Review article

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TOXIC EFFECTS OF CADMIUM

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Cadmium is one of the heavy metals, it is often used in industry, and exerts toxic effects on human health. Cadmium is classified as a carcinogenic substance for humans by the International Agency for Research on Cancer and is in a group I carcinogen. Cadmium affects the development of cell cycle, proliferation, differentiation, DNA repair, replication and apoptosis, as well as promotion of cancer in tissues. Intoxication with cadmium in people usually occurs by inhalation of cigarette smoke, but it is also possible via water, food and air. Cadmium exerts toxic effects on the kidneys, liver, lungs, cardiovascular system, immune system and reproductive system. Metallothionein protects tissues from the toxicity of cadmium. Cadmium-metallothionein complex is distributed in various tissues. There is no way for natural cadmium elimination from the human body. The main route of cadmium in the body is through binding with metallothionein, low molecular weight protein that participates in the homeostasis of certain metals. Cadmium-metallothionein complex is distributed in various tissues. The role of metallothionein in detoxification of cadmium is primarily in the large binding affinity of metals for metallothionein. *Acta Medica Medianae 2012;51(4):65-70.*

Key words: *cadmium, toxic effects, carcinogenic substance, metallotionein*

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Introduction

Cadmium was discovered as an element in 1817, but its application was negligible until the last fifty years. It is used in the production of Ni-Cd batteries, ceramics, paints, textiles and plastics. It enters the environment from mining and smelting processes of zinc and lead. Cadmium is absorbed through the respiratory tract by up to 30% from the environment. A significant route of the introduction of cadmium is through cigarette smoke, as one cigarette contains 1-2mg of cadmium. Smokers have 4–5 times higher blood cadmium concentrations than non-smokers.

Gastrointestinal absorption of cadmium is up to 8%, and by inhalation up to 30%. Absorption, however, increases if one takes the food which has a reduced content of calcium, iron and protein. Zinc reduces the absorption of cadmium probably by stimulating the synthesis of metallothionein. Cadmium is transported via blood, bound to erythrocytes and large masses of proteins such as albumin, although a small portion can be transferred to metallothionein. Approximately 50-75% of the total content of cadmium in the body is located in the liver and kidneys. It is not exactly known how long the cadmium retains in the body, but it is assumed that its half-life can be 10-30 years (1).

In 2005, the production of cadmium was about 17.800 tons. However, the use of cadmium in the developed countries has begun to decline because of its toxicity.

Cadmium intoxication in humans usually occurs by inhaling the cigarette smoke; however, it is also possible through water, food and air. During acute intoxication, damages to liver, lung and testis have been reported (2,3). During chronic intoxication, obstructive pulmonary disease, disturbed metabolism, regulation of blood pressure, kidney function, structure of bones and immune system occur (4-6).

Acute cadmium poisoning

Acute toxic effects may be caused by taking large doses of cadmium through contaminated food or drink and smoke inhalation. As symptoms of acute poisoning, nausea, vomiting and abdominal pain have been cited. Inhalation of smoke with increased content of cadmium can cause acute pneumonitis and pulmonary edema, which can result in fatal outcome (1).

Chronic cadmium poisoning

Effects of long-term exposure in small concentrations of cadmium are chronic obstructive pulmonary disease, emphysema, osteoporosis, hypertension, chronic renal tubular damage and lungs, kidneys and pancreas cancer. The effects on the respiratory system are proportional to the time and level of exposure, with pronounced symptoms of chronic bronchitis, progressive fibrosis, lower respiratory tract and damage to the alveoli (1).

Effects of cadmium on cell

Cadmium affects the development of cell cycle, proliferation, differentiation, DNA repair, replication, and apoptosis. Intracellular activated signals inhibit the DNA methylation and/or interfere with E-cadherin that affects the cell adhesion. Cadmium in concentrations higher than 1μM inhibits the DNA synthesis and to a lesser concentration stimulates the DNA synthesis and cell proliferation (7,8). These effects are dose-dependent.

Biomarkers of cadmium detection

The main route of cadmium in the body is binding to metallothionein (MT), the low molecular weight protein that participates in the homeostasis of some metals. Cadmium-metallothionein complex is distributed in various tissues. Human body does not have a mechanism for cadmium elimination. Urinary excretion of cadmium is proportional to body mass. A recent exposure to cadmium is estimated on the basis of its level in the blood. A few months after the exposure, the levels of cadmium decreases, but remain at a higher level than that which existed previously (9).

Carcinogenic effects of cadmium

Cadmium compounds are potential carcinogens. Compounds such as cadmium chloride, oxide, sulfate, and sulfide produce sarcomas in rats after subcutaneous and intramuscular administration. The effect is dose-dependent because higher doses of cadmium caused much more aggressive sarcomas that show a greater effect of local invasion and metastasis (10).

Cadmium also induces the appearance of testicular tumors, especially benign tumor cells, but this is usually associated with high doses that lead to testicular necrosis, testicular atrophy, and excessive secretion of luteinizing hormone. Other studies have shown that exposure to cadmium can induce tumors of the pancreas, adrenal glands, liver, kidney, thyroid gland, and hematopoietic system in mice, rats and hamsters. Cadmium may be carcinogenic after inhalation, oral and parenteral administration (10).

Cadmium was classified as a carcinogenic substance to humans by IARC (International Agency for Research on Cancer) in 1997 and belongs to the group I carcinogen.

The development of lung cancer in experimental animals is associated with inhalation of cadmium (11).

The mechanism by which cadmium affects the process of carcinogenesis is not known. It probably increases cell proliferation and apoptosis by DNA damage (11).

Toxicokinetics

Cadmium is transported in the blood by albumin and has high molecular weight. It is rapidly distributed in tissues and deposited in the liver and kidneys. In the liver, kidneys and other tissues, cadmium induces the formation of metallothionein (12).

Cadmium is deposited in the liver as a complex of cadmium-metallothionein (Cd-MT). Cadmium-metallothionein complex may be released from the liver and transported via blood to the kidneys where it is reabsorbed and broken down into lysosomes of renal tubules. This release of cadmium induces the creation of Cd-MT complexes or cause renal toxicity. When it comes to saturation in developing links with free metallothionein and when there is no possibility of removing free cadmium, tubular damage may occur (13).

Cadmium can pass through the placenta. The placenta is permeable to all substances with a molecular weight less than 1000 Dalton. Thus the placenta does not prevent the passage of toxins from mother to fetus, and therefore nicotine and toxins from tobacco smoke, including cadmium and a large number of drugs, can pass into the fetus. Cadmium was found to cause toxic effects on the level of the placenta by reducing the transport of zinc through the placenta causing zinc deficiency in the fetus (1).

Nephrotoxicity

Cadmium is toxic to the tubules and glomerulus. It significantly impairs the renal function. The lesions consist of initial necrosis of tubular cell degeneration in excess of interstitial inflammation and fibrosis. There seems to be detached critical concentration of cadmium in the renal cortex, which causes tubular dysfunction (18).

Cadmium damages the kidney proximal tubule. It is believed that glomerular lesion is predominant in the initial stage of cadmium exposure. It causes damage to tubular reabsorption, with consequent proteinuria, glycosuria, phosphaturia. The first sign of damage is increased excretion of low molecular weight proteins (tubular proteinuria). Disruption of renal regulation of calcium and phosphorus can cause resorption of these minerals from the bones (occurrence of osteomalacia and kidney stones are described). Cadmium-induced renal toxicity is characterized by proteinuria. Prevalent protein: β2-microglobulin, N-acetyl-β-D-glucosaminidase and metallothionein, and retinol binding proteins, lysosomal enzymes, ribonuclease, α1-microglobulin and immunoglobulins short chains (13,14). The presence of larger proteins such as albumin and transferrin in urine after exposure to cadmium are indicative of glomerulus damage (13). Urinary excretion of protein and cadmium is used as a biomarker of cadmium exposure.

Damage to the renal blood vessels occurs most frequently in the last stage of disease. It is necessary to introduce biomarkers that can provide early detection of blood cells that are damaged by cadmium. Determination of proteins in urine, in subjects exposed to cadmium, has proven to be a good approach to protecting the population from potential health risks of exposure to toxic effects of cadmium (15).

Studies of people living in an area contaminated with cadmium zinc smelter near Poland

have shown the presence of urinary excretion of protein markers: albumin, β2-microglobulin, retinol binding protein above 2 mg/g creatinine (16,20).

The kidney has an effective mechanisms that can compensate for some toxic effects. One example is the compensatory mechanisms of metallothionein in cadmium poisoning. Recovery after toxic renal damage may contribute to the regeneration of tissue in which the intact cells in close proximity differentiate and take proliferous function of damaged tissue. In this case, increased DNA synthesis in the kidneys is observed, promoted by many growth factors arriving to the injury spot through kidneys and circulation (1).

Toxic effects on the respiratory system

Cadmium-induced obstructive lung disease in humans can be slow at first, it results in chronic bronchitis, progressive fibrosis of the lower airways, and alveolar damage which leads to emphysema. Dyspnea, decreased vital capacity and increased residual volume have also been reported. Cadmium-induced oxidative stress seems to play a major role in realizing the negative effects of cadmium in the lungs, which is associated with an increased risk of asthma (21) and pulmonary fibrosis (22). In vitro studies of lung cells have shown that cadmium induces apoptosis through a non-specific dependent mechanism, which is associated with the release of apoptotic factors from mitochondrial depolarization that accompanies mitochondrial membrane and transport apoptosis factors in the nucleus (23).

Effects on the skeletal system

Cadmium affects the metabolism of calcium and renal dysfunction by increasing the excretion of calcium, which appears in the urine. Skeletal changes are probably associated with the loss of calcium in parathyroid hormone and vitamin D. Cadmium can directly affect bone by stimulating osteoclast activity leading to the destruction of bone matrix. Exposure to cadmium causes renal dysfunction that is associated with hypercalciuria, nephrocalcinosis, osteoporosis and osteomalacia. Cadmium-contaminated rice causes Itai-Itai disease, which occurs mainly in older women and is characterized by serious osteomalacia and osteoporosis. This results in bone deformities and accompanying renal dysfunction. The lack of vitamin D, as well as some associated nutrients, may be a cofactor in the development of Itai-Itai disease. Data on bone loss, weight loss and frequent bone fractures were detected in populations exposed to much lower concentrations of cadmium, known as victims of Itai-Itai disease (24).

Effects on the cardiovascular system

Vascular toxic effects of heavy metals such as cadmium, copper, zinc, selenium, lead, mercury are formed after the reaction with sulfhydryl, carboxyl and phosphate groups, although some of them can block the calcium channels. Although cadmium accumulates in the blood vessels less than in other tissues, its presence has been shown in large arteries (1).

Cadmium is localized in the elastic lamina of large arteries. Calcium has an antagonistic effect on cadmium-induced high blood pressure. Cadmium increases retention of salt, induces vasoconstriction and increased cardiac volume. Studies have shown that the vascular system and vascular endothelium are the target of cadmium toxicity (17). Cadmium cardiotoxicity is manifested in the form of reduced heart contractility, conductivity, due to structural changes in the myocardium (1).

Cadmium may be an etiological factor for cardiovascular diseases, including hypertension (1).

Neurotoxicity

Studies in humans suggest a link between abnormal behavior and / or reduced IQ in children and adults exposed to cadmium. Blood-brain barrier is permeable to cadmium. Direct toxic effects occur only when allowed to pass cadmium through the blood-brain barrier, most often in young children or the dysfunction blood-brain barriers in certain pathological conditions. Choroid plexus epithelium can accumulate high levels of cadmium in reducing the level of other parts of the body (25).

Hepatotoxicity

The liver is the major site of metabolism and body for storage of cadmium in vivo. It produces metallothionein, which is then released into the circulation and further transported to the kidneys as well as to other target organs (15). The liver has a large capacity, reserves and the ability to induce antioxidant systems. There is a direct relationship between the levels of cadmium in urine and circulating levels of many antioxidant biomarkers in the blood. Circulating levels of these substances as markers of antioxidant liver are controlled. Chronic exposure of animals to cadmium increases glutathione transferase in the liver, which in turn leads to increased lipid peroxidation in the liver. Oxidative stress is a major reason for the emergence of hepatotoxicity (33). Thus, there might be an indirect connection between the liver and oxidative effects of cadmium in the body. Some of these parameters may in future be used as biomarkers of hepatotoxicity (26).

Tolerance to cadmium-induced acute hepato-toxicity depends on synthesis of MT in the liver which stops the spread of cadmium and cytosol even with simultaneous reduction of the amount of cadmium capable of destroying other organelles (27).

Effects on the immune system

Exposure to cadmium has been shown to interfere with the normal function of immune cells. When given oraly to mice, cadmium increases susceptibility to herpes simplex virus type 2, decreases the production of T and B cells, but increases macrophage phagocytosis. In children of school age who are exposed to cadmium, a

decrease of sensitivity and IgG antibody titers has been revealed. As is the case with many other immunotoxic substances, it is assumed that stress is responsible for the induction of apoptosis. Also, cadmium affects the production of cytokines (19).

Effects on the reproductive system

Cadmium in late pregnancy reduces blood flow to the placenta and inhibits the transport of nutrients through the placenta. Cadmium exposure of pregnant women leads to birth of children with lower body weight and increased incidence of spontaneous abortion. Cadmium accumulates in the ovaries over time, which is associated with reduced development of oocytes. Also, cadmium accumulates in the embryo (28). Low doses of cadmium stimulate ovarian progesterone synthesis, whereas higher doses inhibit it. Cadmium can cause changes in the production of sperm as well as other toxic effects on the reproductive function (1).

The testicles are the main target in the course of acute poisoning caused by cadmium. The effect is rapid. The testicles are first shriveled, which then follows the inflammation, edema, and severe hemorrhage and necrosis that occur in less than 24 hours after the application of a single dose of cadmium (29).

Effects in the pediatric population

Children are particularly exposed to this metal. Children have a larger intake of food than adults relative to their weight, so the intake of cadmium to the body is larger in proportion. It is believed that children in the first months of life absorb from the digestive tract much more cadmium than adults. Low content of calcium, iron and protein, which are commonly found in the diet of children, can increase the absorption of cadmium.

Children who are exposed to adult smokers are at risk because they inhale the same amount of air as the people of middle age and their bodies bring in relatively more toxic metals (18,30).

Treatment

If the patient was exposed to cadmium, the following tests are proposed:

1. The increased concentration of cadmium in blood, urine and hair
2. General urine examination (proteinuria, glycosuria, amino-aciduria).
3. Increased concentrations of calcium and phosphate in the urine.
4. The five-day test mobilization chelates (CaNa2EDTA) is used to estimate the size of the depot
5. Rtg pelvis and lungs
6. Prostate exam after the age of forty is required.

Qualitative tests, for example, a test with sulphosalicylic acid or trichloroacetic acid reveals early tubular proteinuria, but can be used with advanced proteinuria, with the necessary of determination of β2-microglobulin in urine.

Determination of cadmium in blood and urine can be helpful in making the diagnosis (31).

During long-term exposure to cadmium, the cadmium concentration in urine higher than 10 μg/g creatinine indicates the existing or impending renal tubular damage. Concentrations of cadmium levels above 10μg/l (0.08μmol/l) indicate a significant exposure to cadmium (32).

There is no information that chelation therapy in acute poisoning is efficient. In case of poisoning by inhalation, blood tests are performed and the patient's condition is monitored. The exposed person is removed from further exposure to cadmium smoke and given oxygen if needed. In case of ingestion, loss of fluid is compensated and gastric lavage performed, but it does not cause vomiting because of cadmium salts irritants. Use of active charcoal is recommended (not given in case of diarrhea) (27).

Poisoning caused by cadmium inhalation is treated with respiratory insufficiency reanimation and pulmonary edema treatment.

Symptoms of chronic poisoning are due to final degenerative changes and cannot be repaired by chelators. Treatment of intoxication is conducted by administering chelators that bind cadmium, but the complex can cause nephrotoxic effects. However, the most effective is intravenous infusion of EDTA (ethylenediaminetetraacetic acid). Dimercaprol is not effective (1).

In kidney and liver damage, a symptomatic therapy is applied.

This is a correction of fluid and electrolyte imbalance.

People with acute poisoning do not suffer consequences for health in most cases.

More serious forms of acute and chronic poisoning can leave effects on the lungs, kidneys and liver, which can leave lasting effects on health, depending on the severity of organs.

People with professional cadmium poisoning lose their ability to work with cadmium and its compounds (34).

Conclusion

Many studies have shown that there is a direct correlation between exposure to the toxic effects of cadmium with renal impairment. In case of kidney damage, proteinuria is the most important indicator of the nephrotoxicity of cadmium.

Cadmium exerts its toxic effects on many other tissues and organs. Acute effects of cadmium on the body do not have permanent effects in contrast to the chronic effects in the case of which some changes at the cellular level occur.

Owing to the advances in molecular biology, toxic effects of cadmium have been elucidated. However, the mechanism of carcinogenesis caused by cadmium remains unknown.

Protective role of metallothionein has been proven, not only in the acute and chronic toxicity of cadmium, but also in cadmium-induced carcinogenesis with the exception of testicular damage. Its detoxifying role is primarily in the high binding affinity of the metals for metallothionein.

Preventing exposure to tobacco smoke as well as a proper diet which is rich in protein may be an important factor in preventing the toxic effects of cadmium exposure.

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TOKSIČNI EFEKTI KADMIJUMA

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Kadmijum spada u teške metale, često se koristi u industriji i ispoljava toksične efekte na ljudsko zdravlje. Kadmijum je klasifikovan kao kancerogena supstanca od strane International Agency for Research on Cancer i spada u I grupu karcinogena. Kadmijum utiče na ciklus razvoja ćelije, proliferaciju, diferencijaciju, DNK reparaciju, replikaciju i apoptozu, kao i na promociju kancera u tkivima. Intoksikacija ljudi kadmijumom najčešće se dešava inhalacijom dima cigareta, ali je moguća i putem vode, hrane i vazduha. Kadmijum ispoljava toksične efekte na bubrege, jetru, pluća, kardiovaskularni sistem, imunološki sistem i reproduktivni sistem. Glavni put kadmijuma u telu je vezivanje za metalotionein, protein male molekulske težine koji učestvuje u homeostazi nekih metala. Kompleks kadmijum-metalotionein se raspodeljuje u različitim tkivima. Uloga metalotioneina u detoksikaciji kadmijuma je prevashodno u velikom afinitetu vezivanja metala za metalotionein. *Acta Medica Medianae 2012; 51(4):65-70.*

Ključne reči: *kadmijum, toksični efekti, karcinogena supstanca, metalotionein*