A REVIEW ON MACRO AND MICRO-ELEMENTS AND THEIR ROLE TO THE HUMAN BODY

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Abstract

This review is addressed in concentration level of major and trace elements in the blood of human beings since it takes an important role especially during the pregnancy period of the women due to their hormonal changes, the increased level of the progesterone, the digestive problems and vomiting, the fetal and placental growth, micronutrient-poor diet etc. The decrease in the concentrations of electrolytes below the permitted and recommended values could lead to the different symptoms such as the hyposodiamia, hypokalemia, anemia, hypocalcaemia, etc. To maintain the normal functioning of the body it is very important to keep the nutrients at their recommended optimal values.

Keywords: Major elements, trace elements, essential elements, nonesential elements, blood, concentration level.

Përmbledhje

Kjo përmbledhje lidhet pikërisht me nivelin e përqendrimit të elementeve kryesore dhe gjurmë në gjakun e pacientëve, pasi marrin një rol të rëndësishëm sidomos tek gratë gjatë periudhës së shtatzënisë për shkak të ndryshimeve të tyre hormonale, nivelit të rritur të progesteronit, problemet e tretjes, të vjellat, rritja e fetusit dhe placentës, dieta e varfër me mikroelemente etj. Ulja e përqendrimeve të elektroliteve nën vlerat e lejuara dhe të rekomanduara mund të çojë në hiposodiami, hipokalemia, anemi, hipokalcemia etj. Për një funksionim normal të trupit është shumë e rëndësishme të ruhen nivelet e nutrienteve në vlerat optimale që ato rekomandohen.

Fjalëkyçet: Elementët kryesorë, elementët gjurmë, elementët esencial, elementet jo esencial, gjaku, niveli i përqendrimit.

Introduction

Metals are naturally present in soil and minerals and have a wide use in everyday life. The increase of the metals contents in environment (air, water and soil) linked with natural and anthropogenic emission sources that in certain contents could pose a risk to humans, and the environment. Environmental pollution became a serious problem worldwide as it may damage human health and also affect the structure and the function of ecosystems (EEA, Technical report No 11/2014). The increased circulation of toxic metals through the soils, water and air and their inevitable transfer to the human food chain remains an important environmental issue which could cause health risks for future generations (Nriagu & Pacyna, 1988). It shows also the risk of different metals to the human health when they ingested through the direct uptake from the air that we breathe, from drinking water and the food chain process. These processes could cause acute and chronic effects on human health by damaging different organs such as respiratory irritation, heart disease, lung cancer, asthmatic attacks, premature mortality and reduced life expectancy (Kibria, 2016; EEA, 2013). In general, many metals are essential for humans and plants when they occur in normal content, but may turn harmfully in high content and may become toxic that may pose negative consequences to the humans and plants. Essential elements are generally divided between macro minerals such as calcium, magnesium, potassium and Na, and trace minerals including zinc, copper, selenium, iodine, boron and molybdenum (Prashanth *et al.*, 2015; Brit. Nutr. Foundation).

Cu and Zn are essential elements for humans and plants and cadmium (Cd), mercury (Hg), and lead (Pb) are the most toxic metals (Järup, 2003; Tchounwou *et al*,. 2012). Their toxicity depends on several factors i.e. the chemical species, the dose, route of exposure, the age, the gender, genetics, and the exposed status of the individuals (Tchounwou *et al.,* 2012; Mann *et al.*, 2011). Their adverse health effects are related to the chemical forms and the time- and dose-dependence (Järup, 2003; Tchounwou *et al.*, 2012). The role and the status of toxic and essential elements can be evaluated through their concentration levels in urine, blood, faeces and hair (Prashanth *et al.*, 2015).

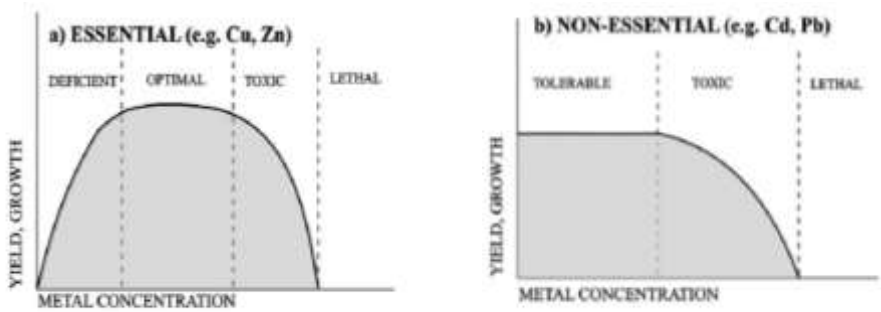

Figure. 1 The effects of essential and nonessential elements (Dissanayake & Chandrajith, 2006)

Trace elements are important for a number of vital functions in the human body, so the study of their concentration in the blood is a topic that has long been widely addressed. Among the most important functions we list:

- Activation of many enzymatic processes;
- Regulation of fibroblast excitability;

- Nerve impulse conduction (Fraser & Harris, 1989);
- Participation in the process of blood coagulation and cell growth;
- Membrane transport mechanism control;
- Reduction of neuromuscular excitation (Brommer & Coburn, 1981; Gindler & King, 1972);
- Participation in protein syntheses (Elin, 1988; Fawcett *et al.,* 1999); Oxygen transport;
- Preservation of red blood colour;
- Functioning of the immune system (Scholl & Hediger, 1994; Cogswell *et al.,* 2003; Arnold *et al.,* 2009), etc.

This review is addressed to the concentration level of major and trace elements in the human blood, particularly in pregnant women. These elements take on important roles, especially during different stages of the pregnancy that is followed by different disorders caused by the hormonal changes, the increased progesterone levels in the blood, digestive problems and vomiting, fetal and placental growth, as well as by micronutrient-poor diet, etc. It is followed with a low concentration of the electrolytes, below the permitted values, leading to a state of hyposodemia, hypokalemia, anaemia, hypocalcaemia, etc (Bank-Nielsen *et al.,* 2019). Consequences for pregnant women can be found in the childbirth premature, the birth of an underweight baby, the risk of placental abruption and miscarriage and haemorrhage during childbirth. For this reason a special importance of monitoring the concentration levels of these elements at pregnant women is necessary.

Sodium (Na)

Na is a major electrolyte of extracellular environment. It is found approximately 4,000 mmol Na in the body which is distributed at:

- extracellular fluids, which contain 45% of the total amount of Na or about 1,800 mmol / L;
- intracellular water spaces, which contain approximately 10% of the amount of total Na or about 400 mmol / L;
- The remaining Na or 45% (1,800 mmol / L) is deposited in the tissue, in the form of chemical bonds and is not affected by normal changes of metabolism.

The human body receives 4-6 gr of Na in days from the external environment, in the form of NaCl. After its dissociation into Na^+ and Cl^-

ions, it is absorbed in the digestive tract. Absorption occurs without any active control, by means of a mechanism similar to the Na-potassium-ATP-aze (Thorsen *et al.,* 2014). Na content in the body is maintained at relatively constant levels by renal regulation. The re-absorption mechanism of Na+ cations in the kidney makes possible the control of Na concentration in the plasma aqueous space. These mechanisms cause the Na concentration to fluctuate in a narrow range, from 135-145 mmol / L (Bonardi *et al.,* 1999; Kruse *et al.,* 1984).

The most important regulatory and control mechanisms in the elimination of Na from human body are that of the action of mineral-corticoid hormones, and the most important the action of aldosterone. Aldosterone is a hormone, which strongly influences Na-potassium exchanges, through cell membranes, especially at the cellular level of the renal tubules. In the distal part of the renal tube, aldosterone increases the absorption of Na ions by exchanging them with potassium (K+) and hydrogen (H+) ions. The secretion of the hormone aldosterone, from the cortical part of the adrenal glands is controlled by the renin-angiotensin system. In this system rennin is composed of a photolytic enzyme secreted by a community of cells located near the renal glomeruli (Osorio & Alon, 1997).

The cells of this system are very sensitive to the reduction of blood volume and respond to the decrease in blood flow by releasing in circulation significant amounts of rennin. Besides, the hormone aldosterone is the most important factor acting on the excretion of Na. Changes in blood flow to the kidneys and changes in plasma osmotic pressure, in the blood vessels of the renal tubules, determine the changes in the reabsorption of Na. Decreased Na concentration in the blood below 135 mmol / L, is termed as hyposodemia. In case the plasma Na values reach 120 mmol / L intensive therapy is required. The main causes of hyposodemia are (Jellema *et al.,* 2008):

a. Increased water retention or increased joint retention. This leads to an expansion of the plasma water space and a decrease in the relative Na concentration which happens for the following reasons:

- Insufficient water excretion as a result of severe damage to kidney;
- Disorders in the secretion of antidiuretic hormone (ADH), such as trauma cranial;
- Hydric overload during excessive intake of glucose solutions;

b. Water and Na loss with predominance of Na losses. The most common pathology of the above phenomenon are:

- Gastrointestinal loss, diarrhea, drainage of fistulas;
- Corticosurenal insufficiency (decreased Aldosterone secretion);
- Profuse sweating, hyperthermia;

Potassium (K)

Potassium is an important essential cation of intracellular fluids. The average concentration of potassium within the cell environment of human body is 140 mmol / L, while in the environment extracellular, this concentration is about 4 mmol / L. Intracellular concentration of K depended on the metabolic activity. Reserves of K in the body are much smaller than those of Na and can undergo ion exchanges with Na that can lead to serious pathology (Fraser & Harris, 1989). In relation to intracellular osmolality, the role of K is not important. The most important metabolic functions of K are (Walsh, 2011):

- Activation of many enzymatic processes;
- Regulation of fibroid cell excitability, in general, and those of myocarditis in particular;
- Nerve impulse transmission;

The potassium content in the body is approximately 3,200 mmol / L. The body receives 26 mmol of potassium for 24 hours mostly from the daily food. Normal plasma concentration of potassium is generally 3.5-5.3 mmol / L. As a result of this low concentration, potassium in contrast to Na does not affect water balance. Another important mechanism, in the displacement of potassium through cell membranes, is that of acid-base balance. In acid environment there is a transfer of H+ ions from the extracellular environment in the intracellular environment. This phenomenon can cause a hypokalemia in the blood when we have loss of potassium from the body. The elimination of potassium from the body takes place at the renal level. Potassium passes into the glomerular filtrate and after it is reabsorbed completely in the proximal part of the renal tubule. The hypokalemia means a clinical situation in which the amount of potassium in plasma is below the lower limit of normal values (Walmsley *et al.,* 1999).

The main causes of hypokalemia are listed down here (Walmsley *et al.,* 1999):

- Potassium loss from the body (vomiting, diarrhea, renal hypersecretion of potassium in primitive or secondary hyperaldosteronism in Cushing's syndrome, in steroid therapy, tubular metabolic acidosis, Fanconi syndrome);
- Insufficient potassium intake through the diet (chronic malnutrition);
- Redistribution of potassium in the body, with the passage of potassium from the extracellular environment in the intracellular environment (insulin and

glucose therapy, periodic familial paralysis);

- Potassium losses from extracellular fluids through various routes (transition from extracellular to intracellular environment, elimination by kidney, intestinal losses);

Hypokalemia is associated with many clinical symptoms, such as:

- Muscular and nervous symptoms;
- Manifestation of tetany;
- Renal symptoms;
- Electrocardiographic signs, T-wave negativity;

In contrary, the hypokalemia means the clinical situations in which the amount of plasma potassium is above the upper limit of normal values. The main causes of hypokalemia are:

- Excess potassium intake during the correction of metabolic alkalosis hyperkalemic with 10% potassium chloride solution;
- Insufficient renal excretion of potassium (decreased tubular activity of Na-potassium exchange, hyperaldosteronism as in the case of morbus Addison, glomerular insufficiency, Na loss);
- Total body K+ depletion may associated with the accumulation of K+ into the interstitial space, limiting blood flow to skeletal muscle and may associate the hypokalemia with rhabdomyolysis (Palmer 2015).
- Decreased renal excretion of potassium due to acidosis, anorexia, diabetic ketoacidosis with Na-potassium pump deficiency.

Calcium (Ca)

Calcium is one of the most important mineral substances for the organism. As an average, one adult contains about 1200 g of calcium in the body. About 1% of this amount is found in the blood, in the plasma aqueous space. The rest, about 99% is deposited in bone tissue and is found in a dynamic equilibrium with quantity of calcium present in plasma aqueous space (Barnett *et al.*, 1973). In the blood plasma calcium is found in three different forms:

- Binded to plasma proteins, mainly albumin. In this form is an average of 40-50% of the total amount of calcium present in blood plasma;
- In free ionic state, Ca^{2+}. Exactly this amount of calcium represents the portion chemically active capable of exerting physiological actions and participate in biochemical processes. Concentration of free calcium ions, at blood plasma, in medical practice is called ionized calcium. Moderate

concentration of ionized calcium in blood plasma represents 40-45% of the total amount of calcium, found in blood plasma;

- In the form of chemical complexes with citrates and phosphates. In blood plasma, calcium associated with citrates and phosphates, represents 5-10% of the amount of general calcium, found in blood plasma;

From the point of view of physical chemistry, ionized calcium and that associated with citrates and phosphates, is considered a diffuse form. Protein-bound calcium, mainly in albumin, is considered a non-diffuse form. The above-mentioned forms of calcium in the body are in a state of a dynamic equilibrium. This balance is a function of blood pH changes. The binding of calcium to plasma proteins is very closely related to the values of blood pH. As blood pH increases, so does the ability of calcium associated with plasma proteins, leading to a decrease in the concentration of ionized calcium Ca^{2+} (Brommer & Coburn, 1981; Gindler & King, 1972; Robertson & Marshall, 1981; Bagrnski *et al.*, 1973). The Ca daily needs of adult body are on average 700 mg/day. In age of childhood, pregnancy and lactation, the average daily needs of calcium increase up to 1000-1500 mg/day.

Absorption of calcium through the food occurs in the intestinal tract under the action of cholecalciferol that is the active form of vitamin D. The pH of intestinal fluids has an important influence on this phenomenon, from the intake of phosphates through food, from the diet and from the normal absorption of fats (lipids). Calcium is eliminated from the body mainly through faecal materials and urinary tract. Its ions have a number of important functions for the body, among which we mention:

- Participation in the process of blood coagulation and cell growth, especially of osteoblasts;
- Serves as an activator of a number of enzymes (metal cofactor) and intervenes in the process of hormonal release and other biological activators;
- Participates in the transmission of nerve impulses;
- Reduces the permeability of capillaries of cell membranes, taking active part in controlling the membrane transport mechanism;
- Reduces neuromuscular stimulation;

Ca is one of the most important electrolytes in the body, with great medical interest. The decreased calcium concentration below the lower limit of the normal range is called hypocalcemia. The most important pathology that leads to hypocalcemia are:

- Decreased thyroid gland function (Hypothyroidism);

- Decreased parathyroid gland function (Hypoparathyroidism);
- Rickets;
- Osteomalacia;
- Operations in the intestinal tract;
- Malabsorption (malabsorption) of calcium in inflammatory diseases and
- degeneration;
- In diseases of the pancreas;
- In cirrhosis of the liver;
- Chronic renal failure;
- Magnesium deficiency;
- Prostate carcinoma;
- Prolonged therapy with anticonvulsant drugs, etc.

If the concentration of calcium in the blood increases above the upper limit of normal values, the organism suffers from the hypercalcemia. The most important pathology that leads to hypercalcemia are:

- Increased parathyroid gland function (Hyperparathyroidism);
- Osteoma (bone system tumor);
- Multiple Myeloma;
- Leukemia and Lymphomas;
- Increased thyroid gland function (Hyperthyroidism);
- Skeletal fractures, etc.

Magnesium (Mg)

Mg^{2+} is an important cations in the body. It belongs to the group of the most important cations of the organism together with Na, K and Ca. The plasma concentration of magnesium in adults varies from 1.7- 2.1 mg / dL (0.6-1.15 mmol / L). Approximately 55% of the amount of Mg in the body is located in the skeleton. The rest, approximately 45% of Mg^{2+} content in organism, belongs to the intracellular environment. Mg and K are two most important cations in the body. Only 1% of the total Mg present in the body is found in the blood. In the blood serum, approximately 55% of Mg is in the form of free Mg^{2+}ions, 30% is bound to proteins (mainly to the albumin) and 15% forms complexes with phosphates, citrates and other anions. The decrease of Mg content in the blood is mostly caused by renal loss, gastrointestinal disorders and some therapeutic treatments. The lack of Mg in the body causes neuromuscular hyperstimulation, heart rhythm disorders, etc. Hypermagnesemia is caused by renal insufficiency, in hemolytic anemias, in adjuvant therapy with antacids that containing Mg. One of the clinical signs of Hypermagnesemia is neuromuscular depression. Mg is a cofactor metal of many enzymes and enzyme systems, that depend on ATP (Adenosine triphosphate) (Pasternak *et al.*, 2010).

Magnesium has several functions, such as:

- Participation as an activator of some enzymes;
- Protein synthesis;
- Has effect on muscle tone and CNS (increased values of magnesium are responsible for nervous depression, while its low values, cause seizures tetanus and convulsions) (Elin, 1988; Fawcett *et al.*, 1999). Like the potassium, magnesium is mostly concentrated in the intracellular space. 30% of dietary magnesium is absorbed at the intestinal level, in the same way as Ca. 70% of plasma Mg, ie the free part (ionized magnesium or complex), filtered at the glomerular level, reabsorbed in bulk into the tubule proximal and then actively eliminated at the level of the distal tubule. A large number of studies have shown that Mg deficiency is associated with disorders of calcium, phosphates and potassium during cardiac disorders especially in arrhythmia ventricular which is resistant to classical medication (Fawcett *et al.*, 1999; Farrell, 1984).

Urinary magnesium excretion varies from 3.1-5.1 mmol/24h or 75-125 mg/24h that depend on hematic concentration and in some cases in circadian rhythm (Greenway *et al.*, 1996). Magnesium found in bone tissue, is in the form of complex salts with calcium phosphate and other ions. The hypermagnesemia symptomatic are mostly found in patients suffering from the renal insufficiency. In other cases such as: cortical insufficiency, hypothyroidism, decompensated diabetes, there are the lack of clinical symptoms of hypermagnesemia. To decide the diagnosis of magnesium deficiency is difficult, knowing the fact that the largest amount of it belongs to the intracellular space and a fraction at all small of this metal is located in the interstitial space, so magnesium does not often reflects the general condition of this metal in the body.

Hypomagnesaemia is the result of insufficient intake of magnesium through diet (such as in cases of prolonged lactation, patients in the postoperative phase) or inadequate absorption (malabsorption, alcoholism, malnutrition, severe diarrhea, etc.) and finally in diseases such as: hyperaldosteronism, hyperparathyroidism, hyperthyroidism, diabetic acidosis, diuretic therapy (Milart *et al.,* 1995).

Recently various studies have shown that the concentration of magnesium varies significantly in alcoholic hepatitis, kidney disease, and diabetes. Magnesium in the vascular space represents only a fraction of the amount of magnesium, which is found in the human body. However, the measurement of magnesium in the blood serum, compared to the measurement of intracellular magnesium is simpler and provides sufficient information for the assessment of magnesium in its state in the body.

Manganese (Mn)

Manganese belongs to the group of trace minerals obtained in small amounts from the daily diet of the human body. The human body needs small amounts of manganese every day to perform its vital functions. Adult contains 15 -20 mg of Mn in the body. The main functions of manganese in human health are as follow:

1) Bone building

From animal studies, very low manganese intake has been linked to the formation of weak bones. This phenomenon is thought to be due to its role in the formation of matrices of proteins that bind minerals such as calcium. The US diets tend to be high in manganese as a necessary element in the prevention or treatment of osteoporosis (Price *et al.,* 2012).

2) Skin health

Mn is a necessary co-factor for an enzyme called prolidazo, which is necessary for the production of collagen as a structural component of the skin. This role of manganese in the production of collagen makes it an important mineral for skin health. Except its role in the production of collagen, manganese functions as an antioxidant in skin cells and other cell types. It helps in protecting the skin from damage caused by oxygen or ultraviolet (UV) radiation. In a study conducted in people who received insufficient amounts of manganese in daily diets, it was evident that they were more predisposed to have skin rashes and by taking supplements containing Mn this symptom disappeared (Treiber *et al.,* 2012; Patel *et al.,* 2006).

3) Blood sugar control

Manganese helps the enzymes in a process called glucogenesis. Glucogenesis is the scientific term for the conversion of substances such as organic amino acids in sugar. Our cells in order to continuously participate in this process require Mn to function properly. Scientists are still unsure for the connection that exists between diabetes and the concentration of Mn in the blood of humans. The diets of animals low in manganese leads to the high blood sugar level similar to those of diabetics. If this is true in humans has not yet been fully validated (Lee & Kim, 2008).

4) Protective role against the free radicals damage.

As mentioned above, manganese is a co-factor for an enzyme called manganese superoxide dismutase (MnSOD), which is a potent antioxidant associated with protection against free radicals damage. Low Mn diets are associated with the damages from free radicals, causing skin problems and asthma (Patel *et al.*, 2006). Regarding the binding of manganese with other minerals, in some studies that have been done in animals has been shown that iron deficiency may be associated with increased absorption of manganese (Smith *et al.*, 2013).

Iron (Fe)

Iron is an important dietary mineral that is involved in the various functions of the body, including the transport of oxygen in the blood that is essential in providing energy for daily life. Normally man needs to absorb only a small amount of iron every day. The body stores iron in various organs including the liver which is the most important organ of the accumulation and metabolism of many substances. Among the roles of iron in the body we can mention:

- Oxygen transport;
- Preservation of red blood colour;
- Functioning of the immune system; etc.

Anaemia has been diagnosed as the main pathology caused by iron deficiency. Other side effects include nausea, vomiting, constipation and diarrhea. However when iron accumulates in large amounts in the body it can cause heart disease and some types of tumours. The body's requirement for iron is observed during the pregnancy. Iron plays a key role in the production of haemoglobin and the red blood cell protein that transports oxygen to other cells. During pregnancy, the amount of blood in the body increases until 50% and more than its usual content, therefore more iron is needed to produce haemoglobin for increased amount of blood. Pregnant women also need more iron for fetal and placental growth. Although the fetus is relatively protected from the effects that iron deficiency can cause due to the role of the placenta to produce proteins (Gambling *et al.*, 1996). Usually, due to several mechanisms the females may have problems with the Fe reserves during the first trimester of pregnancy (Poulakka, 1980; Colomer *et al.,* 1990).

There is evidence for the association between iron deficiency and preterm birth, the birth of an underweight baby, the risk of placental abruption and miscarriage, and postpartum hemorrhage (Scholl & Hediger, 1994; *Cogswell et al.,* 2003; Arnold *et al.,* 2009). Unfortunately, most women start their pregnancy with iron deficiency symptoms, and with increasing requirements for this element, and during the second and the third trimester they become anaemic. The lack of iron during the birth increases maternal mortality, prey and prenatal infants. 40% of the maternal deaths after birth are associated with anaemia. The risk is even higher if females:

- has digestive problems and vomiting;
- had two or three pregnancies within a short period;
- is pregnant with two or more embryos;
- has an iron-poor diet;
- the last menstrual cycle has been with a lot of bleeding (WHO, 2001).

To minimize the risk of side effects that iron deficiency can cause during pregnancy, the World Health Organization proposes a scheme for daily supplements that pregnant women should take (WHO, 2012).

Copper (Cu)

Copper belongs to the metal ions that are necessary for the essential functions of the body, but are toxic in large quantities. Copper is a trace metal present in all tissues and is important for cellular respiration, amino acid peptides, neurotransmitter biosynthesis, pigment formation, connective tissue hardness. It is a cofactor for multiple enzymes, plays an important role in development of the central nervous system and acts as a catalytic cofactor for many enzymes catalyzing the redox reactions, iron absorption, mitochondrial respiration, and scavenging of free radicals (Zahra *et al.,* 2017).

At low concentrations Cu can cause an incomplete development, while in large quantities can be harmful (Brommer & Coburn, 1981; Cox & Moore, 2002). Numerous nervous disorders at humans are caused by the deficiencies in copper transport and abnormal interactions of copper-protein. This is a critical importance of this metal for proper development of nerves and neurological functions. Cu is involved in the functions of some "cuprous-enzymes" that are essential for life (Madsen & Gitlin, 2007). It plays an important role in the mobilization of iron to plasma from tissue deposits (Goel & Misra, 1982). Studies had been done for the deficiency of copper during embryonic and fetal development that may cause numerous structural and biochemical abnormalities (Raman & Leela, 1992; Ebbs *et al.,* 1984). Cu deficiency can also lead to the oxidative damages in the cells (Zahra *et al.,* 2017). The excessive accumulation of copper in liver, kidneys and cornea are responsible for the clinical abnormalities of the disease and the accumulation of Cu in the brain referred to the hepatolenticular degeneration (Zahra *et al.,* 2017).

Zinc (Zn)

Zinc is an essential trace element and has several functions in the body of the humans, such as:

1) Essential interactive compound for more than 300 enzymes involved in the synthesis and metabolism of carbohydrates, lipids, proteins, nucleic acids and other nutrients;

2) Stabilize the cellular components and membranes, so it is very important for the structure and integrity of cells and organs;

3) Essential element for cell division and necessary for normal growth and development during pregnancy, childhood and adolescence.

Zinc is found in all body tissues and fluids and the total zinc content in the body is estimated at 2 g (30 mmol) (WHO & FAO, 2002). The Standard Food Agency and the Department of Health in the Kingdom of United advise that zinc intake should not exceed 25 mg per day (Beattie, 2012). Zn deficiency can be caused by:

1) Unbalanced diet;

2) Gastrointestinal diseases including ulcerative colitis, Crohn's disease, short bowel syndromes and chronic diarrhea;

3) Chronic liver disease;

4) Chronic kidney disease;

5) Alcoholism (decreases the absorption of zinc and increases the secretion of zinc through urine);

7) Diabetes;

8) Pregnancy and breast feeding;

9) Vegetarian diet;

10) People who take large amounts of iron supplements because iron can interfere to the absorption of zinc in the body (National Institutes of Health, 2013).

Cadmium (Cd)

Cadmium is widely dispersed element of the earth's crust in a low content by classifying it as rare element. Cd, Zn, Hg and In show similar geochemical properties (UNEP, 2013) and are often associated with zinc ores (Cheng *et al.*, 2014). Cd is a volatile element and its main anthropogenic atmospheric emissions are mostly from high temperature processes. Da Silva et al. (2005) described the Cd as a nonessential element which shows high toxicity to humans also in very low content. The daily intake is estimated at 25 to 60 µg for a 70 kg body weight. Referring to the Zahra *et al.* (2017) the following information is extracted: Cadmium affects differentiation, proliferation and causes apoptosis at the cellular level. International Agency for Research on Cancer (IARC) has classified cadmium as a carcinogen. DNA damage and production of reactive oxygen species (ROS) result due to indirect effects of cadmium. Cadmium also interferes with DNA repair and reduces the functions of proteins that are responsible as antioxidant defence. Cadmium is a very strong toxic heavy metal and in nature it can't be destroyed. It causes aberrant DNA methylation.

Lead (Pb)

Lead is a toxic metal and its widespread use has caused environmental pollution and numerous health problems in many parts of the world. This refers to the toxic accumulations that affect the human body by affecting different symptoms such as: neurological, haematological, gastrointestinal, cardiovascular, and kidney symptoms. Children are particularly sensitive to the neurotoxic effects of lead, and even relatively low levels of exposure can cause serious, in some cases irreversible, neurological damages (IPCS, 1995; WHO, 2007).

Lead enters the body through the respiratory and digestive systems, binds to red blood cells and is deposited in the liver, kidneys and moreover in bone. This element is eliminated through faeces and in small quantities through urine. The most common poisoning is chronic-occupational (factory workers) containing high levels of lead, etc.), urban pollution, or from lead equipment that used for water transport. Lead absorption from the intestines will decrease in cases of lack of: Fe, Ca, Zn, Mg, P or vitamin D. The use of the above microelements as supplements will serve as an antidote in cases of intoxication with Pb. Although blood lead levels for children should be <100 mg / L, while adults are less sensitive to Pb-induced neurological symptoms compared to children. The values above 300 mg / L should be considered for adults. Young children absorb 4-5 times more lead than adults (except pregnant women) and are more sensitive to the negative effects of lead because in children:

1) lead penetration per unit of body weight is higher,

2) can absorb larger amounts of dust,

3) Pb absorption in the gastrointestinal tract is higher,

4) the blood-brain barrier is not yet fully developed,

5) neurological effects occur at lower levels than in adults (FAO and WHO (2011):

The most important effect of lead in young children is that on the developing nervous system. A summary of the latest scientific evidence in 2010 showing the negative effects of Pb at lower levels, does not give indications for a minimum limit (IARC, 2006). Lead exposure has also been consistently linked to epidemiological issues. Exposure of pregnant women to high levels of lead can cause:

- abortion,
- increases infant mortality,
- premature birth,
- low birth weight,
- minor physical malformations (WHO, 2007).

Mercury (Hg)

Mercury is a naturally-occurring chemical element found in rock in the earth's crust, including in deposits of coal and exists in different forms such as elemental (metallic) mercury, inorganic mercury compounds, and methylmercury and other organic compounds (www.epa.gov/mercury). It's very toxic element that bioaccumulates in living organisms especially in fish or animals and other aquatic plants. Elemental mercury, which is released into the atmosphere as a result of natural or human activity, is easily transported in gaseous form almost all over the globe. It returns to the ground by binding to raindrops or soil particles in the form of dust. In addition to elemental mercury, another form of mercury, mainly in aquatic environments, is ionic mercury (which may be in the form of chlorides, sulfides or bound to organic acids) as well as organic mercury in the form of methylmercury. Methylmercury is bioaccumulative in living organisms as it is maintained by organisms of different levels of the food chain. In the human body, mercury is absorbed by eating foods containing mercury (fish, fruits, vegetables, etc.). It is transported by blood to all organs and usually accumulates in the brain. It affects the nervous system, cardiovascular system, kidneys, lungs, etc.

Human exposure to inorganic mercury can occur both in occupational and environmental settings. Occupations with higher risk of exposure to mercury and its salts include mining, electrical equipment manufacturing, and chemical and metal processing in which mercury is used (www.epa.gov/mercury).

A summary of the review done by Rice *et al.* (2014) is listed down here. They explain that the mercury exposure has been associated with the induction of over 250 symptoms which can complicate accurate diagnosis. As mercury can be quickly removed from the blood, redistributed and sequestered into different tissues it is important to note that there may not be a direct correlation between blood mercury concentration and the severity of mercury poisoning. Indeed, it is quickly becomes tightly bound in the brain, spinal cord, ganglia, autonomic ganglia, and peripheral motor neurons.

The nervous system is the primary repository for mercury exposure. It is evident that a number of organ systems and cellular functions affected by various form of mercury exposure. Evaluation of the epidemiological consequences of mercury toxicity over the years has added greatly to the understanding of mercury toxicity and its human impact. In light of these historic events and the toxicological evidence presenting in this review regarding the systemic effects of mercury on cellular, cardiovascular, hematological, pulmonary, renal, immunological, neurological, endocrine, reproductive, and embryonic development, efforts should be made to insure adequate steps are taken in public health and prevention to reduce the occurrence of mercury exposure and raise public awareness.

Summary

Trace elements are important for a number of vital functions in the human body and the study of their concentration in the blood is a topic that has long been widely addressed. The decrease in the concentrations of electrolytes below the permitted and recommended values could lead to the hyposodemia, hypokalemia, anemia, hypocalcaemia, etc. The balance of micro and macro nutrients in the body is important. To maintain a normal functioning of the body it is very important to keep the nutrients at their optimal values. During the pregnancy there is an imbalance in the content of the nutrients that is reflected through their concentration in the blood. This requires their supplementation by the means of taking various supplements at fully controlled content. A summary of the sources, intake routes, and health effects of nonessential trace metals, as well as their possible food sources (Da Silva *et al.,* 2005) are listed in Table 1 and Table 2, and the normal values of some nutrients are shown in Tables 3 to 5.

Table 1 The sources, intake routes, and health effects of nonessential trace metals (https://nutritionguide)

Metal	Sources	Intake Route	Health Effects	Reference
Cd	High-temperature processes, coal and oil combustion in electric	Inhalation, ingestion and	Emphysema, immune suppression, bone	Da Silva *et al.*,

	power stations and industrial plants, roasting and smelting of ores in non-ferrous metal smelters, melting operations in ferrous foundries, refuse incineration, and kiln operations in cement plants (Pacyna & Pacyna, 2001; UNEP, 2013).	absorption through skin	disorders, obstructive airway disease and irreversible renal failure, damage of DNA.	2005
Hg	Fossil fuel combustion, mining, smelting, solid waste combustion, fertilizers, use in electrical switches, municipal wastes incineration, Hg products	Inhalation, ingestion and absorption through skin	Nervous system disruption, brain, DNA and chromosomal damages, allergic reactions, tiredness and headaches, reproductive effects, birth defects and miscarriages.	ASTDR, 1999
Pb	gasoline, fuel combustion, industrial processes, solid waste combustion, used in paints, some types of PVC mini-blinds ceramics and dishware	Inhalation, ingestion	Anemia (less Pb), hypertension, kidney damage, miscarriages, disruption of nervous systems, brain damage, infertility, intellectual disorders.	ATSDR, 2020

Table 2 Food sources of microelements

	Function	**Sources**
Fe	Part of a molecule (haemoglobin) found in red blood cells that carries oxygen in the body; needed for energy metabolism	Organ meats; red meats; fish; poultry; shellfish (especially clams); egg yolks; legumes; dried fruits; dark, leafy greens; iron-enriched breads and cereals; and fortified cereals
Zn	Part of many enzymes; needed for making protein and genetic material; has a	Meats, fish, poultry, leavened whole grains, vegetables

	function in taste perception, wound healing, normal fetal development, production of sperm, normal growth and sexual maturation, immune system health	
I	Found in thyroid hormone, which helps regulate growth, development, and metabolism	Seafood, foods grown in iodine-rich soil, iodized salt, bread, dairy products
Se	Antioxidant	Meats, seafood, grains
Cu	Part of many enzymes; needed for iron metabolism	Legumes, nuts and seeds, whole grains, organ meats, drinking water
Mn	Part of many enzymes	Widespread in foods, especially plant foods
F	Involved in formation of bones and teeth; helps prevent tooth decay	Drinking water (either fluoridated or naturally containing fluoride), fish, and most teas
Cr	Works closely with insulin to regulate blood sugar (glucose) levels	Unrefined foods, especially liver, brewer's yeast, whole grains, nuts, cheeses
Mo	Part of some enzymes	Legumes; breads and grains; leafy greens; leafy, green vegetables; milk; liver
Cd[1]	Cd is a cumulative toxin that has no known beneficial function in the human body.	Letuce, spaghetti, bread, sunflowers, potatoes, spinach, peanuts, nodles, cocies, strawberry, milk, apple, cereal
Hg[2]	It has no known function in our bodies.	Fish and shellfish, eggs, milk, mushrooms
Pb[3]	[4] The effects Pb need to be clarified. The results of many studies indicate that Pb has a negative effect on the immune system, and in our review, we summarize the most recent evidence that Pb can promote inflammatory response.	Cereal products and grains, vegetables (especially potatoes and leafy vegetables) and tap water

[1] Kim *et al.,* 2019; [2]https://www.medicinenet.com/mercury_poisoning/article.htm; [3]https://www.fda.gov/food/metals-and-your-food/lead-food-foodwares-and-dietary-supplements; [4]Metryka *et al.,* 2018

Table 3 Normal calcium values in children and adults

(https://emedicine.medscape.com/article/2087447-overview)

Children	**Adults**
9- 11 mg / dL	9- 10.7 mg / dL
2.25- 2.75 mmol / L	2.25- 2.67 mmol

Table 4 Normal values of iron in humans

(https://emedicine.medscape.com/article/2087447-overview)

Men	65-176 mg / dL
Women	50-170 mg / dL
Newborns	100-250 mg / dL
Children	50-120 mg / dL

Table 5 Daily supplements recommended for pregnant women the proposed by the World Health Organization (WHO, 2012)

Iron Supplements:	30-60 mg of essential iron
Frequency	One supplement daily
Duration	During pregnancy, daily iron intake should be started as soon as possible
Category	Female pregnancy, teenagers and adults

Note: 30 mg of essential iron is equivalent to 150 mg of ferrosulfate heptahydrate, 90 mg of ferro fumarate or 250 mg of ferro gluconate.

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