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Heavy Metals and Kidney

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ABSTRACT

Metals with a density of more than 5 g/cm^3 are heavy metals, with more than 60 in nature. In acute and chronic exposure, they can damage many organs, such as the central nervous system, kidneys, skin, lungs, and heart. The most harmful ones to the kidney are lead, mercury, cadmium, and arsenic. They cause damage by creating some disorders in intracellular metabolic processes. The main types of kidney injury are acute tubular damage, proteinuria, and chronic kidney disease. This review discusses the basic properties of lead, mercury, cadmium, and arsenic, their nephrotoxicity mechanisms, and studies about them.
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INTRODUCTION

The term “heavy metal” has been widely used in recent years. These are highly toxic metals, regardless of their atomic weight. Heavy metal identification is used for metals with a density greater than 5 g/cm^3. More than 60 metals comply with this definition. Some of them [iron (Fe), cobalt (Co), copper (Cu), manganese (Mn), molybdenum (Mo), and zinc (Zn)] are necessary for life. Simultaneously, the complete physiological functions of certain metals such as lead (Pb), cadmium (Cd), and arsenic (As) remain unclear. Basic industries, paper and petrochemical industry, chlorine–alkali production, fertilizer industry, iron and steel industry, and thermal energy production are essential factors in spreading heavy metals into the environment (Table 1). Heavy metals also have an impact on animals and humans through contamination of drinking water with wastewater or heavily contaminated particles.[1]

CLINICAL AND RESEARCH CONSEQUENCES

Heavy metals can also affect animals and humans by contaminating drinking water through wastewater or heavily polluted particles. Even at trace levels, these metals can accumulate in organisms over time, eventually reaching toxic levels due to prolonged exposure. The effects of a heavy metal on the body depend on the concentration of the heavy metal, the structure of the metal ion, the solubility value, the chemical structure, the way it is absorbed into the body, and the ability to form redox and complexes.

Heavy metals change the enzymatic activity in most pathways via binding to the proteins’ oxygen, nitrogen, and sulfhydryl groups. This affinity to the sulfhydryl groups of metal species also plays a protective role in heavy metal homeostasis. Therefore, the body’s primary response to toxicity at increasing levels of metals is to increase the synthesis of metal-binding proteins. Metalloproteins are rich in thiol ligands that provide high-affinity binding to elements such as cadmium, copper, silver, and zinc. Other proteins involved in the transport, excretion, and formation of ligands of heavy metals are ferritin, transferrin, albumin, and hemoglobin.

Table 1. Metal Types Discarded from Basic Industries[1]

Industry	Cd	Cr	Cu	Hg	Pb	Ni	Sn	Zn
Paper industry	–	+	+	+	+	+	–	–
Petrochemistry	+	+	–	+	+	–	+	+
Chlor-alkali production	+	+	–	+	+	–	+	+
Fertilizer industry	+	+	+	+	+	+	–	+
Iron–steel industry	+	+	+	+	+	+	+	+
Energy production (thermal)	+	+	+	+	+	+	+	+

Cd, cadmium; Cr, chrome; Cu, copper; Hg, mercury; Pb, lead; Ni, nickel; Sn, tn; Zn, zinc.

Some metals may compete with ionizing elements such as calcium and zinc to move through membrane channels in free ionic forms. For example, lead follows calcium pathways in the body, so it accumulates in the bone and gums. Due to its ionic nature, like potassium, thallium is taken into cells. Almost all organ systems are affected by heavy metal toxicity; however, the most commonly affected systems are the central nervous system, peripheral nervous system, gastrointestinal, hematopoietic, genitourinary, and cardiovascular systems. The severity of the affected organ systems and toxicity also varies with the duration, amount of exposure to the heavy metal in question, and the patient's age.[2]

The toxic effects they create in the body are DNA damage, oxidative protein breakdown due to increased oxidative stress, mitochondrial damage, and induction of apoptosis. In Figure 1, the harmful effects of heavy metals on living organisms are schematized. In this article, the effects of arsenic, mercury, lead, and cadmium, which are toxic to the kidney, will be mainly discussed.

LEAD: BASIC PROPERTIES, NEPHROTOXICITY, AND STUDIES

Lead (Pb) was discovered as a by-product during the production of silver. Since both metallic and compound forms of lead are toxic, it is an essential heavy metal that creates environmental pollution (the limit allowed in the working environment is 0.1 mg/m^3). In the early and mid-1900s, it was used as an oxide paint raw material against corrosion. Other important uses are canister lids, lead–tin alloy containers, ceramic glazes, pesticides, and batteries. Foods (such as cereals, legumes, garden fruits, and many meat products) grown in places where industry and city centers are close to each other contain lead above normal levels. Lead exposure has increased in some lines of business, for example, battery usage and production, paints, car radiators, soldering, some cosmetics, ceramic and can production, and lead melting and refining. In the aftermath of natural disasters, soil, particularly in the vicinity of battery factories, can serve as a source of lead (Pb) contamination, especially for nearby residents. X-ray radiographs in Pb-coated boxes and moonshine production are also sources of Pb poisoning. Some herbal products can be dangerous in terms of Pb too.

MAIN POINTS

- The most harmful heavy metals for the kidney are lead, mercury, cadmium, and arsenic.
- The main types of kidney injury due to heavy metals are acute tubular damage, proteinuria, and chronic kidney disease.
- There is no specific treatment for the detrimental effects of heavy metals, so the most essential part of treatment supportive.

Lead is absorbed by the intestines and respiratory system and through the skin. Divalent metal transporter 1 (DMT-1) mediates intestinal absorption, and absorption increases with insufficient iron and zinc intake. The respiratory system is a highly effective way of absorption, allowing more than 40% of Pb to be absorbed into the body. The molecular mechanism of Pb absorption is unknown. Ninety-nine percent of Pb in the serum binds to erythrocyte proteins. With the help of this binding, it can easily be distributed to bone and soft tissues. The main reservoir is the bones, and Pb release into the circulation increases when the bone cycle is high, such as during puberty and pregnancy. The main pathway of Pb excretion is urinary excretion. Less than 1% of the total Pb binding is to low-molecular-weight proteins, and it is freely filtered in glomeruli and reabsorbed by proximal tubule cells by endocytosis. Lead in the cell causes mitochondrial damage, the formation of free radicals, intracellular glutathione (GSH) depletion, and apoptosis.[3]

Lead also affects enzymatic reactions in which calcium plays a role, and calcium-sensitive receptors can also be activated by Pb, suggesting there may be other mechanisms for lead nephrotoxicity.[4] Lead stimulates macrophage migration to the kidney interstitium, transcription activation of the nuclear factor kappa B, and thus plays a role in activating the intrarenal renin–angiotensin system, development of tubulointerstitial injury, and hypertension.[5] Increased free radical formation induced by Pb in endothelial cells reduces nitric oxide production and guanylate cyclase expression. These effects explain the pathogenesis of hypertension after lead exposure.[6] Also, lead stimulates NADP(H) oxidase activity by increasing the production of hydrogen superoxide and hydrogen peroxide, thereby affecting oxidative stress and intracellular redox potential.[7]

Acute exposure to high Pb doses may cause proximal tubular damage, occurring clinically as glycosuria, hyperphosphatemia, and aminoaciduria. Other possible clinical manifestations include hemolytic anemia, acute gout attack, intense abdominal pain, and encephalopathy.[8] Diagnosis of chronic nephritis is rare because urinary symptoms and signs are variable and not specific. Therefore, clinical diagnosis is primarily based on exposure history. Chronic exposure to Pb is associated with tubulointerstitial nephritis and progressive kidney function impairment. Urate excretion in urine decreases due to the effect of Pb on the

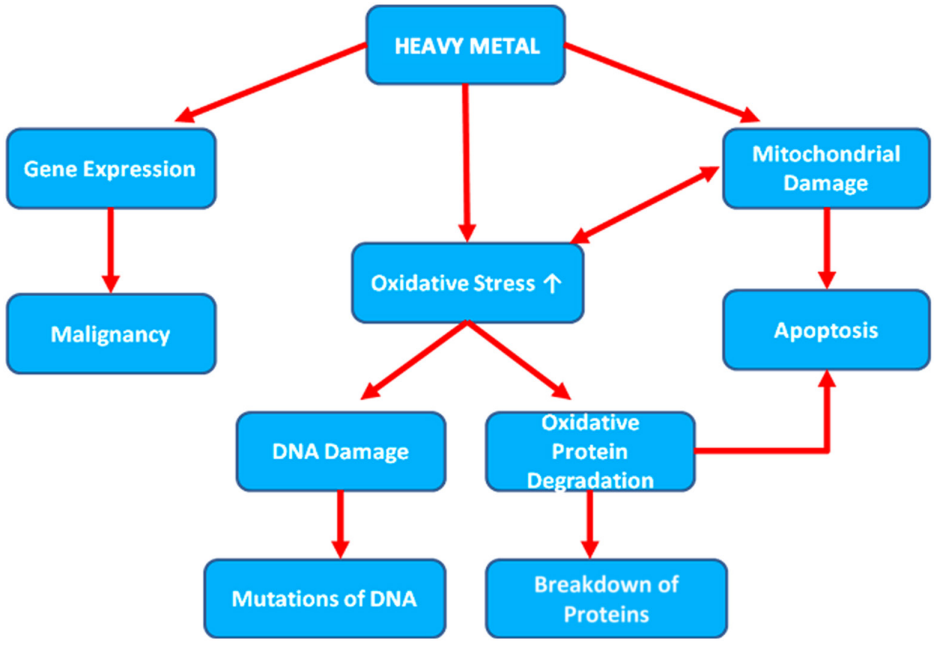

Figure 1. Mechanism of the harmful effects of heavy metals.

proximal tubule; kidney blood flow also decreases, increasing serum urate levels. In addition, Pb has adverse effects on bone formation, osteoblasts, and osteoclasts. Therefore, chronic exposure to Pb may cause and exacerbate osteoporosis.

The first reported case of Pb-related nephrotoxicity was described in the 19th century. Since then, exposure to high Pb concentrations has been considered a risk factor for hypertension and kidney damage. However, recent studies have shown that even exposure to "normal" levels directly affects kidney function and increases the risk of cardiovascular morbidity.[9] Menke et al[10] have monitored a population for over 12 years and showed that elevated Pb levels increase mortality rates (primarily due to cardiovascular problems). In a population of 4813 patients with high blood pressure, Muntner et al[11] found that the risk of chronic kidney failure increases (OR: 2.6; 95% CI: 1.5-4.45) in those with high serum Pb levels.

In a study by Lin et al[12] in Taiwan, people with chronic kidney disease (CKD) [glomerular filtration rate (GFH) <60 mL/min] and high serum Pb levels have been shown to deteriorate kidney function faster, and also chelation therapy with ethylenediaminetetraacetic acid (EDTA) reduced the progression of kidney damage. There are also some studies in which lead exposure and the development of chronic kidney failure were unrelated. For example, Evans et al[13] showed no significant relationship between lead exposure and the development of end-stage kidney failure in workers exposed to lead for more than 20 years. Besides, Evans et al[14] claimed that low-dose lead exposure did not lead to the progression of CKD in their study.

Table 2. Characteristics and Nephrotoxicity of 4 Heavy Metals

Metal	Exposure Source	Mechanisms	Kidney Damage
Cadmium	Contaminated foods; cigarette; industrial wastes; occupational exposure (mines, battery production, steel and plastic production)	Oxidative stress, impaired DNA repair, decreased antioxidant ability, cellular apoptosis	Fanconi's syndrome, decreased GFR
Lead	Contaminated food; petroleum; contaminated air, water and soil polluted with industrial waste; cigarette smoke; occupational exposure (mining, production of batteries, welding and lead soldering)	Oxidative stress, increased TGF-β expression, fat oxidation, mitochondrial dysfunction	Fanconi's syndrome, interstitial fibrosis, tubular atrophy, decreased GFR
Arsenic	Occupational exposure (mines, timber protective materials, metal melting of ores, and pesticide exposure); contaminated seafood and waters; specific drugs	Oxidative stress; decreased DNA methylation; decreased antioxidant defense	TIN, ATN, decreased GFR
Mercury	Contaminated water; fish in polluted waters; fuel exposure; skin whitening creams; metals	DNA damage, mitochondrial dysfunction, decreased enzymatic activity	Membranous nephropathy, TIN, ATN, decreased GFR

ATN, acute tubular necrosis; DNA, deoxyribonucleic acid; GFR, glomerular filtration rate; TGF-β, transforming growth factor beta; TIN, tubulointerstitial nephritis.

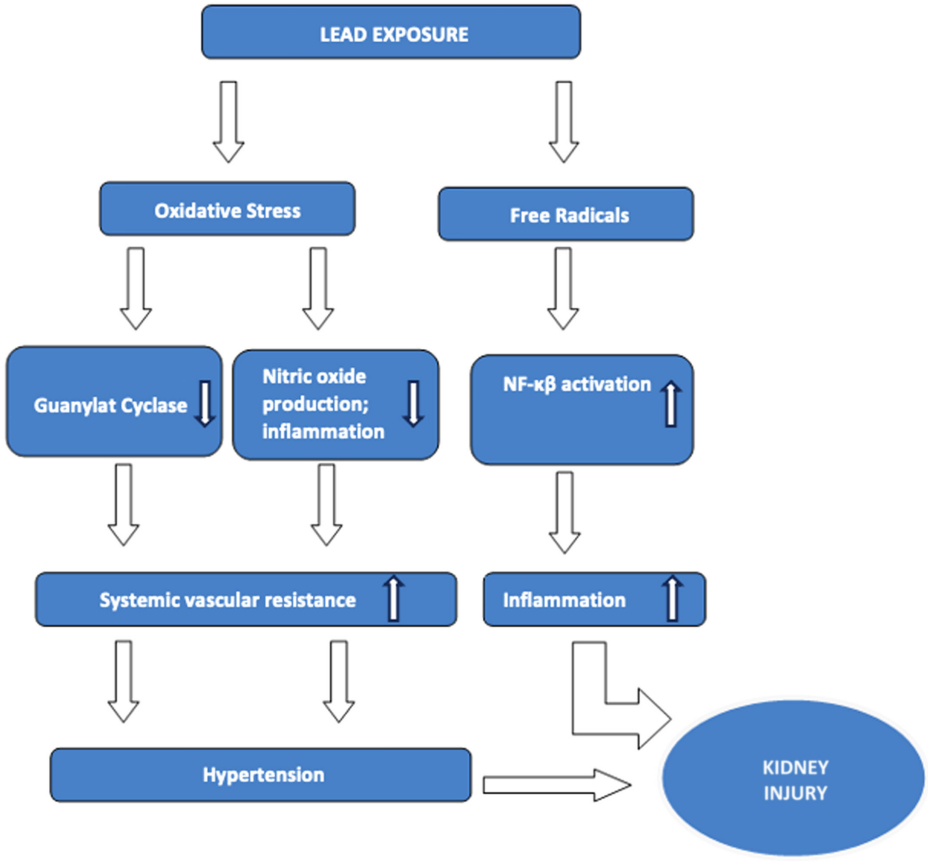

Figure 2. Lead-related kidney damage mechanisms.

Lead nephropathy should be suspected in patients with CKD, hypertension, and gout history. Lead dose evaluation can be done by measuring Pb in the blood. If Pb exposure has decreased or stopped, blood Pb levels may not be high. The blood Pb level also shows the last exposure and Pb released from endogenous sources such as bone and soft tissue. Therefore, cortical bone Pb level measurement may also be helpful. In the original studies describing Pb nephropathy, diagnostic chelation was performed. Seventy-two hours after intravenous infusion of Ca-EDTA (1 g in 1-2 hours), excretion of >600 µmol Pb in urine indicates the body's Pb burden, which will cause Pb nephropathy.[15] There is not enough treatment options to lower high serum Pb levels, but EDTA chelation treatment helps to reduce Pb toxicity (1 g into 200 mL of 0.9% saline, applied weekly for 3 months). In addition, luteolin protected significantly against lead acetate intoxication via antioxidant, anti-inflammatory, and antiapoptotic activities by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element signaling pathway.[16]

CADMIUM: BASIC PROPERTIES, NEPHROTOXICITY, AND STUDIES

Cadmium (Cd) is one of the heavy metals that causes environmental pollution; it emerged with zinc production. Important cadmium sources that affect life are refined foods, the smoke of tobacco products, coffee and tea, water pipes, coal combustion for heating, shellfish products, fertilizers, and flue gases used in industry. In addition, cadmium-containing paints and cadmium batteries, silver welds, spray paints, alloy compositions used during welding, and electrochemical coatings are the causes of cadmium poisoning in the industry.[17]

In industrial areas, the cadmium ratio in the air is much higher than in rural areas. If air with a cadmium concentration of 0.01 mg/m^3 is inhaled for more than 14 days, chronic lung disorders and kidney failure occur. While short-term intake of 0.05 mg/kg cadmium causes stomach discomfort, long-term (>14 days) 0.005 mg/kg/day exposure causes significant problems in kidneys and bones.[18] The toxic Cd value for the kidney is not fully known. However, it is considered that urine 10 µg/g creatinine ratio (200 mg/kg in kidney cortex) is a reliable level in those exposed to Cd occupationally.

Cadmium in foods binds to metallothionein and phytochelatin proteins, which enable other heavy metals to be kept in vacuoles in plants. These proteins break down under the influence of chyme in the stomach. DMT-1 and Zrt-/Irt-related protein (ZIP-8) carriers absorb the released Cd in the gut.[19] It is bound to albumin in the circulation and transported to the liver, where it binds to glutathione (GSH) and metallothionein 1 (MT-1). The Cd–MT-1 complex is secreted into bile and reabsorbed through

the enterohepatic circulation. Since Cd–MT-1 is a low-molecular-weight complex (<7 kDa), it is easily filtered in the glomeruli and is almost completely reabsorbed in the S1 segment with megalin and cubilin-mediated endocytosis.[20] The ZIP-8 transporter is also found in proximal tubule cells and can carry Cd and other divalent metals across the apical membrane of these cells. However, its role in Cd toxicity is not known.

In the intracellular environment of proximal tubule cells, the Cd–MT-1 complex is stored and lysed by lysosomes.[21] Free Cd is then transported to the cytoplasm by lysosomal DMT-1. Activation of protein kinase C increases the expression of DMT-1.[22] Thus, it increases the tubular toxicity of Cd. Free Cd accumulates in mitochondria and blocks the aerobic chain in complex III. This situation results in mitochondrial dysfunction, the formation of free radicals that activate caspase enzymes, and apoptosis. Free Cd also binds to protein sulfhydryl groups, affecting the structure and function of proteins. Cadmium has been shown to affect the enzymatic activity of the calcium–calmodulin complex, inhibit Na^+ -K^+-ATPase activity, and stimulate activity in mitogen-activated protein kinases.[23] Only 10% of filtered Cd is reabsorbed in the distal tubule of the nephron, and the hypercalciuric effect of Cd is probably due to the inhibition of calcium channel activity in the distal tubule.[24]

Acute poisoning caused by cadmium, primarily malaise, headache, fever, sweating, muscle strain, and vomiting with pain, occurs within 24 hours, and on the third day the most severe symptoms appear and begin to disappear within 1 week if there is no new loading. The essential effect of chronic cadmium poisoning is lung and prostate cancer.

In the study of Järup et al[25] with 1021 patients, alpha 1-microglobulin levels, which are tubular damage markers, were significantly higher even in people whose urine Cd levels were within the normal limits.Noonan et al[26] also showed the exact relationship between normal-to-high urine Cd levels and *N*-acetyl-β-D-glucosaminidase) and alanine aminopeptidase, markers of tubular dysfunction. A study of urinary metabolic characterization of nephrotoxicity for cadmium-exposure residents showed that creatinine, L-tryptophan, adenine, and uric acid increased metabolomics in urine in cadmium-related nephrotoxicity.[27]

Preventing cadmium-related kidney damage is possible by smoking cessation and avoiding food and occupational exposure. In addition, zinc and Mg can reduce chronic toxicity. Unfortunately, due to CD, there is no specific treatment for CKD. However, in recent studies, resveratrol attenuated Cd-induced excessive mitochondrial fission and promoted mitochondrial fusion, which reversed PINK1/Parkin-mediated mitophagy initiation.[28] Arctigenin significantly improved kidney function and reduced kidney tubular damage in cadmium-exposed rats by increasing KIM-1 protein expression.[29]

MERCURY: BASIC PROPERTIES, NEPHROTOXICITY, AND STUDIES

Mercury is a heavy metal that commonly causes environmental contamination. Mercury is used in various applications such as mirror making, in instruments like manometers, thermometers, barometers, and sphygmomanometers, as well as in gold mining. It is also used in the treatment of syphilis and psoriasis, for skin lightening, hair dyes, and in dental treatments. However, mercury exposure can lead to toxicity. Vaccines are also possible sources, as they contain mercury as a preserver.[30]

Mercury vapor is absorbed through the respiratory tract, as well; its absorption through the skin and gastrointestinal tract is lower. Mercury taken into the lung is exhaled, and some accumulate in the kidney. Besides, mercury taken from the gastrointestinal tract accumulates in the kidney, hair, and central nervous system. Toxicity mainly affects the central nervous and digestive systems, but nephrotoxicity has also been reported.[31] Since inorganic mercury is mainly reabsorbed in proximal tubules, it is the most sensitive region to nephrotoxicity. In addition, acute effects of mercury have been observed in proximal tubular cells, including mitochondrial and DNA damage.[32] Acute mercury exposure can cause tubular epithelial cell necrosis and low-molecular-weight proteinuria.[33] The harmful effects of chronic exposure to mercury on the glomeruli are also evident. In a series examining 42 patients with mercury-associated nephrotic syndrome, kidney biopsy was performed in 26 patients, and it was found that 15 of them had membranous nephropathy (MN), 4 had minimal change disease, 1 had focal segmental glomerulosclerosis, and 1 had chronic proliferative glomerulonephritis.[34] Another case series from China included 11 patients with mercury-induced MN. The duration of mercury exposure in these patients ranged from 2 months to 5 years. Urine mercury concentrations in these patients were 1.5 to 50 times higher compared to those who were not exposed to mercury.[35]

Unlike patients with idiopathic MN, PLA2R antibody was negative in patients with mercury-induced MN.[36] In addition, while immunoglobulin G1 (IgG1) was the predominant immunoglobulin in glomerular deposits in patients with mercury-induced MN, IgG4 was dominant in patients with idiopathic MN, and more than 80% of patients have been observed to achieve complete remission after mercury exposure has disappeared. The pathogenesis of mercury-induced glomerular diseases has yet to be fully explained. In experimental animal models, mercury induces autoimmune dysfunction characterized by the activation of T cell-bound polyclonal B cells, increased serum levels of IgG and IgE, the production of antinuclear antibodies (ANAs), and the formation of immune complexes in the kidneys.[37] The detectable ANA prevalence and increased serum concentration of inflammatory cytokines such as interleukin 1, tumor necrosis factor (TNF), and interferon gamma are observed in gold miners chronically exposed to mercury. In addition, the activation of glutathione S-transferase alpha 1, TNF ligand superfamily

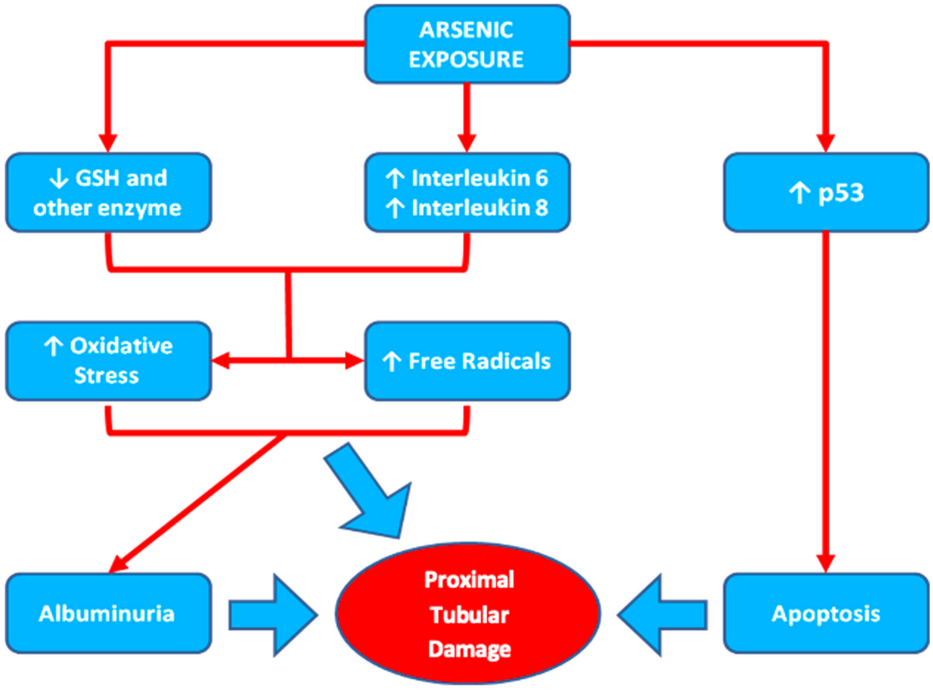

Figure 3. Kidney injury mechanisms due to arsenic toxicity.

member 13, and linker for activation of T cells family member 1 has been identified as a new potential biomarker of mercury-induced immunotoxicity.[38]

British anti-Lewisite (BAL), penicillamine, unithiol, dimer captopropan-1-sulfonate, and dimercaptosuccinic acid are helpful in acute poisoning. In addition, in a recent study, erythropoietin pretreatment was shown to ameliorate $HgCl_2$-induced kidney tubular injury by modulation of the expression of mercury transporters in the kidneys.[39] In another study, trimetazidine showed a renoprotective effect against $HgCl_2$-induced kidney injury, which may mediate the reduction of oxidative stress.[40]

ARSENIC: BASIC PROPERTIES, NEPHROTOXICITY, AND STUDIES

Arsenic (As) is one of the most common environmental pollutants, and millions of people are exposed to arsenic from drinking water.[41] It is used as a medicine for treating acute promyelocytic leukemia, sleep disease, and leishmaniasis; arsenic trioxide is another source of exposure.[42]

It is absorbed through the intestines, through the lungs by inhalation, and through the skin to a lesser extent. Once absorbed, it is transported to all tissues in the body. Intake of selenium and vitamin B reduces the intestinal absorption of As. Arsenic is methylated by a GSH-mediated procedure that reduces liver toxicity and facilitates bile and urine excretion.[30] Arsenic enters the intracellular environment from AQ3 and AQ9 aquaporins. Studies in cell cultures have shown that increased cellular expression of AQ3 and AQ9 increases the intracellular accumulation of As. AQ9 is essential for the biliary excretion of As in the liver.[43] Another group of proteins carrying arsenic is MRP-1 and 2 (ATP-binding multidrug resistance protein) proteins, described in the liver, carrying the GSH-bound As. The MRP-2 carrier is also found in proximal tubule cells that support the entry of As into these cells. Arsenic toxicity in proximal tubule cells is caused by GSH depletion and an increase in the oxidative activity of free radicals (Figure 3).

In acute poisoning, nausea, vomiting, watery diarrhea, and abdominal pain develop within minutes and hours. The smell of garlic can be noticed in the patient's breath or stool. Dehydration, hypotension, elongation of QTc on ECG, arrhythmias, respiratory distress, delirium, coma, seizures, and death can be seen. Kidney damage may occur in acute poisoning. The cause of kidney damage may be a hypotensive shock, effects of arsenic on tubule cells, or hemoglobinuria or myoglobinuric tubular damage. Kidney damage may result in proteinuria. Besides, acute TIN is also a result of acute As poisoning.[44]

There are also some publications in the literature showing that arsenic exposure causes CKD. For example, Zheng et al[45] have shown a relationship between urinary arsenic excretion and the development of incidental CKD. Besides, a study by Hsueh et al,[46] which included 125 people with GFR <60 mL/min and 229 people with normal kidney functions, found a weak relationship between urine levels of arsenic and decreased kidney function. (r^2 = 0.04, $P \leq .001$). Meliker et al[47] showed that high

As levels were associated with high mortality rates in patients with reduced kidney function (OR: 1.11; 95% CI: 1.09-1.13). Evaluation of the causality of the relationship between arsenic exposure and kidney disease outcomes is limited to a few studies.

Protection from As exposure is essential. Supportive treatment to protect organ functions, hemodialysis, and extracorporeal membrane oxygenation may be beneficial in acute poisoning. In chelation therapy, dimercaprol (BAL), meso-2,3-dimercaptosuccinic acid, and sodium 2,3-dimercapto-1-propane sulfonate can be used by considering the side effects. There have yet to be studies on this subject in humans. However, in animal studies, resveratrol has significantly reduced arsenic accumulation in kidney tissue, improving oxidative stress, morphological damage, and acute tubular necrosis.[48] Tannic acid potentially ameliorates arsenic trioxide-induced nephrotoxicity, which is related to inhibiting oxidative stress, inflammation, and apoptosis via the nuclear factor kappa-light-chain enhancer of activated B cells/Nrf2 pathway.[49]

CONCLUSION

In summary, heavy metals are prevalent in our environment and can cause kidney damage through either acute or chronic exposure. It is important to consider heavy metal exposure in individuals with a history of occupational exposure or unexplained kidney disease. Blood and urine tests can be conducted to measure levels of these metals. Unfortunately, there is no specific treatment for heavy metal poisoning, so it is crucial to take preventive measures to avoid exposure.

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