IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES

ISSN PRINT 2319 1775 Online 2320 7876

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A CASE STUDY ON MAJOR, MINOR AND TRACE ELEMENTS IN HUMAN BODY : INTERPRETATION & ANALYSIS OPERATIONAL PROCESS

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Abstract

The dietary requirement for an essential trace element is an intake level which meets a specified criterion for adequacy and thereby minimizes risk of nutrient deficiency or excess. Disturbances in trace element homeostasis may result in the development of pathologic states and diseases. This article is an update of a review article “Trace Elements in Human Nutrition-A Review” previously published in 2013. The previous review was updated to emphasis in detail the importance of known trace elements so far in humans’ physiology and nutrition and also to implement the detailed information for practical and effective management of trace elements’ status in clinical diagnosis and health care situations. Although various classifications for trace elements have been proposed and may be controversial, this review will use World Health Organization (WHO) classification as previously done. For this review a traditional integrated review format was chosen and many recent medical and scientific literatures for the new findings on bioavailability, functions, and state of excess/deficiency of trace elements were assessed. The results indicated that for the known essential elements, essentiality and toxicity are unrelated and toxicity is a matter of dose or exposure. Little is known about the essentiality of some of the probably essential elements. In regard to toxic heavy metals, a toxic element may nevertheless be essential. In addition, the early pathological manifestations of trace elements deficiency or excess are difficult to detect until more specific pathologically relevant indicators become available. Discoveries and many refinements in the development of new techniques and continual improvement in laboratory methods have enabled researchers to detect the early pathological consequences of deficiency or excess of trace elements. They all are promises to fulfill the gaps in the present and future research and clinical diagnosis of trace elements deficiencies or intoxications. However, further investigations are needed to complete the important gaps in our knowledge on trace elements, especially probably essential trace elements’ role in health and disease status.

Keywords: *Biological bioavailability, deficiency diseases, nutritional essentiality classification, toxic heavy metals, trace and ultra-trace elements*

Introduction

There are two faces about trace elements: They are beneficial and/or toxic. Minerals form only 5% of the typical human diet but are essential for normal health and function. For the known essential elements, essentiality and toxicity are unrelated and toxicity is a matter of dose or exposure. In the past years, considerable research has been carried out to better understand the physiological role and the health consequences of trace elements. This article is an update of a review article “Trace elements in human nutrition: A review” previously published in 2013. The previous review was updated to emphasis in detail the importance of known trace elements so far in humans’ physiology and nutrition and also to implement the detailed information for practical and effective management of trace elements’ status in clinical diagnosis and healthcare situations. For this review (Materials and Methods), a traditional integrated review format was chosen, and many recent medical and scientific literatures for the new findings on bioavailability, functions, and state of excess/deficiency of trace elements were assessed and of trace elements were assessed and related articles were studied. Although various classifications for trace elements have been proposed and may be controversial, this review will use World Health Organization (WHO) classification as previously done: *essential elements*, *probably essential elements*, *and potentially toxic elements*. This classification includes 19 elements that are based on the nutritional significance. Within each of these groups, elements for which there is clear evidence that either deficiency or excess causes significant health problem are considered first. Trace elements (or trace minerals) are usually defined as minerals that are required in amounts between 1 and 100 mg/day by adults or make up less than 0/01% of the total body weight. Ultra-trace minerals generally are defined as minerals that are required in amounts less than 0/001 mg/day.

Essential elements

Chromium

Chromium (Cr) as an essential nutrient (glucose tolerance factor) potentiates insulin, and thus influences carbohydrate, lipid, and protein metabolism. However, the nature of the relationship between chromium and insulin function has not been defined. In addition, the results of investigations indicated that chromium supplementation did not appear to ameliorate insulin resistance or impaired glucose metabolism, and thus is unlikely to attenuate diabetes risk. The mechanism of absorption of chromium from intestine has not been clearly identified, but it apparently involves processes other than simple diffusion. It has been claimed that many factors such as oxalate, iron, and high dietary intakes of simple carbohydrates change the bioavailability or absorption of chromium. In addition, it has been found that chromium absorption is elevated by chemically induced diabetes and depressed by aging. The adequate intake of chromium for adults is 20–35 μg/day. Chromium deficiency is generally limited to hospitalized patients with increased catabolism and metabolic demands in the setting of malnutrition. Some of the first case reports of chromium deficiency were from patients receiving parenteral nutrition. Studies have indicated that in diabetic patients receiving chronic total parenteral nutrition, human chromium deficiency has been associated with increased insulin requirements. Chromium supplementation in these patients improved glucose tolerance. Thus, an abnormal glucose tolerance may indicate a low chromium status, and an improvement in glucose tolerance after chromium supplementation may be a valid indicator of chromium deficiency. Chromium is a transition element and exists in multiple ionic states. Dietary chromium is in the trivalent state. Depending on the route of exposure (e.g., oral, dermal, or inhalation) and chromium significant chemical forms, the effect related to a given dose would be different. Trivalent chromium has low toxicity that deleterious effects of excessive intake of this form of chromium do not readily occur and there are no reports of adverse effects of dietary chromium (trivalent chromium). However, airborne hexavalent chromium (VI) toxicity has been established as a work-related etiology of lung cancer in stainless steelworkers. Oral administration of 50 μg/g diet has been found to induce growth depression together with liver and kidney damage in experimental animals. Apart from acute intoxication, chromium toxicity through oral ingestion is apparently not of practical importance for humans.

Copper

Copper (Cu) in biological systems may be present in both +1 and +2 valance states. Thus, its major function involves oxidation–reduction reactions. It is an integral component of many enzymes, including ceruloplasmin (copper transporter and ferroxidase), cytochrome c oxidase (electron transport), zinc-copper superoxide dismutase (antioxidant defense), dopamine-mono-oxygenase (neurotransmitter synthesis), lysyl oxidase (collagen cross-linking, bone formation), dopamine beta-hydrolase (skin pigmentation), and tyrosinase (melanin production). Several constituents occurring naturally in food have been found to affect the absorption of copper from the intestine and to increase or decrease its bioavailability. Apart from a low intake of dietary copper, which appears to increase the efficiency of copper absorption, the other main dietary factor which enhances the bioavailability of copper appears to be a high level of protein intake. Absorption occurs by active transport process at lower levels of dietary copper and by passive diffusion at high levels of dietary copper. Absorbed copper is loosely bound to plasma albumin and amino acids in the blood and taken to the liver and is incorporated into the copper-containing protein ceruloplasmin, which serves to transport copper from the liver to peripheral tissues. Furthermore, ceruloplasmin has an independent role in iron metabolism, in which it serves as a plasma ferroxidase, converting iron to a valence that can be bound by plasma transferring. Copper deficiency or hypocupremia is defined as a serum copper level of 0.8 μg/mL or less (normal serum Cu 0.64–1.56 μg/mL). About 93% of serum copper is normally bound to ceruloplasmin and is usually accompanied by hypoceruloplasmin (normal serum ceruloplasmin 0.18–0.40 μg/mL). Hypercupremia occurs naturally during pregnancy and is associated with the so-called “acute phase” reaction of a number of diseased states. It is almost always accompanied by hyperceruloplasmin. Extreme form of copper deficiency is Menkes disease, also known as Menkes kinky (steely) hair syndrome, a congenital x-linked genetic disorder with an incidence of about 1:100,000 live births. The formation of steely hair is attributed to the loss of copper catalyzed disulfide bond formation. Menkes disease is caused by a mutation of the transport protein mediating copper uptake from the intestine, encoded by the ATP7A gene. Inactivating mutations in this gene result in severe copper deficiency with progressive neurologic deterioration and death during early childhood. This gene is closely related to the gene responsible for copper overload in Wilson's disease. Intravenous administration of copper may help raise plasma copper concentrations; however, urinary copper excretion increases accordingly, and the course of vascular and cerebral degeneration is irreversible. Red cell copper is not decreased and neutropenia and anemia in Menkes disease do not appear. Wilson's disease is characterized by excessive copper accumulation and is caused by a mutation in a copper-ATPase enzyme that prevents the incorporation of copper into ceruloplasmin. It is an autosomal recessive disorder with a frequency of 1:30,000 to 1:100,000 live births. Copper deposition occurs in hepatic parenchymal cells, brain, periphery of the iris, and kidneys. The age of onset and form of presentation are very variable. Wilson's disease can be controlled, and in some cases halted by early and persistent treatment with zinc acetate or copper chelators, such as penicillamine. Zinc competes with copper for absorption in the gastrointestinal tract. Furthermore, copper toxicity may occur subsequent to ingestion of copper-contaminated solutions, the use of copper-containing intrauterine devices, the use of copper salts in animal feeds, and exposure to copper-containing fungicides.

Zinc

Most biochemical roles of zinc (Zn) reflect its involvement in a large number of enzymes or as a stabilizer of the molecular structure of subcellular constituents and membranes. Zinc participates in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids. It has recently been shown to play an essential role in polynucleotide transcription and translation, and thus in the processes of genetic expression. Its involvement in such fundamental activities probably accounts for the essentiality of zinc for all forms of life. Zinc plays an important role in cell proliferation, differentiation, and metabolic activity of the cell as well. In addition, it supports normal growth and development during pregnancy, childhood, and adolescence. Several studies have suggested a benefit of zinc supplementation in children with acute diarrhea in resource-limited countries. Zinc absorption is concentration-dependent and occurs throughout the small intestine. Under normal physiological conditions, the transport processes of uptake are not saturated. Absorption is inhibited by the presence of phytates and fiber in the diet that bind to zinc, as well as dietary iron and cadmium. Mild zinc deficiency appears to be common, especially in resource-limited countries because the diet is relatively low in zinc. A reduced growth rate and impaired resistance to infection are frequently the only manifestation of mild deficiency in human. The genetic disorder related to zinc metabolism is acrodermatitis enteropathica (AE), which is an autosomal recessive disease and there is an inability in zinc absorption. AE is characterized by signs and symptoms of severe zinc deficiency including diarrhea, poor growth, and poor immune function. Humans are very tolerant to high zinc intakes up to 100 mg/day. However, high zinc intake from contaminated food or beverages and acute zinc poisoning has been associated with nonspecific gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting. Long-term exposure to high zinc intakes have been shown to interfere with the metabolism of other trace elements such as copper absorption. Furthermore, both type 1 and type 2 diabetics can exhibit hyperzincuria, which may have a role in the immune dysfunction associated with diabetes mellitus. Zinc supplementation in diabetic patients may improve immune function and also increases the HbA1c levels and leads to worsening glucose intolerance.

Selenium

Selenium (Se) is an essential trace element in humans and animals with high metabolic activity. Its main functions in humans are the antioxidant defense activity of glutathione peroxidase as a selenoprotein in the regulation of immunity, thyroid function, and reproductive system. Selenium is part of the active site of glutathione peroxidase (GSH-Px), an antioxidant enzyme. Adequate level of dietary selenium intake and optimal selenoprotein expression guarantees protection from free-radical oxidation, which is observed in neurodegenerative, cardiovascular, thyroid disease, and some forms of cancer. The optimal daily intake is 20–70 µg/day, and the toxic level is 5 mg/day. Its half-life in the body is 50–60 days. Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine. Around 80% of dietary selenium is usually absorbed, but the amount is affected by chemical form in the diet and a range of other factors including intake of protein and the presence of any considerable levels of toxic elements in the diet, such as mercury and arsenic. The absorption of selenomethionine occurs through active transport. Selenium, in the form of selenocysteine, is incorporated into selenoproteins structure. The best known of these enzymes is glutathione peroxidase, which plays an important role in protecting cell membranes from damage by free radicals. The highest concentrations of selenium are observed in liver, kidneys, pancreas, skeletal muscle, thyroid gland, and myocardium. Selenium content is decreased with aging, smoking, inflammation, and some types of cancer. Selenium deficiency leads to impairment of both innate and adapted immunity. Persons with insufficient selenium intake are characterized by impaired antiviral defense, immune response, and increased risk of autoimmunity. In particular, selenium deficiency is associated with the development of systemic connective tissue diseases such as sclerodermia, lupus, rheumatoid arthritis, and raynaud's syndrome. Moreover, a significant relationship between selenium deficiency and allergic reactions and infective allergic asthma was demonstrated. In addition, at selenium deficiency, there is an increased accumulation of arsenic, cadmium, and mercury in the body. Selenium is an antagonist of mercury and arsenic and it is able to protect the body against cadmium, lead, thallium, and silver. Although the biochemical mechanism of selenium toxicity has not been clearly established, selenium can have toxic effects at high doses. Its toxicity occurs with excess dietary intake, either through diets naturally high in selenium or “mega dose” supplementation. Chronic selenium poisoning in people is defined as hair loss, nail discoloration or brittleness, or two or more of the following symptoms: muscle or joint pains, headache, foul breath, fatigue/weakness, gastrointestinal symptoms, or cutaneous eruption. There are many hypothesis suggested by different studies regarding selenium deficiency/toxicity; however, hypothesis that relates with the deficiency of selenium is the most accepted hypothesis.

Molybdenum

Molybdenum (Mo) is a trace element essential for micro-organisms, plants, and animals. Initially, mistaken for lead, molybdenum was named after the Greek word molybdos, meaning lead-like. In humans, only four enzymes requiring molybdenum have been identified to date: sulfite oxidase, xanthine oxidoreductase, aldehyde oxidase, and mitochondrial amidoxime-reducing component (mARC). Xanthine oxidoreductase is present in two forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO). Molybdenum takes part in the active site of these enzymes and functions as an enzymatic cofactor. In addition, it plays a role in the detoxification of the organism and production of important intermediary products. A total of 59%–94% of dietary molybdenum is absorbed in the gastrointestinal tract depending on the ingested dose. In humans, molybdenum deficiency is rather rare and is associated with impaired reproductive functions and growth retardation.

Molybdenum deficiency is accompanied by decreased blood and urinary uric acid concentration, and increased xanthine and hypoxanthine excretion. High amounts of molybdenum are toxic. Increased XDH activity results in accumulation of uric acid, gout development, and reactive oxygen species (ROS)-related diseases. Increased XDH activity and hyperuricemia are observed in ischemia, cardiovascular diseases, metabolic syndrome, and diabetes complications.

Iodine

Iodine (I) is an essential constituent of the thyroid hormone triiodothyronine (T3) and thyroxine (T4) with plasma half-lives of approximately 2 and 8 days, respectively. Iodine from the diet is absorbed throughout the gastrointestinal tract. Dietary iodine is converted into the iodide ion before it is absorbed. The iodide ion is 100% bioavailable and absorbed totally from food and water. This is, however, not true for the iodine within thyroid hormones ingested for therapeutic purposes. In the circulation it is taken up by the thyroid gland and any excess amount is filtered by the kidneys and excreted. All biological actions of iodide are attributed to the thyroid hormones. The physiological actions of thyroid hormones can be categorized as (1) growth and development and (2) control of metabolic processes in the body. Thyroid hormones play a major role in the growth and development of the brain and central nervous system in humans from the 15th week of gestation to 3 years of age. If iodine deficiency exists during this period and results in thyroid hormone deficiency, the consequence is derangement in the development of the brain and central nervous system. The other physiological role of thyroid hormones is to control several metabolic processes in the body. These include carbohydrate, fat, protein, vitamin, and mineral metabolism. For example, thyroid hormone increases energy production, increases lipolysis, and regulates neoglucogenesis and glycolysis. In addition, it has been suggested that the effective utilization of iodine depends on a selenium-containing enzyme, and thus on an adequate selenium status. Selenium is a necessary component of the deiodinase enzyme that removes iodine molecules from T4 converting it into T3. When patients suffering from various forms of thyroid disease were tested for selenium levels, all were found to be lower than normal healthy people. The risk of thyroid diseases depends on iodine intake and is characterized by the U-shaped curve where both excess and deficiency exert a negative effect. Iodine deficiency is associated with goiter, hypothyroidism, increased risk of miscarriage, preterm birth, congenital fetal abnormalities, and elevated incidence of neonatal death. In hypothyreosis, the development of decreased blood sodium is observed. One should not simultaneously take supplements containing iodine and lithium carbonate. Lithium reduces the activity of thyroid gland, while iodine enhances the manifestation of lithium side effects. Thyrotoxic states are observed in Graves' disease, autonomous toxic adenoma. Most frequently these diseases are associated with thyrotropin receptor mutation and G-protein α-subunit stimulation. Moreover, the development of benignant and malignant tumors in the thyroid gland in women occurs more frequently when compared with men.

Probably essential elements

Manganese

Manganese (Mn) is an essential element in the human body that is mainly obtained from food and water. Manganese is absorbed through the gastrointestinal tract and then transported to organs enriched in mitochondria (in particular the liver, pancreas, and pituitary) where it is rapidly concentrated. Excretion of manganese is primarily through bile into the gastrointestinal tract. Manganese acts as an activator of many enzymes and as a component of metalloenzymes such as manganese superoxide dismutase (MnSOD) that is mainly responsible for scavenging ROS in mitochondrial oxidative stress. In addition, it is involved in the glucose and lipids' metabolism, acceleration of protein synthesis, vitamin C, and vitamin B, catalysis of hematopoiesis, regulation of the endocrine, bone and tissue formation, skeletal growth, reproduction, and immune function improvement. Both deficiency and intoxication are associated with adverse metabolic and neuropsychiatric effects. Manganese deficiency in humans is very unusual, but has been reported in individuals on a highly restricted diet. In experimental studies in humans, manganese deprivation was associated with scaly dermatitis and dyslipidemia. Environmental or occupational manganese overexposure in at-risk populations such as miners, welders, and steel makers is toxic. Manganese ore mining and its processing cause air and water pollution, threatening the health of workers and general populations residing near factories through oral ingestion, inhalation, and dermal contact. Furthermore, excessive exposure to manganese may cause Parkinsonian-like motor and tremor symptoms and adverse cognitive effects, including problems with executive functioning, resembling those found in later-stage Parkinson's disease. Furthermore, it is known that homeostasis of iron and manganese is tightly interrelated. In particular, manganese possesses a high affinity to transferrin receptors even in comparison to iron (III). Ferroportin is also considered to be a possible manganese transporter.

Silicon

Silicon (Si) is a beneficial trace element that is widely distributed in foods with several dietary sources of grains, root vegetables, bean, corn, fruits, dried fruits, nuts, and also drinking water. Various alcoholic beverages also contain considerable amounts of silicon. Silicon compounds from food in the presence of hydrochloric acid and other gastric acids in the gastrointestinal tract are hydrolyzed into bioavailable forms of silicic acid (ortho, meta, di, and tri-silicates) that readily diffuses into the blood circulation where it is distributed and accumulated into various tissues and organs such as kidneys, liver, bone, spleen, lungs, skin (collagen synthesis), and connective tissues. It also improves the structural integrity of skin, hair, and nails, and bone calcification; modulates the immune system and inflammatory response; accelerates the rate of bone mineralization; and mitigates the risk of atherosclerosis. The amount of silicon in tissues decreases with age. Silicon is filtered by the glomerulus because it does not form any bonds with plasma proteins. Hence, about 70%–80% of plasma silicon is eliminated by kidneys within 3–8 h after meal ingestion. It has also been suggested that silicon may decrease the bioavailability of aluminium by blocking the uptake of the latter by the gastrointestinal tract and impeding its reabsorption in the kidneys, and thus protecting against the toxic actions of aluminium. Silicon levels tend to be higher in foods derived from plants than foods from an animal source. In addition, although there are several potential dietary sources, silicon bioavailability from foods is low. Thus, it may be prudent to increase intake through other innovative means such as biofortification of edible parts of plants.

Nickel

It is well-accepted that nickel (Ni) is as an essential trace nutrient in plants, animals, and humans. However, less than 10% of nickel ingested with food and drinking water is absorbed by the gastrointestinal tract. Although the biological function of nickel is still somewhat unclear in the human body, however, nickel is found in the body in highest concentrations in the nucleic acids, particularly RNA, and is thought to be somehow involved in protein structure or function. It has been speculated that nickel may play a role, as a cofactor, in the activation of certain enzymes related to the breakdown or utilization of glucose. Nickel may aid in prolactin production, and thus be involved in human breast milk production. More research is needed to reveal the properties of this interesting mineral in the human body. Small quantities of nickel are essential for the body, but when the uptake is too high it can be toxic to human health. Studies have shown that humans may be exposed to nickel during breathing air, eating food, or smoking cigarettes and acute exposure of human body to nickel may cause several health problems such as liver, kidney, spleen, brain and tissue damage, vesicular eczema, lung, and nasal cancer. In addition, acute toxicity can follow exposure to nickel carbonyl, a gas generated as part of the refining process for the metal. Occupational exposure to nickel and its compounds can also cause allergic dermatitis known as “nickel allergy” in sensitized individuals. Dermatitis due to wearing nickel-plated objects such as jewelry is well-documented. Nickel deficiency has not been shown to be a concern in humans; despite this, it may cause biochemical changes, such as reduced iron resorption that leads to anemia. It can disturb the incorporation of calcium into a skeleton and lead to parakeratosis-like damage, which finds expression in disturbed zinc metabolism. It has found that nickel deficiency particularly affects carbohydrate metabolism.

Boron

Boron (B) and its compounds have been known for a while as beneficial for the metabolism of humans and animals. It has important roles in physiological and metabolic activities of microbial and plant systems. The essentiality of boron for human has not been reported; instead, it is considered as a probably essential element by the WHO. It is ingested from the diet and absorbed from gastrointestinal tract completely and presented in body as boric acid, and then it excreted completely in the urine. Very little is known about its transport in the body. Boron has roles in steroid hormone metabolism, healthy bone development, and cell membrane maintenance. It does not tend to accumulate in tissues. However, bone, nails, and hair have been found to have higher boron levels, whereas fat tissue has low boron levels. People consume many products containing boron in their daily life mostly from fruits and vegetables. It exists abundantly in leafy vegetables, fruits, nuts, and legumes. When consumed at high doses, it can cause developmental and reproductive abnormalities. There is only limited number of cases for boron intoxication involving human subjects. Reports suggest that environmental or industrial boron exposure is not a treat for human health. People who work in boron mine plants have a mean blood boron level of 224 ng/g and show no symptoms of toxicity. Oral exposures of humans to high levels of boric acid have resulted in little or no observable toxicity. Chronic exposure to boron causes neurological effects, kidney damage, diarrhea, anorexia, weight loss, and testicular atrophy. Boron deprivation results in impairment of growth, abnormal bone development, decrease in blood steroid hormone levels, and an increase in urinary calcium excretion in humans and animals. In addition, it is found that in animals and humans, boron deficiency is also related to the decrease in the electrical activity of the brain, short-term memory, and decrease in skills in performing tasks, whereas boron supplementation increases brain functions. These effects of boron could be attributed to the changes in membranes providing nerve-impulse transmission by boron. Boron deficiency is also suggested to be the possible causal agents in Kashin–Beck disease which is a bone disease having a high incidence in China.

Vanadium

Vanadium (V) is widely distributed in all organisms. In humans, the vanadium content in blood plasma is around 200 nM, while in tissues it is around 0.3 mg/kg and mainly found in bones, liver, and kidney. The two main routes for absorption of vanadium are breathing and ingestion. The daily dietary intake in Iran is estimated to be 32.6–135 μg/g. Also, vanadium is found in potable water in concentrations around 1 μg/L; thus, its intake by this source depends on the daily ingested volume. Therefore, the typical daily dose consumed by humans corresponds to 10–30 μg of vanadium per day. However, most of the dietary vanadium is usually excreted in the feces, meaning that the vanadium accumulation in the body does not constitute a potential hazard. Toxic effects usually occur only as the result of industrial exposure to high levels of airborne vanadium. Toxic effects resulting from the intake of large amounts of vanadium in the diet are unlikely. Vanadium deficiency in human is very rare and vanadium deficiency disease has not been identified in humans. The only epidemiological study in which an association between vanadium low intake and human cardiovascular disease is reported is that of Masironi. Experimentally, vanadium compounds have been shown to be effective against many types of diseases including diabetes type 2, cancer, endemic tropical diseases, bacterial infections (tuberculosis and pneumonia), and HIV infections. Furthermore, they can be operative in cardio- and neuroprotection. However, so far, vanadium compounds have not yet been approved as pharmaceuticals for clinical use. The key facts on the probably essential trace elements are summarized.

Potentially toxic elements

Fluorine

Fluorine (F) in the form of fluoride occurs in nature ubiquitously and enters the body through drinking waters and foods. Its concentration in water is very variable, which explains much of the variability in total fluoride intake. Other important sources of fluoride are tea, seafood that contains edible bones or shells (e.g., canned sardines), and fluoridated tubes of toothpaste. Most of ingested fluoride is absorbed from the upper intestines and is taken up by bones and teeth and the rest is lost in the urine. Body fluoride status depends on multiple factors. Fluorine has been suggested as a therapeutic agent in the treatment of osteoporosis. It is thought that fluoride in conjunction with calcium stimulates osteoblastic activity, increasing the hardness of bones. Low levels of fluorine in drinking water lead to dental decay and possibly osteoporosis. High levels of dietary fluoride cause dental fluorosis and mottling of tooth enamel is a well-known feature of excess fluoride ingested. Dental fluorosis may be easily recognized; however, the skeletal involvement is not clinically obvious until the advanced stage and early cases may be misdiagnosed as rheumatoid arthritis or osteoarthritis. The total quantity of fluoride ingested is the single most important factor in determining the clinical course of skeletal fluorosis; the severity of symptoms correlates directly with the level and duration of exposure.

Lead

Lead or plumb (Pb) is the most important toxic heavy metal in the environment. Important sources of environmental contamination include mining, smelting, manufacturing, and recycling activities. In addition, in some countries, the continued use of leaded paint, leaded gasoline, and leaded aviation fuel are other sources. More than three-quarters of global lead consumption are for the manufacture of lead-acid batteries for motor vehicles. Lead is also used in many other products, for example, pigments, paints, solder, stained glass, lead crystal glassware, ceramic glazes, jewelry, toys, and in some cosmetics and traditional medicines. Drinking water delivered through lead pipes or pipes joined with lead solder may also contain lead. An additional source of exposure is the use of certain types of unregulated cosmetics and medicines. People can become exposed to inorganic lead through occupational inhalation (pulmonary absorption) of lead particles generated by burning materials containing lead and environmental sources from ingestion (gastrointestinal absorption) of lead-contaminated dust, water (from leaded pipes), and food (from lead-glazed or lead-soldered containers). Inorganic lead is not absorbed through the skin, although organic lead compounds are absorbed. The health effects of lead are the same regardless of the route of exposure. Lead is a highly poisonous metal affecting almost every organ in the body. The nervous system is the most affected target in lead toxicity, both in children and adults. The toxicity in children is, however, of a greater impact than in adults, which may contribute to behavioral problems, learning deficits, and lowered IQ because children absorb four to five times as much ingested lead as adults from a given source. In addition, children's innate curiosity and their age-appropriate hand-to-mouth behavior result in their mouthing and swallowing lead-containing or lead-coated objects. This route of exposure is magnified in children with a psychological disorder called Pica (persistent and compulsive cravings to eat nonfood items). After absorption, 99% of the lead is bound to the hemoglobin portion of erythrocytes and is circulated through the vascular system to soft tissues, liver, kidneys (organs of lead excretion), bone, and hair. During systemic circulation, lead interrupts the hemoglobin biosynthesis pathway primarily through inhibition of ∂-amino levulinic acid, an effect observed when blood lead level exceeds 5 μg/dL. Elevated levels of zinc protoporphyrin (ZPP) often accompany elevated lead, and as such, ZPP is routinely included in testing for those who may be at risk for occupational exposure to lead. Interestingly, an elevated ZPP may increase the risk of lead exposure 6 months later. The body stores lead in the teeth and bones, where it accumulates over time. Evidence supports that teeth and bone share similar qualities, such as a high affinity for metals and similar accumulation rates. The appearance of a “lead line” also known as a “Burtonian blue” line, at the gum line, is indicative of chronic lead poisoning. The blue line is a common manifestation occurring in individuals with poor dental hygiene and is best described as the deposition of lead between collagen fibers’, around blood vessels, and within cells. Lead stored in bone may be remobilized into the blood during pregnancy, thus exposing the fetus. Undernourished children are more susceptible to lead because their bodies absorb more lead if other nutrients, such as calcium or iron, are lacking. Children at highest risk are the very young (including the developing fetus) and the impoverished. Lead exposure can have serious consequences for the health of children. At high levels of exposure, lead attacks the brain and central nervous system to cause coma, convulsions, and even death. Children who survive severe lead poisoning may be left with mental retardation and behavioral disorders. At lower levels of exposure that cause no obvious symptoms, lead is known to produce a spectrum of injury across multiple body systems. Lead also causes long-term harm in adults including anemia, hypertension, renal impairment, immunotoxicity, and toxicity to the reproductive organs. The neurological and behavioral effects of lead are believed to be irreversible. Exposure of pregnant women to high levels of lead can cause miscarriage, stillbirth, premature birth, and low birth weight. There is no known safe blood lead concentration. But it is known that as lead exposure increases, the range and severity of symptoms and effects also increase. Even blood lead concentrations as low as 5 µg/dL, once thought to be a “safe level,” may be associated with decreased intelligence in children, behavioral difficulties, and learning problems.

Cadmium

Cadmium (Cd) is a trace element that is not believed to play a role in higher biologic systems or human nutrition. The primary source of cadmium exposure for nonsmokers is from the food supply. In general, leafy vegetables such as lettuce and spinach, potatoes, grains, peanuts, soybeans, and sunflower seeds contain high levels of cadmium. Tobacco leaves also accumulate high levels of cadmium from the soil, and thus regular use of tobacco-containing products is a common route of cadmium exposure for smokers. Smoking is estimated to at least double the lifetime body burden of cadmium exposure.

Mercury

Mercury or hydrargyrium (Hg) is a common chemical exposure and environmental pollutant. It exists in organic and inorganic forms. The inorganic form could be further subdivided into elemental (or metallic/quicksilver) mercury and mercury salts. People may be exposed to mercury in any of its forms under different circumstances. However, exposure mainly occurs through consumption of fish and shellfish contaminated with methylmercury (organic mercury exposure) and through worker inhalation of elemental mercury vapors during industrial processing of amalgam and in the manufacture of scientific instruments and electrical control devices. Elemental and methylmercury are toxic to the central and peripheral nervous systems. Mercury vapor, in the atmosphere, is typically low and not considered a major route of exposure. However, inhalation of mercury vapor can produce harmful effects on the nervous, digestive, immune systems, lungs, and kidneys, and may be fatal. The inorganic salts of mercury are corrosive to the skin, eyes, and gastrointestinal tract and may induce kidney toxicity if ingested. In addition, a study finding suggests that in experimental data from animal research and *in vitro* studies there are a strong influence of inorganic mercury on the nervous system. *In vitro* models showed all pathological changes seen in Alzheimer's disease (AD), and in animal models, inorganic mercury produced changes that are similar to those seen in AD. Its high affinity for selenium and selenoproteins suggests that inorganic mercury may promote neurodegenerative disorders through disruption of redox regulation. However, epidemiological and other studies suggest a much weaker relationship. It is likely that two processes play a modifying role here: humans may be differentially susceptible to mercury toxicity, when compared with other species, and some individuals might be better able to chelate and detoxify mercury than others, reducing the strength of correlations between mercury exposure and AD. Excretion of mercury depends on its original form. Elemental and inorganic salts are primarily excreted through the kidney and minimally through the gastrointestinal tract with a total half-life of 30–60 days. Excretion of organic mercury compounds is primarily fecal with enterohepatic recirculation leading to a longer half-life of approximately 70 days.

Aluminium

Aluminium (Al) occurs naturally in the environment as hydroxides, oxides, and silicates. It also combines with other elements, such as sodium and fluoride, and as complexes with organic matter. Aluminium sulfate [$Al_2(SO_4)_3$] is a common additive to drinking water worldwide used as a “clarifying agent.” Aluminium can enter the body through inhalation of dust and particles in the air, ingestion of food and water, dermal contact (cosmetic products), and drugs (antacid agents). Aluminium is poorly absorbed through ingestion and inhalation pathways and is essentially not absorbed dermally. In the diet, aluminium bioavailability is highly dependent on its form and the presence of other food constituents with which it can form complexes, such as citric acid. In an investigation, neurotoxic effects in dialysis patients treated with aluminium-containing dialysis fluids have been demonstrated and it has been shown that following high aluminium dust exposures in the workplace can cause particle-related diseases called aluminosis. However, there is currently no evidence for an association between aluminium exposure and the development of breast cancer or AD. The primary route of excretion for absorbed aluminium is through urine. Due to the natural presence of aluminium and its intake through common food items, all people will have some level of aluminium in their urine. In a survey of blood and urine levels of various metals, blood aluminium concentrations were typically less than 10 μg/dL.

Arsenic

Arsenic (As) is widely distributed throughout the environment in the air, water, and soil. It is highly toxic in its inorganic form. Inorganic arsenic is a confirmed carcinogen and is the most significant chemical contaminant in drinking water globally. Arsenic can also occur in an organic form. Inorganic arsenic compounds (such as those found in water) are highly toxic, while organic arsenic compounds (such as those found in seafood) are less harmful to health. People are exposed to elevated levels of inorganic arsenic through drinking contaminated water, using contaminated water in food preparation and irrigation of food crops, industrial processes, eating contaminated food and smoking tobacco, breathing sawdust or burning smoke from arsenic-treated wood, living in an area with high levels of arsenic in rock, and working in a job where arsenic is made or used.

Tin

Tin or stannum (Sn) is used principally in food industry to line canned food and beverages and this represents the major route of human exposure to it. In addition, tin has been proposed for use as a corrosion inhibitor. There is no evidence that tin is an essential element for humans. Tin as single atoms or molecules is not very toxic to any kind of organism. The toxic form is the organic form (organotin), and its toxicity, on the other hand, has been epidemiologically linked to several markers of impaired health and growth in animal models. Tin and inorganic tin compounds are poorly absorbed from the gastrointestinal tract after oral (eating/drinking) or inhalation (breathing in) and dermal exposure (skin contact) and they do not accumulate in tissues. They are rapidly excreted, primarily in the feces, and therefore, they do not usually cause harmful effects. The main adverse effect on humans of excessive levels of tin in canned beverages (above 150 mg/kg) or other canned foods (above 250 mg/kg) has been acute gastric irritation. There is no evidence of adverse effects in humans associated with chronic exposure to tin. In addition, for the general population, drinking water is not a significant source of tin.

Lithium

Lithium (Li) gets its name from “lithos,” the Greek word for stone, because it is present in trace amounts in virtually all rocks.[184] Lithium remains the first choice in treating bipolar disorders. Yet, about half of all individuals may stop their treatment at some point. Although this observation is multi-factorial, one obvious potential contributor is the side effect and toxicity burden associated with lithium.

Conclusion

Trace elements (or trace minerals) are usually defined as minerals that are required in amounts between 1 and 100 mg/day by adults or make up less than 0.01% of total body weight. Ultra-trace minerals generally are defined as minerals that are required in amounts less than 0/001 mg/day. This review is an update of the previously published article in 2013. The previous review was updated to emphasis in detail the importance of known trace elements so far in humans’ physiology and nutrition, and also to implement the detailed information for practical and effective management of trace elements’ status in clinical diagnosis and healthcare situations. In addition, it applied WHO classification for trace elements’ classification as previously done. In this classification, the trace elements have been divided into three groups from the point of their nutritional significance in humans, as follows: (1) essential elements; (2) elements which are probably essential; and (3) potentially toxic elements, some of which may nevertheless have some essential functions at even low levels. Homoeostasis for different trace elements is maintained by different mechanisms regulating absorption or excretion in response to changes in nutritional status.

For the past decades, the biological role, biochemical functions, signs of excess, and deficiency of the essential trace or ultra-trace elements in humans are studied and identified in depth. For these elements, essentiality and toxicity are unrelated and toxicity is a matter of dose or exposure. Little is known about the essentiality of some of the probably essential elements such as vanadium, boron, and nickel in advanced organisms and humans’ physiology and possibly treatment of diseases. For toxic heavy metals, a toxic element may nevertheless be essential; however, two elements with beneficial pharmacological properties are lithium (antimanic) and fluorine (anticariogenic). Investigations indicated that for most of the trace-element-related disorders, the pathological manifestations will remain difficult to detect until more specific pathologically relevant indicators of deficiency or excess become available. In addition, researchers indicated the chemical and physiological factors may modify the bioavailability of trace elements in the diet and influence the risk of trace-element-related diseases. Discoveries and many refinements in the development of new techniques and continual improvement in laboratory methods have enabled researchers to detect the early pathological consequences of deficiency or excess of trace elements. They all are promises to fulfill the gaps in the present and future research and clinical diagnosis of trace elements deficiencies or intoxications. However, further investigations are needed to complete important gaps in our knowledge on trace elements especially probably essential trace elements role in health and disease status.

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