

ESSENTIAL TRACE METALS IN HEALTH AND DISEASE

ESENCIJALNI METALI PRISUTNI U TRAGOVIMA U ORGANIZMU
U ZDRAVLJU I BOLESTIVedrana Makević¹, Silvio R. de Luka¹, Anđelija Ilić²¹ Univerzitet u Beogradu, Medicinski fakultet, Institut za patološku fiziologiju, Beograd, Srbija² Univerzitet u Beogradu, Institut za fiziku, Beograd, Srbija**Correspondence:** vedrana.parlic@gmail.com**Abstract**

Essential trace metals (Fe, Zn, Cu, Mn, Mo, Co) are involved in high number of physiological and metabolic activities and therefore have a substantial role in organisms. Thus, their balance is tightly regulated by levels of absorption, transport, and storage in the organism. They can alter human health in both deficiency and overload conditions. On one hand, deficiency health problems are due to reduction of their physiological activities. On the other hand, Fe, Cu and Co are redox active metals and their increase can cause severe tissue damage through oxidative stress. Numerous well-established diseases like iron and copper deficiency anemia, hemochromatosis, Menkes and Wilson disease, acrodermatitis enteropathica are consequence of essential metal alterations. Nowadays, trace metals alterations are also found to be implicated in neurodegenerative disease, cancers, atherosclerosis, and diabetes. Those diseases represent enormous health problems in contemporary society and trace metals might help to further elucidate their pathogenesis and potentially even treatment. In the present study, essential trace metals kinetic and physiology are reviewed, as well as their roles in disease pathophysiology.

Keywords:essential metals,
microelements,
toxicity

Sažetak

Esencijalni elementi koji su u organizmu prisutni u tragovima (Fe, Zn, Cu, Mn, Mo, Co) učestvuju u velikom broju fizioloških i metaboličkih procesa i stoga imaju značajno mesto u funkcionisanju organizma. Shodno tome, njihova ravnoteža u organizmu mora biti dobro regulisana kroz procese apsorpcije, transporta i skladištenja. Posledice po zdravlje ljudi nastaju kada ovih metala ima nedovoljno u organizmu, ali i usled njihovog suficita. Deficit dovodi do remećenja fizioloških procesa u koje su uključeni, dok, s druge strane, višak redoks aktivnih metala - gvožđa, bakra i kobalta može dovesti do oksidativnog stresa i time oštećenja tkiva. Mnoge dobro poznate bolesti, poput sideropenijske anemije, hemohromatoze, Vilsonove, Menkesove bolesti i enteropatskog akrodermatitisa posledica su poremećaja na nivou esencijalnih metala. U poslednje vreme se, međutim, sve više pokazuje njihova povezanost sa karcinomima, aterosklerozom, dijabetesom i neurodegenerativnim bolestima. Ove bolesti predstavljaju veliki zdravstveni izazov savremenog društva, a proučavanje uloge esencijalnih metala u njima može pomoći rasvetljavanju njihove patogeneze i doprineti razvoju novih terapija. Ova studija sadrži pregled kinetike i fiziologije esencijalnih metala, kao i njihovih uloga u razvoju bolesti.

Ključne reči:

esencijalni metali, mikroelementi, toksičnost

Introduction

The human body is 98% composed of 9 non-metallic elements. The remaining two percent are predominantly electrolytes (Na, Mg, Ca, K), with one small percentage - 0.02% belonging to trace elements (1). Although their amount in organisms is insignificant, they are involved in a high number of physiological and metabolic activities and therefore have a substantial role in organism (**table 1**).

Table 1. Trace metals in health.

Essential metal	Functions
Fe	oxygen carrying in blood and cells as a part of myoglobin and hemoglobin, Fe dependent enzymes: cytochromes (A, B, C, 450), cytochrome C reductase, xanthine oxidases, catalases, peroxidases, tryptophan pyrrolase, succinate, choline and glucose 6 phosphate dehydrogenase
Zn	protection from oxidative stress, neuromodulation, immunity, cell proliferation, maintenance of epithelial barrier function in gut
Cu	energy metabolism, mitochondrial respiration (cytochrome oxidase), oxidative stress defense, Zn/Cu - superoxide dismutase, collagen cross linking (lysyl oxidase), pigmentation (tyrosinase), catecholamine biosynthesis (dopamine -b-monoxygenase)
Mn	gluconeogenesis, oxidative stress defense, glutamine and mucopolysaccharides synthesis, (superoxide dismutase 2)
Mo	catabolism of purine and cysteine (xanthine dehydrogenase/oxidase and sulfite oxidase), drug metabolism (mitochondrial reducing component and aldehyde oxidase)
Co	part of vitamin B12, enhances erythropoietin synthesis and erythrocyte production in the bone marrow

An element is considered essential for humans if it meets the following three conditions (2):

1. Presence in the human tissues
2. Unrepairable and severe damage occurs to vital functions in the case of its complete absence in the human body
3. Impaired physiological function could be repaired with adequate supplementation of this element.

There are 20 elements that meet the essentiality criteria with equal participation of metals and non-metals. Essential metals for human health are macro minerals needed in amount higher than 100 mg/dl, namely Na, K, Ca, Mg and six trace metal elements required in amounts less than 100 mg/dl - manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn) and molybdenum (Mo). Once considered essential, chromium (Cr) is now more widely understood as useful trace metal (2). Essential trace metals can alter human health in both deficiency and overload conditions (**table 2** and **table 3**) (3).

Table 2. Trace metals deficiency in diseases.

Essential metal	Examples of diseases and pathological states caused or connected with metal deficiency
Fe	iron deficiency anemia
Zn	acrodermatitis enteropathica, neurodegenerative diseases
Cu	Menkes disease, neurological symptoms, reduced body temperature, anemia, neutropenia, hypercholesterolemia, bone fractures, hair and skin hypopigmentation, and vascular abnormalities, atherosclerosis
Mn	clotting impairment, dermatitis and decreased cholesterol, osteoporosis, epilepsy
Mo	molybdenum cofactor deficiency
Co	thyroid impairment, presence of birth defects, B-12 deficiency symptoms

Table 3. Trace metals excess in diseases.

Essential metal	Examples of diseases and pathological states caused or connected with metal excess
Fe	implicated in pathogenesis of heart and liver disease, neurodegenerative diseases, cancers, atherosclerosis, hemochromatosis
Zn	eye diseases, increased susceptibility to infection, autoimmune disease, male fertility problems, skin diseases
Cu	Wilson disease, Alzheimer disease, amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Creutzfeldt Jakob disease, carcinomas, atherosclerosis, diabetes mellites
Mn	Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, neurotoxicity, manganism, cognitive impairment
Mo	painful joints, symptoms similar to gout and hyperuricosuria
Co	vision and hearing problems, connection to lung cancer, cardiomiopathy

The aim of this paper is to provide information about trace metal roles in human health and disease.

Iron

Iron is among the most important trace metals for human organism. It is present in the diet as non-heme inorganic iron and heme iron. Inorganic iron is usually in ferric (Fe^{3+}) state and requires reduction in ferrous (Fe^{+2}) state which is more suitable for absorption in enterocyte via divalent cation transporter (DMT-1). The transporter has a role in iron homeostasis considering it is upregulated in iron deficiency. On the other hand, hem is taken over and broken down to iron by the intestinal cells. Once they are in the intestinal cell, both forms of iron enter a common pool and share the same destiny (4). Iron leaves enterocytes through transporter ferroportin. The same transporter is present in liver cells and macrophages. The regulation of ferroportin by the protein hepcidin is of great importance for iron homeostasis. Hepcidin is elevated in conditions in which organism tries to reduce iron blood amount such as in iron excess and inflammation and decreased in iron deficiency and higher iron demands (erythropoietin elevation) (5). Two other iron regulatory proteins hephaestin and ceruloplasmin play a role in facilitating the transport of iron in the blood and its binding to transferrin. Liver and reticuloendothelial system function as storages for this metal in one of two forms - ferritin and hemosiderin (4). Iron as a part of myoglobin and hemoglobin performs its main role in the body by transporting oxygen to muscles and blood. Further, Fe functions as an electron donor and acceptor in oxidation/reduction reactions (6). Enzymes connected with iron are various cytochromes (A, B, C, 450) and cytochrome C reductase and others (table 1) (1). It is important in processes such as growth and development, cell function (synthesis and proliferation of DNA and RNA, electron transport) and in

synthesis of connective tissues and hormones (4,6). This metal is also required for dendritic development, myelination formation and neurotransmitter synthesis (4). When the body lacks iron, iron deficiency anemia develops with symptoms such as fatigue, epithelial atrophy, memory impairment and irritability (1). Conversely, Fe can be harmful to the organism. Free Fe is capable of producing reactive oxygen species via oxidation/reduction in the Fenton reaction (4) with consequent tissue damage, fibrosis and organ dysfunction. Moreover, iron excess can contribute to serious diseases such as tumors, heart and liver diseases and neurodegenerative diseases (6). In neurodegenerative diseases such as Parkinson's disease (PD) (7) and Friedrich's ataxia (8) iron accumulates in some parts of brain despite normal serum levels (5). In Alzheimer's disease it is excessively transferred into brain cells due to alteration of iron regulatory proteins. Increased iron in the brain may also increase free oxygen species via Fenton pathway and the rate of β amyloid oligomer formation (4). A typical iron overload disease is hereditary hemochromatosis, a disease with unnecessary Fe absorption. Consequently, iron accumulates in the liver, pancreas, and heart. Symptoms include liver cirrhosis and carcinoma, cardiac failure, arrhythmia, diabetes mellitus, white nails, osteoporosis and melanoderma (9). Furthermore, overload can also occur due to transfusions common in some cancer patients, thalassemia in which iron absorption is increased (5) and following exposure to static magnetic field (10).

Zinc

Zinc has enormous biological and public health significance. To maintain Zn balance in cell great number of zinc transporters and other proteins are required. The protein Zrt-Irt-Protein (ZIP family) family members are responsible to provide Zn influx into cell and Zn-transporters (ZnT) are responsible for Zn cell efflux and sequestration into organelles. Zinc homeostasis is also mediated through Zn binding proteins - metallothionein. They are in charge for buffering Zn in regular conditions and tune down Zn when it is elevated (10). Importantly, these proteins have great antioxidative potential (3).

Numerous enzymes, transcription factors, receptors and cytokines need Zn for their function (11). This metal is component of hundreds of enzymes (3) and can serve as first and second messenger in inter-cell communication. As a first messenger Zn is neurotransmitter or neuromodulator (12), and as second messenger, various external stimuli deliver information to the cell through change of intracellular Zn concentration (10).

It functions like "atypical" neurotransmitter. Like other transmitters, it is concentrated in presynaptic vesicles, released upon presynaptic stimulation from hippocampal fiber terminal vesicles, and taken up by surrounding cells. Rapid Zn influx in neurons via Ca-ion-permeable channels can trigger ROS production and is potentially neurotoxic. In ZnT3-Knock Out (KO) mice hippocampal

mossy fibers extracellular-signal regulated kinase 1 and 2 (Erk1/2) activation is depleted. This indicates that ZnT3 is important for Erk1/2 signaling and hippocampus-dependent memory. Additionally, G-protein-coupled receptors 39 (GPCR39) are identified as Zn sensing receptor in brain and two Zn binding sites are found on γ -aminobutyric acid receptor. Interestingly, Zn receptor, GPCR39, is involved in epithelial cell repair and endocrine pancreatic function. In addition, Zn can prevent N-methyl-D-aspartate receptor action through voltage dependent and voltage independent channel block. All these evidence support Zn neurotransmitter role (11).

Zinc also serves as second messenger i.e. intracellular signaling molecule. This function is observed in starfish oocyte, but also in vertebrate fertilization. Its signaling function is supported with the fact that Zn binds to a great number of signaling molecules protein kinase C, Ca/calmodulin dependent protein kinase II, Erk1/2, cAMP-dependent protein kinase, protein tyrosine phosphatase, and caspase-3 - to mention some examples. Further, it activates more than a few ion channels like transient receptor potential ankyrin 1, ATP sensitive K, and large-conductance Ca-activated K channels. In epithelial pulmonary cells and dendritic cells, toll-like receptor 4 (TLR4) activation decreases Zn intracellular level. Furthermore, activation of protein kinase C in mast cells upon Fc ϵ RI stimulation depends on ZnT5 transporter (11).

As a part of signal systems, Zn modulates, among other things reproductive, immune, and neural functions (10). Cell proliferation is not possible without zinc, as it is part of proteins involved in transcription, it is, also, important for DNA synthesis, and delivers mitogenic signal to the cell (13). Severe intracellular zinc deficiency can initiate apoptosis while milder reduction makes cell more sensitive to programmed cell death (14). Conversely, Zn is found to be proapoptotic in several cell types (e.g. ovarian, esophageal, prostate epithelial cells, neurons and glial cells and some tumor cells) (15). It is demonstrated that Zn has a role in differentiation of adipocyte (16) and myoblasts (17), but probably also helps differentiation in all other cells. Both Zn insufficiency and excess cause oxidative stress in cell (6). This metal protects organism of free oxygen species by binding to -SH groups of proteins and thus protecting them from free radicals induced damage. Further, Zn can replace Cu and Fe on their binding sites in the cell. Displaced from their spots, these metals are subsequently removed from the cell and thus, less available for deleterious Fenton reaction. Finally, Zn increases expression of antioxidant enzymes (3).

Since it is required for enterocyte renewal, tight junction preservation, stabilization of mucus covering and production of antibacterial substance, this element is also important for maintenance of epithelial barrier function in gut (18).

It can be used in prevention and treatment of diarrhea in children, can help children that are fighting serious bacterial infection, and it also might be beneficial in ameliorating symptoms of common cold. Further, Zn

supplementation was capable of reducing the risk of age related macular degeneration (19) and protection from Alzheimer's disease probably by reducing oxidative stress (3).

Various immune cells – monocytes, natural killer cells, neutrophils and T-cells are hypofunctional in zinc depletion. Others, like B cells are prone to apoptosis. Interestingly, in state of Zn deficiency T cells are more inclined to lose tolerance against its own tissue (20). Therefore, Zn deficiency relates to pathogenesis of autoimmune disease.

Naïve CD4 T cell can differentiate into one of three different T-cell subsets (Th1, Th2, Th17) depending on cytokines present (e.g. IL-6 and TGF- β for Th17 subset). Additionally, Th17 subset is important for the development of autoimmunity and inflammation. Zinc plays its role in suppressing autoimmune disease (e.g. experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis (CIA)) through inhibition of STAT3 tyrosine phosphorylation by Janus kinase and preventing its IL-6 mediated activation. To be more precise, Zn binding triggers STAT3 unfolding and consequent loss of function (11).

In case of highly severe Zn deficiency, manifestations of various organs include bullous pustular dermatitis, alopecia, hypogonadism, emotional and neurosensory disorders, diarrhea and malabsorption, weight loss and ophthalmic symptoms. Furthermore, patients are prone to infections and have altered cellular immune response and prolonged ulcer healing (19). Acrodermatitis enteropathica (AE) is the most pronounced example of severe Zn deficiency. The disease is consequence of disabled Zn absorption due to impairment of zinc transporter (ZIP4) in the bowels (21). Zinc deficiency is connected with various health problems like male infertility (22), eye disease (age-related macular degeneration) (23), increased susceptibility to infection, atherosclerosis (10), skin (acrodermatitis enteropathica, spondylocheiro dysplastic form of Ehlers–Danlos syndrome, epidermodysplasia verruciformis) (24), autoimmune (rheumatoid arthritis, systemic lupus erythematosus), inflammatory disease (Crohn disease and ulcerative colitis), and neurodegenerative disease (AD and PD) (25).

Despite its well establish essentiality and its various health promoting roles, even Zn excess is found to be deleterious for organism. Namely, ingestion of zinc salts may be followed with hematemeses and renal injury. Further, accidental parenteral zinc overdose may produce acute respiratory distress syndrome, liver necrosis and coagulopathy. In addition, inhalation of Zn containing fumes is connected with flu like symptoms (26). Interestingly, like Zn deficiency, Zn excess is also connected with degeneration of dopaminergic neurons and PD (27).

Copper

Copper is component of many important enzymes in human organisms. The metal is absorbed in duodenum

and small intestine, excreted via biliary tract, and stored in the liver. It is present in two oxidate states cuprous (Cu^{+1}) and cupric (Cu^{+2}). As transitional metal it easily binds or releases electrons. This feature makes it suitable for oxidation-reduction reactions, in which it is engaged as part of mitochondrial enzyme cytochrome oxidase (6). Other important Cu - dependent enzymes are dopamine B hydroxylase included in neurotransmitter synthesis and lysine oxidase that provide strength and elasticity to connective tissue of skeleton, muscular, and cardiovascular system (28) through collagen cross linking. Copper's role in oxidative stress defense system is mediated through enzyme Zn/Cu superoxide dismutase (SOD), lysine oxidase and ceruloplasmin (6). Further, Cu is important for pigmentation considering enzyme tyrosinase is also copper dependent (29).

It showed a beneficial role in animal model of diabetes mellites type one probably through decrease in oxidative stress and lowering level of glucose (30), but on the other hand, diabetes mellites patients had higher copper levels than controls (31). In addition, copper can cause specific type of programmed cell death called cuproptosis (28). In this type of cell death copper causes mitochondrial stress via their enzymes aggregation and loss of Fe-S proteins (32).

Copper balance should be carefully maintained because both increase and deficiency may impair health (**figure 1**). Severe Cu deficiency is seen in Menkes disease. In core of this disorder is genetic mutation of Cu intestinal exporter. Consequently, Cu accumulates in enterocytes and is deficient in other tissues (28). Acquired Cu deficiency might be consequence of nephrotic syndrome, kwashiorkor, vomiting, diarrhea and zinc overload (6, 26). Severe deficiency is represented with neurological symptoms, reduced body temperature, anemia, neutropenia, hypercholesterolemia, bone fractures, hair and skin hypopigmentation, and vascular abnormalities (28, 30). Anemia in Cu deficiency is multifactorial and complex. However, the mechanism is usually explained through development of iron deficiency. Namely, copper dependent protein hephaestin is needed for normal iron absorption, and other copper dependent protein ceruloplasmin is required for iron conversion in suitable valence state for transferrin binding. Thus, copper deficiency impairs iron intestinal absorption and transferrin binding and consequently causes iron deficiency and anemia. Further, copper roles in cell division and protein synthesis are impaired in deficiency which results in macrocytosis and neutropenia (33). When mutation occurs on Cu transporter that exports Cu in biliary tract, Cu accumulates in liver, brain and other tissues causing Wilson disease. It exerts toxicity in liver through DNA damage, mitochondrial impairment, and lipid peroxidation. Apart from hepatic symptoms, in half of patients' disease manifestations are of neuropsychiatric nature. Its excess in these patients also may cause hemolysis, bone and renal abnormalities and cardiac arrhythmia (28).

Copper excess relates to neurodegenerative disease like Alzheimer's disease (AD) (34), amyotrophic lateral sclerosis (35), Huntington disease (36) and PD (25). It can

interact with key elements in AD pathogenesis such as amyloid- β ($\text{A}\beta$) (34) and tau protein (37). Namely, Cu enhances $\text{A}\beta$ precursor processing and $\text{A}\beta$ aggregation (38). In case of tau protein copper also facilitates aggregation. In addition, tau protein fragments cause chemical reduction of this metal and thus initiate formation of free oxygen species. Moreover, cuproptosis might be also implicated in development of AD (38). Furthermore, high Cu is closely connected to various tumors (39, 40). Its concentration is increased in tumor tissue and cancer cells have higher demand for Cu (39). In carcinoma Cu promotes proliferation of cancer cells, angiogenesis and increases metastatic potential (28). Copper homeostasis alteration are also a factor in development of atherosclerosis (41). It promotes atherosclerosis probably through promotion of inflammation, and interaction with atherosclerosis risk factors such as LDL and homocysteine. On the other hand, even Cu deficiency can promote atherosclerosis through increasing cholesterol levels and decreasing NO via reduced SOD1 activity (28).

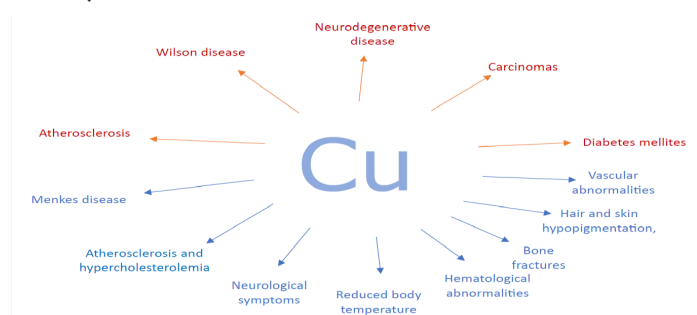


Figure 1. Copper deficiency and excess in disease; red color – conditions and diseases connected to copper excess; blue color conditions states and diseases connected to copper deficiency.

Manganese

Approximately 2 mg of Mn is a daily requirement for an adult and maximal intake should not exceed 9 mg/day in women and 11 mg/day in men (42).

Manganese gut absorption is up to 5% and depends on pH and presence of different metals with whom Mn competes for transporters such as Fe, Cu, Zn, Ca. This metal is transported from intestines mostly through divalent metal transporter (DMT-1), and the same transporter mediates Mn transport across brain blood barrier. As mentioned above, Fe also uses this transporter in intestine and therefore Mn is usually increased in iron deficiency (42). Within a cell, Mn is predominantly sequestered in mitochondria (43). Numerous enzymes require Mn for their function. It activates gluconeogenic enzymes, acts on enzymes included in glutamine and mucopolysaccharides synthesis. It also activates SOD2 in order to protect mitochondrial membrane (43). Manganese acute overload usually happens due to occupational exposure and results in neurotoxicity. In this case, Mn concentrations are up to one-hundred-time above limits. On the other hand, chronic exposure might cause cognitive impairment. Chronic intoxication usually occurs in infants and persons with

iron deficiency. Primary route of prolonged exposure is through ingestion of drinking water with elevated levels of manganese. Further, manganese overload is possible in chronic liver failure due to inadequate excretion. Moreover, milk formulas for infants contain more manganese than humane milk and thus might increase manganese levels in this population (42). Deficiency is rare in humans. It presents symptoms like clotting impairment, dermatitis and decreased cholesterol (43). In animal models, deficiency is presented as altered carbohydrate and lipid metabolism, growth retardation, skeletal defects, and reproductive problems. It is sometimes reduced in patients suffering from osteoporosis (44) and epilepsy (45). Its neurotoxicity is connected to increasing oxidative stress, apoptosis, functional changes on neurotransmitters and mitochondrial and astrocyte dysfunction (42,43). Manganese is highly connected to PD (46), but it might be involved in pathogenesis of other neurodegenerative disorders as well (**table 3**) (47). One more example of manganese neurotoxicity is manganism. This condition clinically resembles to PD, with different brain structures involved. Furthermore, protein aggregates typical for PD - Lewy body are absent in neurons of people suffering from manganism (48).

Molybdenum

Molybdenum exhibits its enzymatic activity when it is bound to pterin-based cofactor. It is involved in function of four enzymes - xanthine dehydrogenase (XDH)/oxidase (XO), sulfite oxidase (SO) (included in catabolism of purine and cysteine) and also in, insufficiently examined, mitochondrial reducing component (mARC) and aldehyde oxidase (AO) (included in drug metabolism) (49). The enzyme cofactor, complex of Mo and organic compound, is essential for the function of all four Mo dependent enzymes and innate defect in its synthesis is lethal in most cases (6). In such cases, infants have trouble in feeding, they are prone to resistant seizures, and later develop psychomotor retardation with cerebral atrophy. The symptoms are caused mostly due to impairment of SO and sulfite accumulation. Additionally, XO deficiency cause xanthinuria, decreased uric acid and potential renal impairment (49). Interestingly, Mo have Cu antagonistic properties (50). Therefore, Mo intoxication in animals is connected with symptoms similar to ones present in copper deficiency. However, potential for Mo toxicity in humans is low. Symptoms that are connected with toxicity are painful joints, symptoms similar to gout and hyperuricosuria (51).

Cobalt

Cobalt owns its essentiality mainly to vitamin B12, considering Co is functional part of this vitamin (52). It can enter body trough GI, respiratory and dermal route. It can enhance erythropoietin synthesis and erythrocyte production in the bone marrow. This function is once used for treatment of anemia. On the other hand, Co increases aerobic capacity and therefore, might be misused for

athletes doping cause (3).

Preterm and low weight children are in risk of cobalt deficiency, since they have diminished cobalt reserve. Moreover, the deficiency is more common in population of children on vegetarian food regime and children with innate disturbances of cobalt metabolism (53). Cobalt deficiency is directly related to disturbed synthesis of B12 (3). Patients with acute deficiency exhibits symptoms of anemia, loss of appetite and weight reduction, impaired growth, squamose ears and watery eyes. In case of severe deficiency sensory defects in feet and hand, along with hyporeflexia and muscle cramps, confusion and dementia can occur (53). Furthermore, cobalt deficiency causes thyroid impairment and birth defects (3).

In industry, Co is mainly used in electrochemical facilities and workers in those facilities have significantly higher risk of developing lung cancer. Ionic cobalt in Fenton-like reaction catalyzes production of highly damaging hydroxyl radical. Moreover, Co is capable of cross linking DNA proteins and causing DNA damage (3). In addition, this metal alters mitochondrial function and calcium homeostasis. (54). Except from industry, people with hip implants can also be exposed to cobalt and the metal can be ingested in form of popular food supplements (54). Cobalt can interfere with function of other trace elements. It interacts with Zn in various enzymes e.g., alcohol dehydrogenases and its interaction with iodine can result in suppression of thyroid function and goiter (3). Moreover, this metal can cause reversible vision and hearing problems, it has been connected to cardiomyopathy (54) and higher blood cobalt is related to increased prevalence of cardiovascular disease (55).

Conclusion

In conclusion, trace metals are part of a number of important enzymes and other proteins in organism. They have roles in highly important processes like immunity, neurotransmission, cell division, oxygen transport, metabolism, and energy production. Trace metal balance is important for maintaining healthy state of organism and many well recognized diseases are consequence of trace metals alterations. However, in the last decades, diseases connected to trace metals alterations are increasing. Considering their enormous role in human health and promising results from above mentioned studies, trace metal investigations should be encouraged.

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