Heavy Metal Toxicity: The Role of Cadmium in the Animal Body

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Abstract: Heavy metal toxicity is a major public health concern. Exposure to such metals as cadmium, arsenic, lead etc. in human body causes deleterious effect. World Health Organization informed that the emission rate of cadmium is maximum in developing countries than in the developed part. Cadmium poisoning is reflected in the form of renal dysfunction, poor bone mineral density. It’s occurrence in nature is in association with zinc and lead. Extraction and processing of these metals often lead to environmental contamination with cadmium.

Keywords: Heavy metal toxicity, cadmium, renal dysfunction, bone mineral density, emission.

I. Introduction

Heavy metals have been used by humans for thousands of years. The main threats to human health from heavy metals are associated with exposure to lead, cadmium, arsenic and mercury. These metals have been extensively studied and their effects on human health regularly reviewed by international bodies such as the World Health Organization [1], [2].

Recent study by Nordberg GF in 1996 on Cadmium and health in the 21st century reported that in many countries Cadmium (Cd) exposure are now under better control than in the past, thus the target for the 21st century is to achieve a totally acceptable exposure situation without adverse health effects from Cd. The binding of cadmium to the protein metallothionein was found in the subsequent toxicokinetic and toxicodynamic study [3].

Recently, cadmium has been classified as a human carcinogen. It ranks close to lead and mercury as a metal of toxicological concern. It is an element whose essentiality has not yet been established, although there is evidence of participation in certain adverse biological reaction [4]. The present paper attempts to review a number of individual studies on the availability of Cadmium, its historical evidence along with its effect on humans and animals with particular emphasis on sensitive biomarkers.

The first health effects of cadmium (Cd) were reported in 1858. The first experimental toxicological studies are from 1919. The effects of Cd on bone and proteinuria in humans were reported in the 1940’s. The itai-itai disease originated in Japan after World War II was a bone disease with severe pain and fractures due to Cd-induced renal osteomalacia [5]. Not only long term exposure to Cadmium decreases Bone Mineral Density (BMD), even low environmental exposure to Cd, as indicated by cadmium body burden is related with increased urinary excretion of marker protein that symbolizes renal dysfunction and increased risk of cadmium induced bone disorder [6]. Early toxicological studies showed that Metallothionein (MT) is a protein that carries Cadmium (Cd) to the kidney thus clearly explains the reason of kidney dysfunction after long time Cd exposure [7].

A. Transport and Occurrence

Cadmium occurs in nature in the form of various compounds as in association with zinc and lead. Extraction and processing of these metals often lead to environmental contamination with cadmium. Organic compounds are very unstable and have not been detected in nature. Transport of Cadmium in the environment may takes place through air or water.

B. Sources of exposure

There has been alarming rise in the levels of Cd in air, water and soil exceptionally in industrial areas, although recently government and policy makers in developed nations put down certain limits on cadmium exposure. Food is not a very important source of Cd exposure, only plants from non-industrial areas may contain small or moderate amounts of it. High levels of Cd are found in liver and kidney of adult animals. The real intake of Cd through food depends geographically [8,9]. The WHO standard for cadmium in food items is 0.07 mg/day [10].
Tobacco smoke is an important source of Cadmium exposure. One cigarette contains 1-2 µg of Cadmium, and with 10% pulmonary absorption, the smoking of one pack of cigarettes per day results in a dose of approximately 1mg of Cadmium per year from smoking alone [10,11].

C. Regions in India affected with Cadmium toxicity

Various regions in India are affected with Cadmium poisoning.

- To observe the current status of toxic metal content of Indian rivers, government of India, Ministry of Water Resources through Central Water Commission assessed the status of trace and toxic metals in Indian rivers. A total of four Indian rivers viz. Cauvery, Pennar, Yamuna and Hindon are contaminated through cadmium at 7 water quality monitoring stations. The highest cadmium concentration (4.0 µg/l) was observed in the Delhi Railway Bridge and Mathaura water quality monitoring stations at Yamuna river during June 2012. Bureau of Indian Standard (BIS) have recommended an acceptable limit of 3µg/l of cadmium in drinking water [12].
- Industrial area of Chattisgarh state is badly affected with cadmium toxicity. Sinha D in 2013 analyzed the concentration of three metals around those areas and its effect on the humans. He found increased concentration of these three toxic elements in the polluted water and the result was statistically significant (p<0.0001) [13].
- Another study by Radha RV, Kumutha K, Marimuthu P on assessment of cadmium contamination of soils in sewage disposal areas of Coimbatore district, Tamil Nadu, showed high levels of more than 3mg/kg of cadmium were identified as hotspots [14].
- National Thermal Power Corporation in Tanda, Uttar Pradesh were contaminated with fly-ash hence, native plants and algae growing near it were screened so that various aquatic, terrestrial and algal species of plants may be used in a synergistic way to remediate and restore the fly-ash contaminated areas [15].

D. Biomagnification of Cadmium in human body

Cadmium is not essential for human body, but it is a major source of environmental pollution which has found a strong place in civilization. Like, lead and mercury it is also accumulative poison, which accumulates in the body with advancing age.

At birth cadmium is absent in an infant. As the body ages the metal absorbed from air, water and food tends to accumulate in the body. As compared to a 10% - 40% absorption when inhaled as fumes or dust, dietary cadmium is retained only to the extent of 5 - 10% depending on factors such as the intake of Protein, Vitamin, Iron, Zinc and Calcium.

- Sensitive biomarkers of Cadmium

Cadmium is a renowned nephrotoxic agent with extremely long biological half-time of 15-30 years in humans. To prevent nephrotoxicity induced by cadmium, it is necessary to identify specific and sensitive biomarkers of cadmium exposure and renal damage. Epidemiological study among occupational population in China revealed urinary beta 2-microglobulin (UB2M), N-acetyl beta-D-glucosaminidase (UNAG) and albumin (UALB) as effective biomarkers of tubular and glomerular dysfunction [16].

Another study by Nordberg GF et al in 1990 identified urinary retinol binding protein (URBP) as biomarkers of renal dysfunction [17].

- Provisional Tolerable Weekly Intake (PTWI)

Various population studies indicated that the present provisional tolerable weekly intake (PTWI) for cadmium is 500µg, corresponding to a daily intake of 70µg or 1µg/kg body weight [18].

Gastrointestinal studies demonstrated high oral intake of cadmium (16mg/lit) via food or drink in a single dose by humans gives rise to vomiting, abdominal pain and diarrhea. Recent data demonstrating renal dysfunction in humans at even lower lifelong oral exposures signifying PTWI needs to be lowered in the future [19].

Report obtained from the review stated Cd exposure situation in Sweden and updates the information on health risk assessment. The main motto is on the health effects of low Cd doses and the identification of high risk groups. Findings are that the diet comprising of high fiber and shell fish increase the dietary Cd intake substantially signifying considerable Cd concentrations in agricultural soil and wheat particularly in the last century [20].

Animal experiments too showed kidney dysfunction, reproductive and developmental effects at long term Cd exposure in occupational and general environments as well as in oral and other exposures ([21], [25]).

E. Reproductive dysfunction- effect on males and females

- Testicular necrosis, a common characteristic of short- term exposure to cadmium in experimental animals. Testicular damage occurs within a few hours of a single exposure to cadmium and results in necrosis, degeneration and complete loss of spermatozoa. Cadmium reduces blood flow through the testis and ischaemic necrosis results from the lack of oxygen and nutrients reaching the tissue [10].

- The damage to the embryo during pregnancy through the exposure of the mother to the cadmium or any toxin is recognized as Teratogenesis, which is cadmium induced zinc deficiency. Female rats exposed to cadmium four to five months before mating and gestation showed damage to offspring [10].
Current study on cadmium-induced ovarian pathophysiology is mediated by change in gene expression pattern of zinc transporters in zebra fish revealed the potential for expression pattern of genes encoding zinc (Zn) transporters to be involved in the cadmium-induced reproductive toxicity in female of zebra fish. Result indicated decrease in the expression of zn transporter 1 (zn T1) and caused up-regulation of Ir-ap-related protein 10 (ZIP 10) and zebra fish metallothionein (zmTH) gene expression. Apart from gene expression, other changes include increased accumulation of Cd and metallothioneins (MTs), decreased Zn contents and histopathological damages in ovarian tissues [22].

**Mechanism of Kidney affected**

Some Cadmium binds to metallothionein in the liver leaks into the plasma and then is taken up by the kidney. A sufficient concentration (200μg/g) damages the kidney cell, resulting in proximal tubular injury and proteinuria [23]. With more severe exposure, glomerular injury occurs, filtration is decreased and there are aminoaciduria, glycosuria and proteinuria. The nature of glomerular injury is unknown but may involve an autoimmune component [24].

**II. Effects of cadmium on animals**

- Animal study by Leffler P, Jin TY and Nordberg GF (1994) reported kidney dysfunction and increased urinary excretion of the major minerals like calcium, magnesium, sodium and potassium as well as protein and metallothionein following the injection of cadmium-metallothionein (CdMT) in rats [26].
- Another study by Liu X et al in 1987 observed that the Cd retention level was markedly reduced in renal cortex and increased in liver by copper pretreatment, while the urinary excretion of Cd was significantly lower in these rats. The levels of endogenous Zinc in renal cortex and liver increased significantly in rats pretreated with Copper. The production of Metallothionein in liver and renal cortex was induced more efficiently by Copper than by Zinc [27,28].
- In a study by Jin T, Nordberg GF, Nordberg M in 2006 showed higher metallothionein concentration in kidney cortex when groups of rats were pretreated with cadmium chloride constituted a clear explanation of the protective effects of pretreatment against the development of increased proteinuria after ‘challenge dose’ i.e. 109Cd- metallothionein 0.05 or 0.4mg Cd/kg body weight is given [29].
- The authors Liu J, Nordberg GF, Frech W in 2004 studied compromised kidney function including tubular damage induced by a low dose of Cd MT [30].
- One of the significant animal study by Leffler PE, Jin T and Nordberg GF examined nephrotoxic impact after multiple short interval Cadmium-Metallothionein (Cd MT) injection instead of a single dose. A marked proteinuria and a progressive unreversed calciuria are suggestive of residual tubular damage [31].
- The authors Jin T et al (1995) observed the effect of cadmium metallothionein induced nephrotoxicity in diabetic, obese and Swedish mice. According to him low doses (0.1mg/kg) of CdMT induced proteinuria and calciuria in obese hyperglycemic Swedish mice than in the normal mice which also developed the same condition but at a much lower dose of 0.4 mg Cd/kg. A dose-related increase in glycosuria was observed in both types of mice, in spite of decreased levels of serum insulin and glucose. The result of the present study thus indicate that metabolic changes like those in diabetes may increase susceptibility to Cadmium induced renal tubular damage [32].
- It has been postulated that Aluminium was toxic to the kidney tubule cells of rats but adequate supply of Calcium in food give protection to some extent to the renal tubules as indicated by a higher creatinine clearance and less tubule damage by histological examination [33].
- A dose related findings from the author Jin T, Nordberg G, Sehlin J, Wallin H and Sandberg S in 2009 are that diabetic rats induced by streptozotocin are more susceptible to Cd nephrotoxicity than normal non-diabetic rats when they are sub chronically exposed to cadmium chloride in drinking water in doses of 0, 50 and 100ppm for 90 days [34].
- Another study by the author Gunnarsson D, Nordberg G, Lundgren P, and Seistam G in 1996 demonstrated statistically significant decrease in lutenizing hormone (LH) receptor mRNA level in the testicular tissue at the highest dose of CdCl2 (10 micromol/kg) [35].
- In an epidemiological study in China Lu J, Jin T, Nordberg G, Nordberg M in 2009 measured MT mRNA levels using reverse transcription polymerase chain reaction (RT – PCR) in peripheral blood lymphocytes from residents living in a cadmium contaminated area. MT mRNA levels were found to increase with the increase of blood cadmium and urinary cadmium levels [36].
- One important study by Jin T, Nordberg G, Sehlin J, and Vesterberg O in 2005 revealed protection against the development of nephrotoxicity following the administration of cadmium-metallothionein (CdMT) at a dose of 0.4 mg Cd per kg body weight in streptozotocin (STZ) induced diabetic rats. Induction of increased MT synthesis in liver and kidney as the result of the STZ treatment was observed in this study [37].
III Conclusion

Heavy metals are toxic to both humans and animals. Cadmium causes deleterious effect in the kidney resulting in nephrotoxicity (kidney tubular damage) and bone damage either via a direct effect on bone tissue or indirectly as a result of renal dysfunction. It acts as an environmental pollutant releasing from industrial and agricultural sources. It is taken through food in the non-smoking general population and is efficiently retained by the kidney for at least 10-30 years. It has been seen that Cd produces its maximum toxic effect when the level of iron in the body is poor. Furthermore, recent data also suggest the risk of cancer and mortality rates are increased threefold among Cd exposed population [38]. The Government of India needs to take appropriate measures to tackle the menace.

References


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