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A mini-review on importance and role of trace elements in the human organism

Tarik Attar [a, b,*]

[a] *Higher School of Applied Sciences of Tlemcen, BP 165, Bel Horizon, 13000 Tlemcen, Algeria*
[b] *Laboratory of Toxicomed, University AbouBekerBelkaidTlemcen, BP119, 13000 Tlemcen, Algeria*

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ABSTRACT

Trace elements are minerals present in living tissues in minute quantities. Some of them are known to be nutritionally essential and the remainder is considered to be nonessential. The body requires certain essential elements and their deficiency or excess may result in serious dysfunction of the body and even death in extreme cases. The low intakes dietary of trace element produce changes in biochemical pathways that can raise the risk of diseases over time. On the other hand, excessive levels, a level higher than needed for biological functions, of these elements can be toxic for the body health. This review evaluates the role and importance of the essential trace element in the human organism. The potential importance of key essential trace elements; Magnesium, Manganese, Iron, Zinc, Copper, Cobalt, Iodine, Selenium, Nickel, Molybdenum and Chromium; and nonessential trace such as Cadmium, Lead, Arsenic and Mercury are discussed.

1. Introduction

Trace elements, also called trace metals, are present in small amounts as constituents of all living organisms and despite the minuscule level of their presence, are vital for the growth, development and general well-being of those organisms. It plays a crucial role in many biochemical processes, mainly as components of vitamins and enzymes [1, 2]. Trace elements has been shown that the imbalances in trace elements may negatively affect biological processes and are linked with many fatal diseases [3]. The Interest of trace elements in human physiology began over a century ago with the discovery that a number of compounds in living organisms contained metals not previously considered to be of biological significance [4]. Trace elements are present in every biological process, from the production of energy and hormones, associate with some protein, nerve transmission, cholesterol and blood sugar levels, and muscle contraction to the regulation of pH, digestion, metabolism and others [5]. These elements are part of cells, enzymes, hormones in the body [6]. A few elements donate or accept electrons in redox reactions, which results in generation and utilization ofmetabolic energy and have an impact on the structural stability and to import certain biologicalmolecules. Many searches have focused on the relationship of various trace elements levels in blood with biological disorders such as thyroid dysfunction, heart diseases and diabetes, gastrointestinal cancer, breast and lung cancer, sclerosis, neurodegenerative disorders,
schizophrenia and Alzheimer's disease and Parkinson's [7-12]. This review article evaluates the role and the importance of essential trace elements in the human organism.

2. Trace Elements

2.1. Magnesium

Magnesium (Mg) is an essential element required as a cofactor for more 300 enzyme systems that regulate diverse biochemical reactions in the human organism, including protein synthesis, blood glucose control, nerve and muscle function, and blood pressure regulation [13]. Magnesium may also be considered for adjunct or treatment for depression, as a prevention of renal calculi and cataract formation, and as a therapeutic intervention for many other health-related disorders [14]. Generally, Mg deficiency is due to these factors: low dietary magnesium intake in food and drinking water, excessive losses of magnesium due to certain health conditions, chronic alcoholism and may occur as a result of using certain medications [15]. Early signs of magnesium deficiency include loss of appetite, fatigue, weakness, nausea and vomiting. As magnesium deficiency becomes severe, muscle contractions and cramps, an irregular heartbeat, hallucinations, delirium, seizures, coronary spasms, numbness, tingling and personality changes. Consuming higher quantities of Mg in diets are linked

* Corresponding author. Tel.: +213662218567; e-mail: t.attar@essa-tlemcen.dz

with a significantly lower risk of diabetes, possibly because of the important role of magnesium in glucose metabolism [16]. However, the diabetes leads to increased urinary losses of magnesium, and the subsequent magnesium inadequacy might impair insulin secretion and action, thereby worsening diabetes control [17]. Metabolic and experimental studies indicate that magnesium may have a role in the regulation of blood pressure and also associated with a significantly lower risk of ischemic heart disease caused by a reduced blood supply to the heart muscle [18, 19]. The disorders and diseases in which Magnesium deficiency might be involved: muscle spasms, high blood pressure, migraines, diabetes, cerebral infarction and osteoporosis and it can result in hypokalemia or hypocalcemia [20-24]. In addition, both excessively low and high manganese levels in body, appear to be detrimental to bone health [25]. In the presence of Mg deficiency, stress may increase risk of cardiac arrhythmias, constriction or occlusion of coronary or cerebrovascular arteries, cardiovascular damage and sudden death [26]. Stress, whether emotional stress (including depression, anxiety, or excitement), physical stress (including surgery, trauma, exertion, heat or cold), or dyspnea such as that found in asthma, increases the need for Magnesium [27]. Mg also plays an important role in diminishing the risk of glaucoma by improving ocular blood flow and preventing loss of ganglion cells [28]. Magnesium is required for the transformation of vitamin D into its active form which, in turn, supports calcium absorption and metabolism, as well as normal parathyroid hormone function [29].

2.2. Manganese

Manganese (Mn) is an important trace mineral that is present in very small amounts in the human organism. It's one of the most important nutrients for body health. Mn is absorbed by the gastrointestinal tract, which is the main route for physiological Mn absorption, and then transported to organs enriched in the mitochondria where it's rapidly concentrated, the rest is excreted in the feces [30]. Its absorption via the lungs occurs principally at professional settings, which are considered the primary source of Manganese toxicity for humans [31]. Manganese is an essential element that is associated in the activation and synthesis of various enzymes (e.g., isomerases, hydrolases, ligases, transferases, lyases, oxidoreductases, glutamine synthetase, pyruvate decarboxylase and arginase); acceleration in the synthesis of protein, vitamin B, and vitamin C; regulation of the blood sugars and endocrine; improvement in immune function; catalysis of hematopoiesis and also works with vitamin K to support clotting of the blood [32-36], and it plays a role in controlling blood pressure due to its anti-oxidative function [37]. In addition, Mn is as well important in bone mineralization, immunological response, cellular energy and metabolic regulation, and cellular protection from reactive oxygen species [38]. It has been found that the deficiency of Mn in the body can causes a number of detrimental effects, such as impaired growth, poor bone formation and skeletal abnormalities, hypercholesterolemia, changes in hair color, dermatitis, abnormal glucose tolerance, reduced fertility, deafness, and associated also with adverse metabolic and neuropsychiatric effects [39-41]. Excessive Mn accumulated in mitochondria could disrupt mitochondrial homeostasis and cause mitochondrial dysfunction [42]. On the other hand, it has been observed that the abnormal concentrations of Mn in the brain, especially in the basal ganglia [43], which may precipitate a form of parkinsonism with some clinical features that are similar and some that are different to those in Parkinson's disease [44]. Moreover, the overexposure manganese in the brain can be neurotoxic, implicated in several neurodegenerative disorders such as Alzheimer's disease [45-48]. It has been shown that Mn treatment can rise insulin secretion to improve glucose tolerance under conditions of dietary stress [49], lower the risk of endothelial dysfunction in diabetes [50], and reduce oxidative stress [51]. Manganese supplements can be taken as capsules or tablets, generally along with other minerals and vitamins in the form of a multivitamin [52].

2.3. Iron

Iron (Fe) is one of the most important and abundant in metals which present in all body cells and its role in human life cannot be underestimated. As a component of myoglobin and hemoglobin, it functions as a carrier of oxygen in the blood and muscles [53]. Iron participates directly as an acceptor or donor in electron transfer reactions, it exists in two states are the divalent ferrous (Fe^{2+}) and the trivalent ferric (Fe^{3+}) [54], but most dietary iron is in the ferric form. Thus, iron needs to be reduced before it can be absorbed. Iron element is an indispensable for synthesis of some hormones and connective tissue, and development, growth and normal cellular functioning [55], and it has also a central and critical role in synthesises many of the proteins involved in iron metabolism. The most common symptoms of Fe-deficiency anemia are weakness, dizziness, shortness of breath, difficulty concentrating, heart palpitations and tiredness due to the inadequate oxygen provide to the body's cells and paleness in the eyelids and hands due to the decreased levels of oxygenated hemoglobin. These symptoms can be treated by using iron supplement [56].
Disturbances of iron metabolism in the human organism are among the most popular diseases and include a wide spectrum of health problem with various clinical manifestations, ranging from anemia to iron overload and, probably, to neurodegenerative diseases.The excess iron may catalyze reactions cause oxidative damage to tissues and cells that can lead to tissue fibrosis and organ dysfunction long term.Iron accumulates in many organs,

most notably in the pancreas, heart and liver [57]. Clinical consequences of this accumulation include increased risk of hepatocellular carcinoma, cardiomyopathy, diabetes, arthritis and hepatic cirrhosis and fibrosis [58, 59]. Iron overload is a known contributor to multiple degenerative diseases, including cancer, heart attack, liver fibrosis and oxidative stress [60-63]. Iron amounts in body tissues must be absolutely regulated because excessive iron leads to tissue damage, as an outcome of formation of free radicals [64].

2.4. Zinc

Zinc (Zn) plays an important part in human growth and nd development during pregnancy, childhood, and adolescence; it has a recognized action on over 300 different enzymes, by participating in their structure or in their catalytic and regulatory actions [65]. Zn is one of the most abundant trace elements in the human body [66]. It's of fundamental relevance for many molecular, cellular, metabolic, and immunological processes, including anti-oxidative, anti-inflammatory, and anti-apoptotic responses [67]. The zinc is an essential element for normal spermatogenesis and maturation, genomic integrity of sperm, for normal organogenesis, proper development of thymus, proper functioning of neurotransmitters, taste sensation, gastric enzymes and secretion of pancreas, it functions in cells and tissues is dependent on metalloproteinase and these enzymes are associated with dermatological, neurological systems, and immune [68].

It can be biochemically classified as these involved in protein and nucleic acid synthesis and degradation, carbohydrate, lipid, metabolism alcohol and protein metabolism [69]. Zinc insufficiency has long been associated with chronic liver disease, cirrhosis and chronic viral hepatitis [70], as well as number of physiological disorders including dermatologic conditions such as eczema, acne, psoriasis [71-74] and poor wound healing [75], in the other hand, the low levels of Zn showed an inverse correlation with the degree of liver damage [76], liver fibrosis [77], and markers of liver dysfunction such as bilirubin, albumin, and cholesterol [78].

Its deficiency is also associated with pneumonia, abnormal sexual function, neurologic abnormality, growth retardation, poor appetite, immune system dysfunction and diarrhea [79]. The deficiency symptoms also include compromised energy metabolism, acidosis, blockage of protein biosynthesis, alcohol intoxication, transmutation reaction blocked cell destruction by superoxide radicals [80]. Zinc deficiency is aggravated by low dietary intake, malabsorption, alcohol abuse, chronic renal disease and has a destructive impact on neuronal development [81]. The improper regulation of zinc homeostasis and zinc may play a substantial role for the onset and progression of Alzheimer's disease [82]. It has been shown that zinc deficiency or excess cause cellular oxidative stress [83]. Oral ingestion of excessive quantities of Zn quickly causes about noticeable abdominal pain, nausea, vomiting and eventual anemia [84], and the inhalation of zinc can bring about shaking, fever and fatigue [85]. Some recent studies showed that zinc supplementation improved glucose metabolism and insulin sensitivity in diabetic patients [86].

2.5. Copper

The scientists identified copper compounds to treat diseases in 400 B.C, they still discover novel information concerning the physiology, biochemistry, toxicology, many clinical, laboratory and other indicators of the impact of copper in the organism [87, 88]. Copper (Cu) is one of various fundamental trace metals that are necessary in supporting biological functions for the human organism, forming part of many copper dependent enzymes and proteins [89, 90]. In the human body, copper shifts between the cuprous (Cu^{1+}) and cupric (Cu^{2+}) forms, though the majority of the body's copper is in the second form oxydation [91, 92]. Like other transition metals, the ability of Copper to easily accept and donate electrons explains its important role in oxidation-reduction reactions and free radicals from the organism which is involved in the cell metabolism [93], and is a part of differents enzymes such as uricase, tyrosinase and cytochrome oxidase [94]. It constitutes integral important parts of certain enzymes such as superoxide dismutase, lysyloxidase and ceruloplasmin, which protects cells from oxidative degradation [95]. The copper is a precious element in body healthy because it also associated in the formation of red blood cells [96]. In combination with iron, copper is employed for treatment of hypotrophy, hypochromic anemia and other diseases, Copper-containing drugs and food supplements are also used in treatment and prophylaxis of musculoskeletal diseases, hypothyroidism [97].

When deficiency copper occurs, symptoms include neutropenia, cardiac disorders, osteoporosis, and anemia [98, 99]. Copper insufficiency is more and more recognized cause of neurologic degeneration and is also an established cause of anemia and the myelodysplastic syndrome [100]. Acquired copper deficiency is also thought to affect cardiovascular and bone health, weakness, fatigue, skin sores, poor thyroid function and low body temperature [101-103]. Decreased levels occur in the nephrotic syndrome, Kwashiorkor, Wilson's disease, vomiting and severe diarrhea [104]. Excessive in exposure of copper either from diet or through any other sources acquired rapidly produces vomiting, diarrhea, nausea, profuse sweating, and renal dysfunction [105]. Copper excess accompanies the development of multiple neoplastic processes like the intestine, lung, breast, prostate and brain cancers and also lead damage to various tissues and organs [106, 107]. Higher

concentrations of copper in blood serum were significantly observed in type 2 diabetes against those in controls [88]. For this reason, many experiments with animals are effected in order to discover a treatment for impaired copper status in diabetes by uses chelating agent [108].

2.6. Cobalt

Cobalt (Co) is an essential trace element for the human body, where it's a key constituent of vitamin B12 [109]. The cobalt ions enter the body and bind with proteins within the bloodstream and get transported with blood to be deposited in tissues and cells [110]. The excess level of Co in the human organism might cause overproduction of erythrocytes and hypothyroidism, occupational asthma and fibrosis in lungs and it can lead to disturbance of iodine metabolism in the thyroid gland [111-113]. Moreover, complications of toxicity cobalt may be observed: thyrotoxic, neuro-ophthalmic and cardiotoxic [114]. It was indicated that a low-cobalt diet reduced the dyshidrotic eczema flares in cobalt allergic patients [115]. Cobalt normalizes blood glucose and vascular reactivity and stimulates adiponectin, thus ameliorating diabetes mellitus, weight gain, hypertension, vascular thrombosis, and myocardial hypertrophy, and in turn attenuating cardiovascular risk [116-118]. It has been appeared that cobalt infusion resulted in muscle tremors, hypertension, tachycardia, as well as elevation of cortisol hormone, adrenocorticotropic, and troponin I levels [119], that may subsequently result in cardiac arrest and death [120]. Exposure to cobalt results in the formation of cobalt protoporphyrins, which exert anti-inflammatory and cytoprotective effects in the injured myocardium, thereby preventing endothelial and myocardial cell injury and adverse cardiac remodeling [121-123]. Furthermore, excessive cobalt exposure or prolonged cobalt chloride treatment are accompanied by allergic rhinitis, lung disease, and, hypothetically, increase lung cancer risk. Additionally, cobalt overconsumption may result in adverse health effects, including gastrointestinal, liver, sensory damage, the development of hearing loss, sensorimotor polyneuropathy, bilateral optic atrophy, retinopathy, and thyroid dysfunction may also be observed [124, 125]. One suggested mechanism by which cobalt may induce goitrogenic effects is via inhibition of one or more of the enzymatic reactions at different levels of thyroid hormone formation [126]. Cobalt has been also used for the treatment of anemia and by athletes to increase red blood cell mass and enhance sportive performance, as an alternative to blood doping [127, 128].

2.7. Iodine

Iodine (I) is an essential trace element that our human organism need for normal growth and development. It is a necessary element involved in regulation of protein, carbohydrates, and lipid as well as balance between anabolic and catabolic processes. The increased ratio of differentiated papillary cancer to follicular in the regions with iodine excess as compared to the ones with normal iodine status and deficiency [129]. On the other hand, the increase of thyroid cancer was observed both in regions with iodine deficiency and its excessive intake [130]. Goiter and hypothyreosis are detected in all age groups caused by inadequate dietary iodine consumption [131].

Iodine is an essential component of triiodothyronine (T3) and thyroxine (T4). Thyroxine is a thyroid hormone with four atoms of iodine in its structure, plays the most important role in brain development. Under the influence of brain isoform of deiodinase thyroxine is transformed into the more active triiodothyronine (three iodine atoms instead of four) [132, 133]. In the human body, T4 and T3 are required for the regulation of various physiological processes including temperature, rate of oxidation in cells, neurological development, growth and body weight [134]. Iodine deficiency is related for hypothyroidism, goiter, increased risk of miscarriage, preterm birth, congenital and development fetal abnormalities, and elevated incidence of neonatal death [135, 136]. Moreover, Iron deficiency was more commonly seen in subjects with hypertension and also among postmenopausal females [137]. Chronic excessive iodine supply can also lead to goiter [138] and may accelerate the development of thyroid disorders (hyperthyroidism or hypothyroidism), increase the incidence of autoimmune thyroiditis, and increase the risk of thyroid cancer [139-141]. Recently, high iodine intake was suggested as a risk factor for type 2 diabetes [142]. Overloading by Mn, Co, toxic metals like Cd, Pb, and deficiencies of Se, Zn and Cu in food and in the body are factors affecting I metabolism and thyroid functions [143, 144]. Moreover, high consumption dietary of iodine influences trace element balance and is capable to block iodine organification and synthesis of thyroid hormones. In the first trimester of pregnancy thyroxine takes part in development of brain cortex, basal ganglia, inner ear, whereas in the third trimester its primary role is participation in growth and differentiation of all brain regions [145].

2.8. Selenium

Selenium (Se) is a fundamental trace element which is found in small quantities in the human organism [146]. Adequate levels of bioavailable selenium are functionally important for several aspects of human biology including regulation of immunity, the male reproductive biology, thyroid functioning, the central nervous system, the cardiovascular system, the endocrine system and muscle function [147, 148]. Selenium is an element associated with the activity of the antioxidant enzyme glutathione peroxidase [149, 150]. The selenium is considered to be a protective agent against free radicals through enhanced

enzyme activity [151]. Selenium deficiency-associated oxidative stress results a development of atherosclerosis, alteration of vascular endothelium, hypertension, and progressive heart failure [152]. Selenium deficiency results in microangiopathy, muscular dystrophy, impaired immune response, edema, necrosis of the liver, hemorrhage and sudden death, as well as increases the risk of diffuse enlargement of multinodular goiter and thyroid [153, 154]. Moreover, a significant relationship between selenium low concentration in body and allergic reactions and infective allergic asthma was demonstrated [155]. In addition, it has been shown relationship between the low selenium intake and HIV prevalence [156, 157]. Selenium deficiency is also observed in Crohn diseases patients and in other inflammatory states [158]. Decreased selenium content in brain tissue is allied with various neurological disturbances including ataxia and epilepsy [159]. There is some evidence that Se can modulate the pathology that accompanies chronic inflammatory diseases in the liver and gut as well as in inflammation-associated cancers [160, 161]. It has been observed that the selenium level of hepatitis B and C patients is less than in the healthy individuals [162]. Selenium deficiency have been involved in in a variety of tissues diseases including the mammary gland tissues [163], the gastrointestinal tract [164, 165], the uterus [166], and others. At selenium deficiency, there is an increased accumulation of arsenic, cadmium and mercury in the body. The maximal selenium concentration was noticed in the cerebellum, hippocampus, brain cortex and olfactory bulb [167]. There have been several epidemiological studies such as poliovirus [168] and as well as intervention studies involving different types of cancer, which suggests beneficial effects of higher selenium status [169].

2.9. Nickel

Nickel (Ni) is both essential and toxic in the body. Nickel helps in iron absorption, improves bone strength, as well as glucose and adrenaline metabolism, hormones, lipid, cell membrane, and may also play a role in production of red blood cells [170]. When nickel enters the body, it is distributed to all organs, but mostly in the lungs, kidney and bone [171]. Urinary excretion is the major route for the elimination of absorbed nickel [172]. Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake [173]. The food is also considered to be a major source of exposure to nickel, and therefore, it's recommended that individuals with food-related flare-ups of nickel dermatitis consume a low-nickel diet [174]. The lung and the skin are the principal target organs upon occupational exposure. Nickel has been classified as a cancer causing agent and shows high cancer rate in the nasal and lungs in refinery workers [175]. Inhalation of soluble nickel causes irritation of the nose and sinuses and can also lead to loss of the sense of smell or perforation of the nasal septum. Exposure with nickel compounds can cause a variety of adverse effects on human health, such as nickel allergy in the form of contact dermatitis, lung fibrosis, cancer of the respiratory tract, and kidney and cardiovascular diseases [176-179]. Moreover, Acute health effects generally result from short-term exposure to high concentrations of pollutants and they manifest as a variety of clinical symptoms (nausea, giddiness, headache, visual disturbance, vomiting, cough, abdominal discomfort and diarrhea). Nickel can have an effect on human health through infectious diseases arising from nickel dependent bacteria. It deficiency is accompanied by biochemical and histological changes and reduced iron resorption and leads to anaemia [180].

2.10. Molybdenum

Molybdenum (Mo) is an essential trace element for the human organism. It takes part in the active site of enzymes and functions as an enzymatic cofactor [181], a complex of molybdenum and an organic component, molybdopterin [182, 183]. Four of these enzymes are present in the human organism: xanthine dehydrogenase (XDH)/oxidase (XO), sulfite oxidase (SO), aldehyde oxidase (AO), and mitochondrial amidoxime reducing component (mARC) [184]. Increased XDH activity and hyperuricemia are observed in ischemia, cardiovascular diseases, diabetes complications, and metabolic syndrome [185]. Molybdenum shuttles between two oxidation states, Mo(IV) and Mo(VI). A deficiency in the biosynthesis of molybdenum cofactor results in a pleitropic loss of all four human molybdenum-enzyme activities and in most cases in early childhood death [186]. Mo deficiency is accompanied by decreased blood and urinary uric acid concentration, and increased xanthine and hypoxanthine excretion [187]. The Low level of uric acid in the organism is associated with impaired antioxidant defense [188]. High amounts of molybdenum are toxic. Overconsumption of this element results in increased absorption and is decreased at lower molybdenum doses [189]. After excessive dietary molybdenum consumption, the risk of toxicity is increased in copper-deficient persons [190]. Moreover, experimental studies have indicated that Mo increases urinary copper and molybdenum excretion [191, 192].

2.11. Chromium

Chromium (Cr) is a trace element that body need in trace amounts, and it's found primarily in two forms: Cr^{3+}, which is biologically active and found in food and Cr^{6+}, a toxic form that results from industrial pollution [193]. It has been found that chromium produces significant improved sugar metabolism through the activation of insulin, increases in enzyme activity and serves an important function in carbohydrate metabolism, and

stimulation of fatty acid and cholesterol synthesis from acetate in the liver. In addition, Chromium is a critical cofactor in the action of insulin [194-196]. Chromium deficiency is characterized by reduced highdensity lipoprotein level leading to increased incidence of cardiovascular diseases [197]. An investigation has demonstrated that trivalent chromium suppresses cholesterol synthesis, and also play a protective role in prevention of development and deposition of amyloid in tissues [198]. Overconsumption of dietary lipids results in metabolic impairments like increased body mass index, impaired glucose transport, elevation of blood glucose and insulin, decreased chromium depots in liver, alteration of cellular signaling. Further, these changes may be reversed by chromium histidinate treatment [199]. Overexposure of chromium especially hexavalent from the environment the risk of lung and stomach cancer is increased [200]. The highest chromium levels are in renal, liver, thyroid gland, intestine, bones and cartilages. Chromium-containing preparations may be used in treatment of atypical depression [201], where it has been shown that chromium possess antidepressant activity acting on serotonin and glutamine receptors [202].

2.12. Lead

Lead (Pb) is a non-essential trace element because it has no known essential role in living organisms. It exhibit extreme toxicity even at very low exposure levels and have been regarded as the main threats for human health. Through the bloodstream, lead is distributed among three main compartments: blood, soft tissue that includes kidney, liver, brain, bone marrow, and mineralized tissue that includes bones and teeth [203]. Pb is absorbed into blood plasma from which it enters the blood cells. About 99% of lead in blood are present in erythrocytes and 90% of the total body burden of lead is found in the skeleton [204]. The nervous system is the most affected target in Pb toxicity, both in children and adults. Early symptoms of lead encephalopathy include dizziness, irritability, lethargy, vomiting, loss of appetite and a reduced level of consciousness which may lead to coma and death [205, 206]. Lead also causes long-term harm in adults including anemia, renal impairment, immunotoxicity, hypertension, and toxicity to the reproductive organs [207, 208].The toxicity in children is, however, of a greater impact than in adults, which may contribute to behavioral problems, learning deficits, lowered intelligence quotient (IQ), and affect also fetuses because children absorb four to five times as much ingested lead as adults from a given source [209-212]. The ionic mechanism of lead toxicity occurs mainly due to the ability of lead metal ions to replace other bivalent cations like Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations like Na^{+}, which ultimately disturbs the biological metabolism of the cell [213, 214]. The ionic mechanism of lead toxicity causes significant changes in various biological processes such as cell adhesion [215], intra- and intercellular signaling, protein folding, maturation, apoptosis, ionic transportation, enzyme regulation, and release of neurotransmitters [216]. People can become exposed to inorganic lead through occupational inhalation of lead particles generated by burning materials containing lead and environmental sources from ingestion of lead-contaminated dust, water and food. The health effects of lead are the same regardless of the way of exposure.

2.13. Cadmium

Cadmium (Cd) is a metal that can present severe chronic or acute toxicity in the human organism. It can accumulate in various organs and tissues, but mainly in kidney cortex [217]. In fact, kidney has been considered as the most sensitive organ for Cd effects [218]. In cells, Cd mostly accumulates in cytosol, followed by nucleus, and the lowest quantities in mitochondria and endoplasmic reticulum [219]. Cd^{+2} crosses the cell membrane through calcium channels, especially when extracellular calcium levels are low [220]. Cadmium is found in food, water, soil, air, tobacco smoke and nd other media, thus, it can enter human bodies through ingestion, inhalation and dermal contact [221-225]. Smoking is well known as a risk factor for chronic kidney diseases [226]. Cd is known for its high binding capacity to biomolecules and especially to the enzymes present in the respiratory chain, thus leading to oxidative stress and physiological problems, including cancer [227]. Many diseases, such as aging and neoplastic diseases, have also been linked to cadmium toxicity [228, 229]. The transport of Cd into cells might be linked with various organic compounds, such as, glutathione and cysteine [230]. The overexposure of this element has been observed to be related with the risk of a variety of cancers, especially liver carcinoma [231]. Moreover, chronic exposure of cadmium in liver produces nonspecific inflammation, mild necrosis, and hepatocyte swelling [232]. A various studies highlight the adverse effect of cadmium on zinc equilibrium. Supplements containing zinc decreased absorption, accumulation, and toxicity of cadmium [233]. Metallothionein protein is mainly associated in the detoxification of heavy metals such as cadmium; these metals bind to the protein by sequestering them anddecreasing the severe effects of these toxic metals [234, 235].

2.14. Arsenic

Arsenic (As) is one of the most toxic elements that can be found. Exposure can be monitored by measuring urinary excretion of arsenic, which is present in two oxidation states as arsenite (As^{3+}) and arsenate (As^{5+}) which are both highly toxic. Human organism may be exposed to arsenic through air, water and food. It exposure may be higher for the professional that work with arsenic, for those who live on farmlands where arsenic-containing pesticides and for people that live in houses that contain conserved wood of any kind, and is

also found in some pharmaceuticals and in ceramic production and glass. Exposure to arsenic can cause many health problems. Arsenite is generally more toxic than arsenate due to its preferential reaction with sulfhydryl groups in mammalian enzymes, resulting in inhibition of the pyruvate and succinate oxidation pathways and the tricarboxylic acid cycle, reduced oxidative phosphorylation, and impaired gluconeogenesis. Arsenic acid and inorganic arsenic compounds have potential to damage chromosomes, positive results having been reported both in cultured mammalian cells and in somatic cells in humans. Longer-term poisoning may cause skin complaints and skin and liver cancer [236]. The first symptoms of long-term exposure to high levels of this element are usually observed in the skin and include pigmentation changes, skin lesions, and hard patches on the palms and soles of the feet. In pregnant women, exposure to arsenic resulted in the death of the foetus and of toxic levels of arsenic in foetal organs [237]. Numerous studies have shown negative impacts of arsenic exposure on cognitive development, memory, and intelligence [238]. Chronic lung disease, peripheral neuropathy, hepatomegaly and peripheral vascular disease have frequently been reported in cases of chronic exposure to arsenic. Other systemic manifestations include cardiovascular effects, cerebrovascular disease, abdominal pain, nausea, anorexia, diarrhoea, non-pitting oedema of hands, feet or legs, anaemia and generalised weakness. Exposure to arsenic has been related with an increased risk for diabetes mellitus. Previous studies have identified that arsenic trioxide induces apoptosis in acute promyelocytic leukemia cells, gastric cancer cells, glioblastoma cells, and inhibits cell growth in breast cancer [239-242], and it is also being evaluated for the treatment of certain malignancies, including hepatocellular cancer and lung cancer [243, 244].

2.15. Mercury

Mercury (Hg) is a toxic and non-essential metal that is hazardous to the environment and all living organisms, including human beings [245]. It has three forms: elemental mercury, inorganic and organic mercury compound. All three forms of mercury can accumulate in the kidneys, brain, and central nervous system. Symptoms of toxicity of mercury depend on the form, duration of exposure, and route of exposure and include changes in skin pigmentation, headaches, fever, nausea and vomiting, dyspnea, and thrombocytopenia. However, inhalation of mercury vapor can produce harmful effects on the nervous, immune systems, digestive, chest pain, impaired pulmonary function, and kidneys, and even coma and death. Acute exposure to mercury vapor by inhalation can produce central nervous system toxicity such as tremors, paresthesia, hyperexcitability, mental disturbances, impairment of verbal learning and memory loss, reduction of concentration, and delayed reflex, which are commonly reversible [246, 247]. Moreover, overexposure to high levels of mercury vapor can lead to severe lung damage, even death due to hypoxia [248]. The major clinical features of chronic mercury poisoning from mercury vapor inhalation have been identified in occupational histories as a triad of tremors, psychological disturbances or erethism, and gingivitis [249]. Elemental mercury vapor may affect the human immune system and can result in a decreased resistance to cancers, infection, or immune dysregulation that can induce the development of autoimmunity or allergy [250]. Several studies report that mercury levels of blood and urine are associated with amalgam exposure by dental filling in the general population and by occupational practice in dental practitioners [251]. Mercury in its elemental state is the only metal that is liquid at room temperature, and it has the properties of the reflective surface, low viscosity, high density, and a high electrical conductance.

3. Conclusion

The human organism has an elaborate system for managing and regulating the amount of key trace metals circulating in the blood and stored in cells. The capacity of trace elements to function as substantial affect in a variety of the processes necessary for life, such as regulating homeostasis and prevention of free radical damage, can furnish an answer to the definite correlation between the content of trace elements and many common diseases. For the past decades, the biological role, biochemical functions, signs of excess, and deficiency of the essential or nonessential trace elements in humans are studied and identified in depth. In addition, further investigations are needed to complete important gaps in our knowledge on trace elements especially probably nonessential trace elements role in health and disease status.

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