also regarded as an epidemic. DM and its complications like diabetic kidney disease costs hundreds of billion dollars' expenditure in health sector. DM is regarded as one of the major cause of CKD worldwide. For DM about 190 million people are currently at risk of developing CKD, who are also at risk of exposure to chronic low-level toxicity of Cd that can enhance the progression of both DM and DN. So there is scope for research about whether Cd is a reversible risk factor for developing CKD, especially in diabetic population and for finding ways of proper management steps to prevent the progression of CKD in diabetic patients who are exposed to chronic low level Cd. Thus we will also be able to prevent the unexplained CKD and ESKD. Research should also be carried out to identify any marker suitable for mass screening in any part of the world to detect early Cd toxicity so that we can prevent the adverse situation.

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