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Chapter 2

Biological Implications of Certain Transition Metal Micronutrients

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Abstract

The aim of this study is to examine the biomedical implications of a range of metals, including zinc phosphide, period 5 metals (niobium, molybdenum, silver, and cadmium), and period 6 metals (osmium, platinum, and mercury), and to analyze their adverse effects on human health. This work is a comprehensive review of the scientific literature on the toxicity of these metals was conducted using databases such as PubMed, Elsevier, and Wiley, as well as journals specializing in toxicology and environmental health. Study selection was based on the PRISMA 2020 statement and included articles published within the last 15–20 years. A considerable number of these metals are toxic to humans through various routes of exposure, including oral, inhalation, and injection. The specific effects identified were kidney and lung damage (associated with niobium), liver dysfunction and gout (linked to molybdenum), argyria (a condition caused by silver), and kidney and bone damage (resulting from cadmium exposure). In addition, the toxic effects of osmium, platinum, and mercury on the nervous and cardiovascular systems were highlighted. The exposure to transition metals and other heavy metals can cause a range of adverse effects on human health, from deficiencies to acute or chronic poisoning. Therefore, it is crucial to manage these metals with caution and establish control measures to protect public health. To mitigate the risks associated with these metals, stricter regulations and further research into their biological mechanisms and detection methods are required.

Keywords: Food, Human health, Trace elements, Transition metals, Toxicity.

Introduction

Transition metals can be harmful to living organisms even in small amounts, depending on the maximum permissible dose. Depending on the amount ingested or administered, these metals can cause adverse effects in humans. Proteins with enzymatic activity are the most affected biomolecules, leading to multi systemic pathologies. However, some metals, such as manganese, iron, chromium, cobalt, nickel, copper, zinc, and molybdenum, are essential micronutrients necessary to catalyze key enzymatic reactions. These trace elements are vital for maintaining biochemical systems in living organisms. This review analyzes the deficiency and/or overdose of these metals in a descriptive and weighted manner, grouping them by periods of the periodic table (1-5). Food is one of the main routes of entry for heavy metals into the body, so it is crucial to know the degree of contamination in order to reduce or avoid their consumption, thus ensuring food safety for thepopulation. The presence of high concentrations of heavy metals such as cadmium, mercury, lead, nickel, and zinc can disrupt cellular homeostasis, affecting the body's biological processes and causing various pathologies, including malformations, cancer, and, in extreme cases, death (5, 6). Although heavy metals occur naturally, human activity, especially industrial processes, is the main source of contamination by these transition metals. The origin of these metals is currently a topic of great importance (6-10). The European Commission and member states have requested the EFSA (European Food Safety Authority) to assess the risk of various metals as contaminants, including arsenic, cadmium, chromium, lead, mercury, nickel, and uranium. This work has been carried out under the supervision of organizations such as the UN and FAO since 2009 (11-15).

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Transition Metals in Living Systems

Some metal ions are fundamental in essential biological processes in living systems and are found in various proteins. In metalloproteins, the metal ion defines the geometry of the enzyme's active site, acting as a center of enzymatic activity and facilitating enzymatic redox reactions. In this context, certain transition metals such as chromium, cobalt, iron, manganese, molybdenum, nickel, copper, tin, vanadium, and zinc are considered essential trace elements due to their crucial role in organic processes (1). Many biological processes are of great interest in medicinal chemistry, but the large size of proteins makes their study difficult. Therefore, low molecular weight model compounds are used. These compounds can mimic the properties of the metal centers of proteins, thus allowing the study of the physicochemical characteristics of complexes in biological systems and their processes. As a result, a field of study called "biomimetics" has emerged, which allows for the investigation of potential toxicological behaviors and the performance of pharmacological studies. Recent scientific and technological advances have enabled the integration of disciplines such asinorganic chemistry, analytical chemistry, biochemistry, toxicology, epidemiology, nutrition, pharmacology, and medicine, among others, to investigate the complex role of metals in biological functions and their impact on health (2).

Trace Elements Essential for Human Life

Living beings are composed of non-metallic atoms, such as oxygen, carbon, nitrogen, and hydrogen. However, at least twenty inorganic elements play a crucial role in biological processes (2, 3). Some trace elements, such as iron, zinc, and copper, are essential micronutrients for human health. Despite their presence in minute quantities in the body, they perform vital functions in various biological processes. For example, iron is fundamental for oxygen transport in the blood, while zinc contributes to the immune system and growth. Copper, on the other hand, participates in energy production and the formation of connective tissues (4). These trace elements are not distributed uniformly throughout the body, but rather are concentrated in specific tissues and organs. For example, iron is stored primarily in the spleen, bone marrow, and liver, while zinc is found in high concentrations in bones, muscles, and skin (3). Unlike trace elements, peptides, proteins, carbohydrates, lipids, and nucleic acids are not considered micronutrients, but rather macronutrients. These elements are present in large quantities throughout the body and are essential for its proper functioning, as they supply energy, form cellular structures, and regulate various metabolic processes (5-11). On the other hand, although transition metals are indispensable for life, it is crucial to maintain a proper balance in their intake. A deficiency in trace elements can trigger various diseases, while an excess can result in toxic effects. Trace element requirements vary significantly among different species. What is considered essential for humans may not be essential for other organisms, such as animals or plants. For example, nickel is not an essential trace element for humans, but it can be for certain animals (1-6). Likewise, there are plants that accumulate nickel in their tissues. This variability in trace element requirements has important implications for nutrition, toxicology, and the development of new therapies. Although a deficiency of certain metals, such as iron, can cause anemia, it is also true that excessive levels of this metal in the body can have toxic effects (4). Some metals are essential for the body, such as the elements in groups 1 and 2 of the periodic table, including Na(I), K(I), Mg(II), and Ca(II), which maintain charge and osmotic balance. Metals with a single oxidation state, such as Zn(II), play a crucial role as activators in protein activity. On the other hand, transition metals with multiple oxidation states, such as iron (Fe(II) and Fe(III)), form porphyrin complexes present in hemoglobin and myoglobin, acting as electron carriers in cytochromes and as O_2 carriers and storage carriers. Some facilitate O_2 transport, such as copper in hemocyanin, and serve as catalytic sites in enzymatic catalysis, such as copper ions in superoxide dismutase or the Fe-Mo cofactor in nitrogenase (5). Biomolecules with active sites are biological molecules that contain specific locations where chemical reactions essential for life take place. These biomolecules, especially enzymes and proteins, perform vital functions in living organisms, such as thetransport of molecules, the regulation of processes, and the catalysis of biochemical reactions (5). For example, tyrosinase is an enzyme with a copper active site that catalyzes the production of melanin, the pigment responsible for skin and hair color. Another enzyme with a copper active site is cytochrome c oxidase, essential in the mitochondrial respiratory chain for cellular energy production. Similarly, superoxide dismutase, an antioxidant molecule with a copper active site, protects cells from damage caused by free radicals (5-6). As for zinc, present in more than 200 enzymes in the body, it regulates gene expression and DNA repair. Among them are carboxypeptidase, a digestive enzyme with a zinc active site that breaks down proteins, and alcohol dehydrogenase, which metabolizes ethyl alcohol. It is important to note that the structures of biologically active molecules often contain multiple types of functional groups, which means that the properties of these molecules are a combination of the properties of each of the functional groups present (6-8).

Deficiency and Overdose: Metal Toxicity in Humans

As mentioned previously, the amount or dose of essential elements for the proper functioning of our body is crucial. Iron deficiency is one of the most recognized deficiencies globally. This metal plays a fundamental role in hemoglobin synthesis and mineral absorption; therefore, a lack of balanced intake or adequate absorption can trigger anemia. Given the abundance of iron on our planet, its deficiency represents a significant nutritional concern. This follows from the fact that most of the iron present in the foods we consume is in poorly soluble forms and, therefore, has low bioavailability (9).

Although calcium and magnesium are not transition metals, they illustrate the importance of metals in the body. Calcium is essential for the development and maintenance of the skeletal system, bones, and teeth. It also contributes to muscle contraction, neurotransmitter release, and heart rhythm regulation. Calcium deficiency in childhood can lead to rickets, while in adulthood it can be a predisposing factor for high blood pressure and osteoporosis. Magnesium, for its part, participates in numerous enzymes, muscle functions, and nerve function, so its deficiency can manifest as muscle cramps, headaches, loss of appetite, insomnia, and even increased susceptibility to stress (6-12).

Chromium plays a crucial role in the enzyme system that works with insulin to absorb glucose into cells and, consequently, to regulate blood sugar levels. This system is known as the glucose tolerance factor (GTF), so its deficiency leads to glucose intolerance. Unlike other mineral metals, zinc stands out for its importance in human metabolism, being essential for the proper functioning of the immune system. A zinc deficiency can increase vulnerability to infections (6). The primary importance of certain metals in the body and the negative effects of their deficiency in humans have been emphasized (10). However, it is essential to keep in mind that any excessive consumption can be harmful, and this case is no exception. For example, excess iron can be toxic and trigger symptoms such as vomiting, diarrhea, and intestinal damage, as well as interfere with the absorption of zinc, calcium, and copper. Zinc poisoning can cause a metallic taste in the mouth, vomiting, and stomach upset, and can be fatal with the ingestion of 1 gram or more. In this context, the toxicity levels associated with certain transition metals in humans are examined, classifying them generally according to periods 4, 5 and 6 of the periodic table, emphasizing those with a considerable level of toxicity (11-15).

Toxicity of period 4 metals: V, Cr, Mn, Fe, Ni, Cu, Zn

Vanadium is an essential element for plants and animals. Recent studies suggest that, in small doses, it may help regulate cholesterol levels in humans.

However, its toxicity is manifested at concentrations above 1 mg/kg (16, 17). Although it is a minor component in the Earth's crust, with typical concentrations of around 150 mg/kg, it can be found in higher proportions involcanic regions or in sedimentary rocks rich inorganic matter. The main source of human exposure to vanadium comes from the combustion of fossil fuels, being released as vanadium pentoxide (V_2O_5) adsorbed onto coal particles that are dispersed into the air. Inhalation of vanadium (V) compounds can cause serious toxic effects, even after brief exposure. Intense and prolonged exposure can cause pneumonia, with potentially fatal consequences, although a single exposure usually allows for complete recovery within 1 to 2 weeks (17).

Chromium occurs naturally in the Earth's crust at an abundance of approximately 100 mg/kg. However, its extensive use in the pigment, tannery, and refractory materials manufacturing industries has increased human exposure. Chromium can occur in the forms Cr(0), Cr(III), and Cr(VI), with Cr(VI) being the most toxic due to its high water solubility, which facilitates its mobility and bioavailability in the environment, especially in aquatic systems (18, 19). Chromium(III) is an essential trace element, and its deficiency can cause heart problems, metabolic disorders, and diabetes. However, it is not readily absorbed from the digestive system and can bind to proteins in the superficial layers of the skin. On the other hand, chromium(VI) compounds are rapidly absorbed after ingestion or inhalation, causing corrosive effects through dermal and mucous membrane absorption. Some chromates, such as those of zinc, calcium, and lead, as well as chromium trioxide fumes, are considered carcinogenic and are associated with the development of lung cancer (19).

Manganese, with a concentration of 0.1% in the Earth's crust, is the twelfth most abundant element. Recent studies have found that manganese is a recurring contaminant in water, soil, air, food, and infant formula. Once absorbed, manganese is rapidly eliminated from the blood and distributed primarily to the liver, accumulating in bones over a period of 8 to 9 years (20).

In the blood, manganese is bound to proteins and is distributed primarily to the liver, where bile acts as the main route of excretion, with almost all of it being eliminated through feces. However, in certain cases, it is excreted mainly in the urine due to the biotransformation of manganese compounds in the kidneys. Prolonged exposure to manganese can cause nerve damage, manifesting with symptoms similar to Parkinson's disease, such as tremors and difficulty with movement. On the other hand, iron is one of the most abundant elements in the universe and is a major component of the Earth's crust, forming a variety of minerals, some of which have a fibrous texture, such as asbestos (20). The presence of Fe(II) in the crystalline structure of asbestos appears to be a trigger for certain types of cancer, as it facilitates the formation of highly reactive hydroxyl groups through the Fenton reaction. Recently, iron in the form of nanoparticles, which enters the body through inhalation due to the mechanical wear of various materials in the anthroposphere, has been shown to have harmful effects (21, 22). When inhaled as nanoparticles, iron can irritate the lungs and gastrointestinal tract, negatively impacting lung function. Hemochromatosis, an inherited iron deficiency disease, is life-threatening, and its symptoms typically appear in middle age, including bronzed skin, cirrhosis, liver cancer, diabetes, and heart failure, which can lead to premature death (6, 21, 22). Nickel is abundant in the Earth's crust, but elevated levels of this metal are primarily associated with the burning of fossil fuels and waste management. Nickel and its compounds are a common cause of allergic contact dermatitis, observed in the general population due to exposure to objects such as coins, jewelry, and watches. Nickel compounds have been classified as carcinogenic to humans (Group 1), and metallic nickel as a possible carcinogen (Group 2B) (23). Copper is an essential trace element, required in doses of between 1 and 100 mg/day for adults. Its concentration in the Earth's crust is approximately 70 mg/kg. Human exposure to copper is related to industrial and agricultural activities, with inhalation being one of the main routes of exposure, especially through water pipes. Fragments of copper or alloys can become lodged in the eyes, causing chalcosis, which can lead to uveitis, abscesses, and vision loss. Accidental ingestion of soluble copper salts is usually harmless, as vomiting releases most of the copper.

Chronic toxic effects of copper are observed in people with a specific genetic mutation, leading to Wilson's disease. Copper poisoning is treated with penicillamine, which facilitates its excretion through chelation (6, 24).

Zinc is one of the most abundant heavy metals in the Earth's crust, with a concentration of 78 mg/kg, and is essential for human health (25). Although it does not accumulate in the body, a dose higher than the recommended amount can interfere with the absorption of other elements, such as copper, and cause anemia. Nutrition experts recommend a minimum daily intake of zinc. However, some zinc compounds, such as zinc chloride, are toxic and can cause skin ulcers. Exposure to zinc oxide fumes can cause metal fume fever, the symptoms of which include chills, irregular fever, sweating, nausea, thirst, headache, limb pain, and extreme fatigue. Attacks are short-lived, and tolerance appears to develop. Zinc phosphide, used as a rodenticide, is toxic to humans orally, by inhalation, or by injection, and along with zinc chloride, is one of the most dangerous zinc salts (6, 25).

Toxicity of period 5 metals: Nb, Mo, Ag, Cd

Transition metals, such as yttrium (Y), zirconium (Zr), technetium (Tc), ruthenium (Ru), rhodium (Rh), and palladium (Pd), occur in nature at trace levels (1 to 10 mg/kg). Although their toxicity is not fully established and their abundance is low, these metals and their compounds should be handled with care, as they may be carcinogenic. Ruthenium oxide is especially toxic and volatile, so it should be avoided. Palladium hydroxide, which was used to treat obesity by injection, causes local necrosis, leading to its discontinuation (26, 27).

Niobium (Nb) is also rare in nature, with concentrations below 10 mg/kg. Niobium can be found in higher concentrations in some mineral deposits, especially pegmatite rocks, so exposure to this element is uncommon and generally occurs in mining settings. When inhaled, niobium is retained primarily in the lungs and, to a lesser extent, in the bones, interfering with calcium by acting as an activator of the enzyme system. In vivo animal studies have shown that niobium compounds, such as niobium nitride, niobium pentoxide, and niobium pentachloride, can affect organs such as the lungs and kidneys (28-35).

Molybdenum is an essential trace element for humans, playing a crucial role in the enzymatic transformation of sulfites to sulfates in the body. The WHO states that its natural concentration in drinking water should not exceed 70 µg/L, although it is generally found below 10

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μg/L (36-42). According to animal studies, molybdenum and its compounds are highly toxic. Chronic consumption of these substances can cause liver dysfunction with hyperbilirubinemia and gout-like symptoms, such as pain in the knees, hands, and feet, joint deformities, erythema, and edema. Acute poisoning can lead to severe gastrointestinal irritation, diarrhea, coma, and death from heart failure. Inhalation of molybdenum dust from alloys or carbides can lead to hard metal lung disease (40-42). Silver is a precious metal found in small quantities in the Earth's crust, although it can be found in minerals such as chlorargyrite (AgCl) and other minerals associated with tin and arsenic. Mining can contaminate water systems and increase human exposure to silver. This metal is also used in catalysts, electroplating, medical devices, and photography. Technological advances have increased the production of silver nanoparticles to more than 400 tons annually, increasing their dispersion in the environment,especially through the air (43). Exposure to silver (Ag) can cause a benign condition called argyria. If silver dust or its salts are absorbed, the silver is deposited in tissues in its metallic state and cannot be eliminated from the body. This reduction to the metallic state occurs in parts of the skin and mucous membranes exposed to light or through hydrogen sulfide in other tissues. Silver dust is an irritant and can cause ulcerations of the skin and nasal septum. Soluble silver salts, such as silver nitrate (AgNO3), are lethal at concentrations above 2 g. Silver compounds can be slowly absorbed by body tissues, causing skin problems such as argyria (28, 43).

Cadmium (Cd) occurs naturally at trace levels, but activities such as burning trash and recycling electronic equipment increase its environmental concentration, affecting both ecosystems and humans. Once in the body, cadmium is not easily transformed or excreted, leading to a high rate of bioaccumulation. When ingested, cadmium is transported to the liver by the blood, where it binds to proteins to form complexes that are then transported to the kidneys. There, cadmium accumulates and impairs the filtration mechanism, causing the excretion of essential proteins and sugars from the body, resulting in kidney damage (34). In severe cases of chronic cadmium poisoning, osteomalacia has been observed, as cadmium is a necessary etiological factor. Kidney damage caused by cadmium is irreversible and can continue to progress even after exposure to the substance ceases (28, 37). In addition to renal effects, chronic cadmium exposure can have other serious health consequences. In the skeletal system, this metal can interfere with calcium metabolism, which can lead to decreased bone density and an increased risk of fractures. It has also been associated with cardiovascular diseases, such as hypertension and atherosclerosis, due to its ability to induce oxidative stress and endothelial damage. In the respiratory system, inhalation of cadmium dust can cause chronic obstructive pulmonary disease and lung cancer (29-32). Occupational exposure to cadmium, especially in industries such as mining and metallurgy, poses a significant health risk. Workers in these sectors may be exposed to elevated levels of this toxic metal, which can trigger a range of health problems (32-36). Scientific studies have linked cadmium exposure to testicular dysfunction in men, menstrual irregularities in women, and adverse effects on fetal development, such as low birth weight and neurodevelopmental delays. In the long term, chronic cadmium exposure has been associated with an increased risk of developing various types of cancer. These harmful effects are attributed to cadmium's ability to generate oxidative stress, inhibit antioxidant enzymes, and damage DNA (34,36,37,44).

Toxicity of Period 6 Metals: Os, Pt, Hg, Pb

Exposure to heavy metals such as osmium (Os), platinum (Pt), mercury (Hg), and lead (Pb) poses a significant risk to human health and the environment. These elements, due to their persistence and ability to bioaccumulate in organisms, can cause a wide range of adverse effects. On the other hand, metals such as lanthanum, hafnium, tantalum, tungsten, rhenium, iridium, and gold, although less well-known for their toxicity, present potential health risks due to their increasing use in various industries. Although some, such as hafnium and tantalum, have low solubility and, therefore, lower bioavailability, their compounds and nanoparticles can be more reactive and hazardous (28-35).

Due to the high toxicity of many osmium compounds, it is essential to handle these materials with extreme caution. The fumes from osmium compounds, such as osmium tetroxide, are extremely irritating and corrosive, so the use of appropriate personal protective equipment, such as respirators and chemical-resistant gloves, is essential. Furthermore, it is crucial to work in laminar flow hoods and well-ventilated areas to minimize exposure to these fumes (28). Despite its low natural abundance, platinum has become a ubiquitous element in our society due to its numerous industrial and medical applications. This increased use of platinum has significantly raised human and environmental exposure to this metal (30-40). Prolonged exposure to platinum, especially in the form of soluble salts, can lead to an occupational disease known as platinosis. This condition is characterized by marked irritation of the respiratory tract, accompanied by symptoms such as coughing, shortness of breath, and fatigue. In addition, platinum and its compounds can cause allergic reactions, including anaphylaxis, and have been linked to DNA damage. The increasing use of platinum nanoparticles in various applications raises new concerns about the long-term effects of this metal on human health (44, 45). Mercury, a highly toxic heavy metal, poses a serious threat to human health and the environment. Its ability to bioaccumulate along the food chain makes it a particularly dangerous contaminant. Inhalation of mercury vapors is the main route of exposure, but it can also occur through ingestion of contaminated food or skin contact. Once in the body, mercury is distributed to various organs, including the brain and kidneys, where it can cause irreversible damage (46, 47). It is important to note that exposure to mercury, even at low levels, can have serious health consequences. This toxic metal primarily affects the central nervous system, causing symptoms such as tremors, memory loss, speech disorders, and blurred vision. In addition, mercury can damage the kidneys and heart and has been associated with an increased risk of cardiovascular disease. Preventing mercury exposure is essential to protecting public health, especially in vulnerable populations such as pregnant women and children (35, 39, 46, 47). Mercury exerts its toxicity by interfering with various biological processes, including neuronal function and energy production. Exposure to this metal can occur through various sources, such as the combustion of fossil fuels, gold mining, and waste incineration. The most toxic form of mercury is methylmercury, which accumulates in the tissues of aquatic organisms and can be transferred to humans through the food chain (6, 28, 32, 34, 35). Therefore, the severity of mercury's adverse effects on human health demands the implementation of rigorous preventive measures. It is essential to strictly regulate industrial mercury emissions, promote safe practices in the management of products containing this metal, and educate the public about the associated risks. Ongoing research is key to developing clean technologies and effective strategies for reducing mercury pollution (36).

Conclusions

Transition metals, which occur naturally and are released by human activities, can have adverse effects on living organisms even at low concentrations. Ingestion or exposure to high doses can have adverse effects on human health, particularly on proteins with enzymatic activity. While some transition metals, such as iron, zinc, and copper, are essential for the human body in small amounts, others, such as cadmium, mercury, and lead, are highly toxic. Exposure to these metals can have adverse health consequences, including birth defects, cancer, and mortality. Food represents a major route of introduction of heavy metals into the body, underscoring the importance of monitoring contamination levels and reducing consumption. Industrial activities represent a significant source of these metals in the environment, highlighting the need for strengthened regulatory controls. Therefore, further research is needed to better understand the molecular mechanisms through which transition metals exert their biological functions. In this regard, the development of more sensitive and specific methods for measuring the levels of these elements in tissues and body fluids is of great importance. Furthermore, new strategies for preventing exposure to toxic transition metals and effectively eliminating them from the body must be investigated. Consequently, new research on bio-inorganic chemistry has the potential to facilitate the development of novel therapeutic strategies for conditions such as cancer, neurodegeneration, and cardiovascular diseases. In conclusion, transition metals play a dual role in living organisms: some are essential for life, while others exhibit high toxicity. Therefore, it is imperative to improve our understanding of their toxicity and implement a series of preventive measures to safeguard human health, the environment, and public safety.

Declaration

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