Review Article

A review on role of essential trace elements in health and disease

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ABSTRACT

Elements are present in different forms in the nature, and these elements are very essential for the body to perform different functions. Trace elements are very important for cell functions at biological, chemical and molecular levels. These elements mediate vital biochemical reactions by acting as cofactors for many enzymes, as well as act as centers for stabilizing structures of enzymes and proteins. Some of the trace elements control important biological processes by binding to molecules on the receptor site of cell membrane or by alternating the structure of membrane to prevent entry of specific molecules into the cell. The functions of trace elements have a dual role. In normal levels, they are important for stabilization of the cellular structures, but in deficiency states may stimulate alternate pathways and cause diseases. These trace elements have clinical significance and these can be estimated using different analytical method.

Key words: Analytical methods, body function, health, trace elements

INTRODUCTION

We have less than 100 years of knowledge on role of elements in the human body. It is estimated that 98% of the body mass of man is made up of nine nonmetallic elements.[1] The four main electrolytes namely sodium, magnesium, potassium, and calcium constitute about 1.89%, while the rest 0.02% or 8.6 g of an average human adults is made up of 11 typical trace elements.[2] However, this tiny fraction exerts a tremendous influence on all body functions. Most of them mediate vital biochemical reactions by acting as a cofactor or catalyst for many enzymes. They also act as centers of building stabilizing structures such as enzymes and proteins. The accumulation of metals or deficiency of these elements may stimulate an alternate pathway which might produce diseases. Interaction among the trace elements may also act as a scaffold upon which the etiopathogenesis of many nutritional disorders lie.[3] Although these elements account for only 0.02% of the total body weight, they play significant roles, e.g., as active centers of enzymes or as trace bioactive substances.[4] Trace elements refers to "elements that occurs in natural and perturbed environments in small amounts and that, when present in sufficient bioavailable concentrations are toxic to living organism."[4]

Elements such as iron, zinc, and selenium are essential components of enzymes where they attract or subtract molecules and facilitate their conversion to specific end products. Few elements donate or accept electrons in redox reactions, which results in generation and utilization of metabolic energy and have an impact on the structural stability and to import certain biological molecules. Iron is involved in the binding, transporting, and release of oxygen in higher animals. Some of the trace elements control important biological processes by facilitating the binding of molecules to their receptor sites on cell

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membrane, by alternating the structures or ionic nature of membrane to prevent or allow specific molecules to enter or leave a cell and in inducing gene expression resulting in the formation of protein involved in life processes.[5]

Essential elements for human body

- Four organic basic elements: H, C, N, O
- Quantity elements — Na, Mg, K, Ca, P, S, Cl.
- Essential trace elements — Mn, Fe, Co, Ni, Cu, Zn, Mo, Se, I.
- Function suggested from active handling in humans, but no specific identified biochemical functions — Li, V, Cr, B, F, Si, As.[6]

BIOLOGICAL CLASSIFICATION OF TRACE ELEMENTS

Various classifications have been proposed by so many authors on elements — both major as well as the trace elements, considered as essential for the normal development and growth.

Classification proposed by Frieden (1981) which divided the elements into micro, trace, and ultra-trace elements based on the amount found in tissues.

1. Essential trace elements: Boron, cobalt, copper, iodine, iron, manganese, molybdenum, and zinc.
2. Probable essential trace elements: Chromium, fluorine, nickel, selenium, and vanadium.
3. Physically promotive trace elements: Bromine, lithium, silicon, tin, and titanium.[7]

CATEGORICAL CLASSIFICATION OF TRACE ELEMENTS

It is observed that there are at least 29 different types of elements including metal and nonmetals in an adult human body. These 29 elements can be broadly classified into five major groups they are as follows:

- Group I: These elements are the basic components of macromolecules such as carbohydrates, proteins, and lipids. The elements belonging to these groups are carbon, hydrogen, oxygen, and nitrogen.
- Group II: These are nutritionally important minerals. They are also called as principal elements or macro elements. Their daily requirement for an adult human is above 100 mg/day. The deficiency of such elements usually proves fatal unless intervened properly. The elements belonging to this group are sodium, potassium, chloride, calcium, phosphorous, magnesium, sulfur.
- Group III: There are the essential trace elements. An element is called as trace elements when their requirement per day is below 100 mg and deficiency leads to disorders and may prove fatal. The elements belonging to this group are copper, iron, zinc, chromium, cobalt, iodine, molybdenum, and selenium. Of these, iodine is a nonmetal, while others are metals.
- Group IV: They are additional trace elements. Their role is not clear and they may be essential. The elements belonging to this group are cadmium, nickel, silica, tin, vanadium, and aluminum.
- Group V: This group of metals is not essential their presence may produce toxicity. They have no known function in the human body. The elements belonging to this group are gold, mercury, cyanide, and lead.[8]

The trace elements included Group III also called as minor elements. Their requirement is below 100 mg/day and their absence may not hinder normal development, but their activity may be substituted by another metal.[8] Analytical methods are used to measure metal concentration in human tissues and body fluids.[9]

Essential trace elements

The essential trace elements are broadly categorized into macro elements and trace or microelements [Tables 1 and 2].[7]

The trace elements in human enzyme system

Copper (Cu)

Copper plays a very important role in our metabolism largely because it allows many critical enzymes to function properly.[10] Acidic conditions promotes the solubility which incorporates copper ions either in cupric form or cuprous form into the food chain. Copper toxicosis in plants is very rare compared to its deficiency while in animals and man toxicosis is usually induced by environmental concentrations in genetically abnormal individual.[11] Mainly copper is available in the liver, shellfish, dried fruit, milk and milk products, sunflower seeds, oysters, sesame seeds, tahini, and sun dried tomatoes.[12] The average content

TABLE 1: MACRO ELEMENTS

Principal cations	Principal anions
Calcium (Ca)	Phosphorus (P)
Magnesium (Mg)	Chlorine (Cl)
Sodium (Na)	Sulfur (S)
Potassium (K)	

Source = Frieden

TABLE 2: TRACE OR MICRO ELEMENTS

Trace	Micro elements'
Iron (Fe)	Fluorine (F)
Zinc (Zn)	Vanadium (V)
Manganese (Mn)	Chromium (Cr)
Copper (Cu)	Molybdenum (Mo)
Iodine (I)	Selenium (Se)
Cobalt (Co)	Tin (Su)
Nickel (Ni)	Silicon (Si)

Source = Frieden

of metal in the plant usually ranges from 4 to 20 mg of copper per kg of dry weight. The average adult human of 70 kg weight contains about 100 mg. The daily requirement is about 2-5 mg of which 50% is absorbed from the gastrointestinal tract (GIT). Rest is excreted via bile and kidney. Copper accumulates in the liver, brain and kidney more than rest of body. Over 90% of plasma copper is associated with ceruloplasmin and 60% of red blood cell (RBC) is bound to superoxide dismutase.[13]

In human blood, copper is principally distributed between the erythrocytes and in the plasma. In erythrocytes, 60% of copper occurs as the copper-zinc metalloenzyme superoxide dismutase, the remaining 40% is loosely bound to other proteins and amino acids. Total erythrocytes copper in normal human is around 0.9-1.0 pg/ml of packed red cells.[14] Copper has a selected biochemical function in hemoglobin (Hb) synthesis, connective tissue metabolism, and bone development. Synthesis of tryptophan is done in the presence of Cu. Besides these Cu as ceruloplasmin aid in the transport of iron to cells.[15] A deficiency of Cu in diet for prolonged period especially during stages of active growth leads to anemia, growth retardation, defective keratinization and pigmentation of hair, hypothermia, mental retardation, changes in skeletal system, and degenerative changes in aortic elastin.[16] Excessive Cu either from diet or through any other sources acquired rapidly produces nausea, vomiting, diarrhea, profuse sweating, and renal dysfunction. When the levels of Cu are acquired very slowly, they cause cirrhosis, hepatitis, tremors, mental detritions, Kayser–Fleischer rings, hemolytic anemia, GIT bleeding and azotemia.[16] Congenital diseases like Wilson's disease, Menke's syndrome, idiopathic fibrosis of lung has been associated with Cu. Vineyard sprayer's lung diseases is an occupational hazard due to Cu intake via aerosol which 75% is in blood.[17]

The serum levels of copper increases in patients with myocardial infarction, leukemia, solid tumors, infections, cirrhosis of liver, hemochromatosis, thyrotoxicosis, and computed tomography disorders. Decreased levels occur in nephrotic syndrome, Kwashiorkor, Wilson's disease, severe diarrhea, and vomiting.[18] The symptoms of copper deficiency are hypochromic anemia, neutropenia, hypopigmentation of hair and skin, abnormal bone formation with skeletal fragility and osteoporosis, joint pain, lowered immunity, vascular abnormalities, and uncrimped or steely hair.[19] High copper intake for prolonged period causes increased copper percentages in serum and tissue that in turn causes oxidative stress and affects several immune functions.[18] Decreased copper levels are observed in few malignancies, mostly in the tumors which have high catabolic rate or which is of highly metastatic type. Some of the trace elements like copper and zinc have an anticarcinogenic role. Copper is involved in the cell metabolism, and is a part of various enzymes such as tyrosinase, uricase, and cytochrome oxidase, which are mainly concerned with oxidation reaction. The mean serum copper levels were significantly higher in the sera of patients with oral potentially malignant disorders such as oral leukoplakia and oral submucous fibrosis and also malignant tumors such as squamous cell carcinoma. In oral submucous fibrosis patients, the serum levels of Cu gradually increases as the clinical stage of the disease progresses.[20]

Iron (Fe)

Iron is present in huge quantities all over the earth crust and also is available to a great extent from the plant kingdom. Acidic condition promotes the solubility of iron as ions either in ferric or ferrous forms. The total body content of iron is about 3-5 g of which 75% is in blood while the rest is in liver, bone marrow and muscles.[21] Heme is the major iron containing substance. It is found in Hb, myoglobin, cytochrome while the enzymes associated with iron are cytochrome A, B, C, F 450, cytochrome C reductase, catalases, peroxidases, xanthine oxidases,

tryptophan pyrrolase, succinate dehydrogenase, glucose 6 phosphate dehydrogenase, and choline dehydrogenase.[21]

An average daily requirement is 1-2 mg which has to provide as 20 mg of iron in food. Phytates and oxalates reduce the iron absorption in the GIT. Iron is absorbed from food when there is a need and the transport form of iron is known as ferritin. Hemosiderin is a golden brown pigment seen in cells of the reticuloendothelial system which is denatured form of ferritin.[2] The metabolism of iron is unique because it maintains homeostasis by regulating the absorption of iron but not excretion. When iron stores in the body are depleted, absorption is enhanced.[21] Deficiency of such an important trace metal will cause severe disorders, most important among them is iron deficiency anemia.[22] Microcytic hypochromic RBC's, tiredness, achlorhydria, Plummer–Vinson syndrome, atrophy of epithelium, impaired attention, irritability, and lowered memory are some of the features of iron deficiency anemia.[22] Iron deficiency anemia can lead to heart failure.[23] Anemia is the second most important cause of maternal mortality in India and it is estimated that about 20% of maternal deaths are directly related to anemia and another 50% of maternal deaths are associated with it.[24]

The deficiency when prolonged will be fatal. When iron is increased in body acutely, nausea, vomiting, diarrhea occurs along with hepatic damage. While chronic or prolonged accumulation of iron in body occurs there is a hepatic failure, diabetes, testicular atrophy, arthritis, cardiomyopathy, peripheral neuropathy, and hyperpigmentation.[25] Bronze diabetes is a triad of hemochromatosis, diabetes, and cirrhosis. The hepatic peptide hepcidin is an important systemic iron regulatory hormone. It regulates intestinal iron absorption, plasma iron concentrations, and tissue iron distribution by inducing degradation of its receptor and the cellular iron exporter ferroportin. Ferroportin exports iron into plasma from absorptive enterocytes, from macrophages that recycle the iron from senescent erythrocytes, and from hepatocytes that store iron. Deficiency of hepcidin causes hemochromatosis.[26] There are very few genetic disorders related to iron. One of them is due to an abnormal gene located on short arm of chromosome number 6 and linked to human leukocyte antigen — A locus.[27] The erythropoietin may be inhibited by cytokines such as interleukin 1, 6, tumor necrosis factor α, and interference. Serum ferritin levels are elevated, serum iron concentrations are decreased with tumor progression in head and neck carcinomas and thus it can be used as a follow-up tool for patients.[28] There are studies related to potentially malignant disorders and iron. In oral submucous fibrosis and oral leukoplakia, there is a significant decrease in Hb and serum iron, whereas in oral submucous fibrosis the total iron binding capacity showed statistically significant changes.[29] Recently, it has been found that iron may play a role in esophageal carcinogenesis.[30]

Zinc (Zn)

The metal zinc is an omnipotent metal that has amphoteric nature. Hence, it is ionized either in acidic or alkaline forms. Content of zinc is 2-3 ng the average body content of zinc is 2-3 g in an average adult.[31] About 99% is intracellular while the rest is in plasma. The average daily requirement is 15-20 mg/day. Phytase decreases fibers, phosphates, calcium, and copper competes with zinc for absorption from small intestine.[32] About 2-5 mg/day is excreted via pancreas and intestine. The other mode of excretion is via proximal tubule and sweat glands.[33]

Plasma zinc levels are decreased in pregnancy, fluid loss, oral contraceptive usage, blood loss, acute myocardial infarction, infections, and malignancies.[34] The function of zinc in cells and tissues is dependent on metalloproteinase and these enzymes are associated with reproductive, neurological, immune, dermatological systems, and GIT. It is essential for normal spermatogenesis and maturation, genomic integrity of sperm, for normal organogenesis, proper functioning of neurotransmitters, proper development of thymus, proper epithelialization in wound healing, taste sensation, and secretion of pancreas and gastric enzymes.[35] They can be biochemically classified as those involved in nucleic acid and protein synthesis and degradation, alcohol metabolism, carbohydrate, lipid, and protein metabolism.[31] They include transferases, hydrases, lyses, isomerizes oxidoreductases, and transcription factors. The enzyme most essential for zinc are alkaline phosphates, alcohol dehydrogenase, carboanhydrase, glutamate and lactase dehydrogenase, and RNA polymerases. The deficiency symptoms include compromised energy metabolism, alcohol intoxication, acidosis, blockage of protein biosynthesis, transmutation

reaction blocked cell destruction by superoxide radicals.[31] Zinc plays an important role in cell proliferation, differentiation and metabolic activity of the cell. These modifications will take place in the presence of many zinc-binding proteins. Intracellular zinc is homeostatically maintained at extremely low levels either by sequestration in intracellular vesicles or binding to intracellular metalloproteinase and low molecular weight ligands.[36] Their reaction causes growth retardation, alopecia, dermatitis, immunological dysfunction, psychological disturbances, gonadal atrophy, faulty spermatogenesis, congenital malformation, keratogenesis, taste disorders, and delayed wound healing. The genetic disorder related with zinc metabolism is acrodermatitis enteropathica which is an autosomal recessive defect where there is an inability in Zn absorption.[37] Zinc also supports normal growth and development during pregnancy, childhood, and adolescence.[38] Zinc plays an important role in the proliferation, differentiation, and metabolic function of mammalian cells. Various extracellular signals, e.g., redox stress, cytokines, and growth factors stimulate the release of zinc from metallothionein or alter the transport of zinc which alters the intracellular level of mobile reactive zinc. Zinc then binds to and activates metal responsive transcription factors or interacts directly with intracellular signaling molecules to modulate the expression of zinc-responsive genes and to regulate specific signal transduction pathways. Mutations that activate H-Ras are oncogenic in most cells and lead to malignant transformation and this Ras signaling pathway is inhibited by zinc.[36]

Chromium (Cr)

Chromium word is derived from Greek in which chrome means "color". First identified as PbCro4. Full name of chromium is chromium acetylacetonate.[39] The total content of chromium is about 0.006 g in an average human adult. The daily requirement is about 0.005 mg/day. The need of chromium is for biosynthesis of glucose tolerance factor. The deficiency causes impairment of glucose tolerance while toxicity results in renal failure, dermatitis, and pulmonary cancer.[40] Processed meats, whole grain products, pulses, and spices are the best sources of chromium, while dairy products and most fruits and vegetables contain only small amounts.[41] Chromium content in animal foodstuff such as meat, poultry, and fish is low which provides 2 μg Cr. Most dairy products are also low in Cr and provide <0.6 μg/serving. Whole wheat and wheat flour contain 5-10 μg of Cr/kg. Pulses, seeds, and dark chocolate may contain more chromium than most other foods. Certain spices such as black pepper contain high concentrations of chromium. Chromium is excreted principally in the urine and in small quantities in the hair, sweat, and bile. The major route of elimination after absorption is fecal.[42] Chromium is a human carcinogen primarily by inhalation exposure in occupational settings. Lung cancer has been established as a consequence of hexavalent chromium exposure in smokers and nonsmokers and some cancers of other tissues such as GIT and central nervous system. The most recent data reveals the induction of skin tumors in mice by chronic drinking-water exposure to hexavalent chromium in combination with solar ultraviolet light.[43,44] Chromium deficiency is difficult to document because of the very low levels present in blood, while tissue levels are 10 times higher. If concentrations of chromium are lower than the normal value of 0.14-0.15 ng/ml for serum or 0.26 or 0.28 ng/ml for plasma it indicates the presence of a severe chromium deficiency. Raised plasma levels can coexist with a negative balance. Hyperglycemia may be associated with raised plasma chromium and increased urinary excretion, without reflecting tissue level. Chromium concentrations in urine, hair, and other tissues or body fluids have also been reported not to reflect chromium status. The role of chromium supplementation was investigated in special subgroups of patients with diabetes.[45] Longstanding exposure with chromium will cause chronic ulcers of the skin and acute irritative dermatitis have been consistently reported in workers exposed to chromium containing materials.[46] Inhalation of Chromium compounds causes marked irritation of the respiratory tract. Rhinitis, bronchospasm, and pneumonia.[45] Chromium is considered to be a one of the risk factor for oral squamous cell carcinoma. Welding fumes involves exposure to many chemicals, including metal dust, irritant gases. Welding in stainless steel is associated with an increased risk of cancer of larynx and pharynx due to exposure to hexavalent chromium.[46]

Cobalt

The average human adult contain about 1.1 g with the daily requirement of 0.0001 mg/day. It is a component of Vitamin B12. It induces erythropoietin and blocks iodine uptake by the thyroid. It has a role to play in methionine metabolism where it controls the transfer

of enzymes like homocysteine methyltransferase. Deficiency produces cardiomyopathy, congestive cardiac failure, pericardial effusion, polycythemia, and thyroid enlargement.[47] The occurrence of cobalt in animal tissues was demonstrated by Bertrand and Macheboeuf in 1925 and a wide distribution was confirmed by other workers employing spectrographic methods.[48] Cobalt is usually found in the environment combined with other elements such as oxygen, sulfur, and arsenic. Small amounts of these chemical compounds can be found in rocks, soil, plants, and animals. Most of the production of cobalt involves the metallic form used in the formation of cobalt super alloys. The term "hard metal" refers to compounds containing tungsten carbide (80-95%) combined with matrices formed from cobalt (5-20%) and nickel (0-5%). For the general population, the diet is the main source of exposure to cobalt. Meat, liver, kidney, clams, oysters, and milk all contain some cobalt. Ocean fish and sea vegetables have cobalt, but land vegetables have very little; some cobalt is available in legumes, spinach, cabbage, lettuce, beet greens, and figs.[47] The recommended daily intake of Vitamin B12 for an adult in the USA was said to be 3 μg, corresponding to 0.012 μg of cobalt.[45] Cobalt compounds are absorbed by the oral and inhalation routes and through the skin. The degree of gastrointestinal absorption depends on the dose; very small doses in the order of a few μg/kg are absorbed almost completely, whereas larger doses are less well absorbed.[46] Cobalt is not easily absorbed from the digestive tract. The body level of cobalt normally measures 80-300 mcg. It is stored in the RBCs and the plasma, as well as in the liver, kidney, spleen, and pancreas.[49,50] Cobalt has both beneficial and harmful effects on human health. Cobalt is beneficial for humans because it is part of Vitamin B12, which is essential to maintain human health. Cobalt (0.16-1.0 mg cobalt/kg of body weight) has also been used as a treatment for anemia, including in pregnant women because it causes erythropoiesis. Cobalt also increases RBC production in healthy people, but only at very high exposure levels.[51] Deficiency of cobalt also leads to fatigue, digestive disorders, and neuromuscular problems. As cobalt's deficiency leads to decreased availability of B12, there is an increase of many symptoms and problems related to B12 deficiency, particularly pernicious anemia, and nerve damage.[51] Cobalt is excreted in both the urine and the feces, independent to the route of exposure (inhalation, injection or ingestion) most cobalt will be eliminated rapidly.[49] In one cohort study of people with hip prosthesis, there was a significant increase in the incidence of lymphatic and hematopoietic malignancies, and significant deficits of breast and colorectal cancer.[51]

Manganese (Mn)

Manganese content of foods varies greatly. Peterson and Skinner and Schroeder *et al*. found the highest concentrations in nuts, grains, and cereals; the lowest in dairy products, meat, poultry, fish, and seafood. Relatively high concentrations of manganese were found in soluble ("instant") coffee and tea and account for 10% of the total daily intake.[52] The total body content average human adult has about 15 mg of manganese, typically seen in nucleic acid. Daily requirement is about 2-5 mg/day. Manganese acts as an activator of enzyme and as a component of metalloenzymes. They have a role to play in oxidative phosphorylation, fatty acids and cholesterol metabolism, mucopolysaccharide metabolism, and urea cycle.[53] Manganese is found in all mammalian tissues with concentrations ranging from 0.3 to 2.9 μg manganese/g. Tissues rich in mitochondria and pigments (e.g., retina, dark skin) tend to have high manganese concentrations. Bone, liver, pancreas, and kidney typically have higher manganese concentrations than other tissues. The largest tissue store of manganese is in the bone.[53] Bone, liver, pancreas, and kidney typically have higher manganese concentrations than other tissues. The largest tissue store of manganese is in the bone.[53] In hydroxyapatite crystals of enamel, more than 49 elements are found, one of them being manganese, mostly in very small percentage. The concentrations of manganese in enamel are 0.08-20 ppm, equivalent 0.08-20 mg/kg, and in dentine are from 0.6 to 1000 ppm. Mn concentration is higher in the outer surface of enamel than in enamel-dentin border, and higher in permanent than in primary dentition.[54]

Some of the enzymes which are present along with magnesium are arginase, diamine oxidase, pyruvate carboxylate, phosphoglucomutase, succinate dehydrogenase, glutamine synthetase, superoxide dismutase. The deficiency cause bleeding disorders due to increased prothrombin time while accumulation over a long period causes anorexia, apathy, headache impotence, leg cramps, speech disturbance, encephalitis like syndrome and parkinsonian like syndrome. Psychosis may also occur.[55]

Selenium

The relationship between selenium and oral cancer has not yet been understood clearly, but there is some evidence observed that there is a relationship between selenium and Keshan syndrome.[55] Few studies have shown that prolonged deficiency of selenium produces this syndrome's features in animals such as failure growth in rats and muscle diseases in sheep.[56] A selenium responsive clinical syndrome in humans is described in some pathological conditions. In humans, they observed that those who take oral self-medication containing selenium causes muscular complications.[57] Low blood levels of selenium observed in some pathological conditions such as colonic, gastric and pancreatic carcinoma and cirrhosis.[58] Increased selenium intake may cause Keshan syndrome.[59] Keshan disease was first described in 1935 in North China. Clinically Keshan disease showed acute and chronic episodes of cardiogenic shock, enlarged heart, congestive heart failure, and cardiac arrhythmias.[60] The etiology of Keshan disease is still perplexing. There are numerous hypothesis suggested by different studies such as viral infections, environmental intoxication, mycotoxins, and nutritional deficiency. The hypothesis that relates with the deficiency of selenium is the most accepted hypothesis.[61]

Fluorine

Fluorine is a lightest element in Group VII of the periodic table, with atomic number 9.[62] Fluorine plays an important role in the hard tissues of the body such as bone and teeth. It helps in producing denser bones and fluoride has been suggested as a therapeutic agent in the treatment of osteoporosis. It is thought that fluoride, in conjunction with calcium, stimulates osteoblastic activity. It gets integrated into the bone matrix as fluorapatite which in turn increases the hardness of bones. Fluorine has profound anti-enzyme properties and prevents dental caries. The increased fluoride utilization could be responsible for the anticariogenic action.[63]

Fluoride or fluorine deficiency is a hypothetical disorder, which may cause increased dental caries and possibly osteoporosis due to a lack of fluoride in the diet. High levels of dietary fluoride cause fluorosis (bone disease) and mottling of teeth. High levels of fluoride cause dental lesions, periosteal hyperostosis, calcification of ligaments, and lameness. Crippling fluorosis in human is observed in persons exposed to very high intake (>20 mg/day) over a period of several years. Acute toxicity of fluoride is very rare and can occur due to a single ingestion of a large amount of fluoride and can be fatal. The amount of fluoride considered lethal when taken orally is 35-70 mg F/kg body weight. Symptoms of acute toxicity occur rapidly. There is a diffuse abdominal pain, diarrhea, vomiting, excess salivation, and thirst. Chronic toxicity is caused due to long-term ingestion of smaller amounts of fluoride in drinking-water. Excessive fluoride more than 8 ppm in drinking water daily for many years can lead to skeletal and dental fluorosis. Severe cases are normally found only in warm climates where drinking-water contains very high levels of fluoride. Due to chronic toxicity, bone density slowly increases; the joints stiffen and become painful.[64,65]

Dental fluorosis may be easily recognized but the skeletal involvement is not clinically obvious until the advanced stage and early cases may be misdiagnosed as rheumatoid arthritis or osteoarthritis. Fluoride increases the stability of the crystal lattice in bone, but makes bone more brittle. 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. Bone changes observed in human skeletal fluorosis are structural and functional, with a combination of osteosclerosis, osteomalacia, osteoporosis and exostosis formation, and secondary hyperparathyroidism in a proportion of patients. At very high fluoride concentrations, stages 2 and 3 of skeletal fluorosis are likely to occur. The clinical signs of these stages are chronic joint pain, dose-related calcification of ligaments, osteosclerosis, possible osteoporosis of long bones, and in severe cases, muscle wasting, and neurological defects. Because some of the clinical symptoms mimic arthritis, the first two clinical phases of skeletal fluorosis could be easily misdiagnosed.[66]

Iodine

Iodine is a vital micronutrient required at all stages of life; fetal life and early childhood being the most critical phases of requirement. Iodine is an essential constituent of the thyroid hormones thyroxine (T4 tetraiodothyronine) and (T3 triiodothyronine).[67] It also plays an important role in the functioning of the parathyroid glands. Iodine also promotes general growth and development within the body as well as aiding in metabolism. Because of its role in the

metabolism, the symptoms of an iodine deficiency can be far reaching. Even though it is so important to proper functioning of the human organism, iodine deficiency is not uncommon. Severe iodine deficiency often occurs in individuals who have thyroid disease and are hyperthyroid or those who have a goiter from thyroid malfunction. Symptoms of iodine deficiency may include extreme fatigue, slowing of both physical and mental processes, weight gain, facial puffiness, constipation, and lethargy. Babies born to iodine deficient mothers may be lethargic and difficult to feed. If they are left untreated, it is likely that they will develop cretinism and end up suffering poor overall growth and mental retardation.[68]

Iodine overload is less common compared with its deficit though it is unfavorable, as well as a lack of it. The literature provides information demonstrating that intake of iodine from seaweeds is safe because iodine is organically bound and is not cumulated in the body. If its intake is exceeded, it is excreted with urine, mainly during the 1st day. Organically bound iodine is harmless, even with prolonged use at high doses. For example, at intake of 1-5 mg of iodine with seaweeds by healthy people, all iodine is excreted with urine within 48 h. Only very high doses of organic iodine from seaweeds may cause unfavorable effects on the function of the thyroid gland. Excess iodine can cause as thyrotoxicosis so as hyperthyroidism as well as chronic thyroiditis, hashimoto's thyroiditis and even may increase the risk of thyroid gland cancer.[69]

CLINICAL SIGNIFICANCE OF ESSENTIAL TRACE ELEMENTS

The clinical interest in trace metal determination for the diagnosis of different diseases has increased in recent years. Distribution of trace metal metabolism influences biochemical pathways in different fields of metabolism and causes characteristic diseases. Trace metal metabolism may be concerned with intake, dietary availability, absorption, distribution, storage, mobilization, biochemical activity, and excretion.

TRACE ELEMENTS AND FIBROSIS

Fibrosis of various organs and tissue have been studied, but only very few studies correlate the trace elements and fibrosis. The role of trace elements may be as a cofactor of any of enzyme involved in fibrosis. There are reports that trace elements abnormalities may be pathologically reflected as liver dysfunction leading to fibrosis. The antioxidant defenses in metal-induced liver damage, mainly iron, and copper overload is not fully understood due to a variety of perturbations in homeostasis. Levels of selected antioxidants may provide additional protection against liver injury and prevent progression of fibrosis and cirrhosis.[30]

Indian childhood cirrhosis leads to fibrosis. There are reports indicate that there are significant deposits of stainable copper in hepatocytes. Reports from Japanese literature say that excess iron and copper accumulation may cause liver damage and fibrosis.[70]

The action of molybdenum and tungsten upon collagen by the administration to rats, showed that there was a lower levels of cross-linking. It was concluded that tritopical binding of molybdenum and tungsten in the collagen is unlikely. The biological effect of these metals was due to competition with copper and the interference with physiological cross-linking reaction based on partial blockade of lysyl oxidase (LOX). The action of molybdenum for a long period in rats caused decreased collagen stability. The cobalt — chromium- molybdenum powder had no apparent effect on the growth of fibroblast when they were exposed to these metal powders *in vitro* studies.[54]

Role of trace elements in oral submucous fibrosis

- Areca nut in any form have high level of soluble copper in them
- The tissue of submucous fibrosis patients had increased copper and decreased zinc and iron than the normal patients
- In submucous fibrosis patients, the serum levels showed decreased copper and increased zinc and iron contents than the normal patients.

This clearly shows that there exists a sort of interaction of metals copper, iron, and zinc. It is known fact that excess of iron produces a deficit of copper and zinc while an excess of zinc produces a deficit of copper and iron, it is assumed that the local increase of copper is due to the content of areca nut. The decrease of zinc and iron content may be attributed or secondary to an increase of copper levels.[30]

Dental aspects of trace elements

Since 1908, when in Texas Dental Society meeting at El Paso, mottled teeth were attributed to drinking-water; researches started on influence of trace elements on dental diseases. It was reported that about 41 elements are incorporated into a dental tissues during development of the tooth. The amount of each element reflected the environment which the process was exposed. After the development of hard dental tissue, there are only mild changes. Posteruptive uptake of trace elements is limited to surface and when restorations are done.[66]

Trace elements of teeth

Elements occurring above 1000 ppm are Na, Cl, and Mg. The elements that are found in a range of 100-1000 ppm are potassium, sulfur, zinc, silicone and Fl. While those are found b/w 10-100 ppm are iron, aluminum, lead, boron, and barium. 1-10 ppm of Cu, molybdenum, cadmium, iodine, titanium, chromium and Mg and found nickel, lithium, silver, selenium, cobalt are found in the range of 0.1-0.9 ppm.[71]

Trace elements in saliva

Saliva normally does not contain trace elements. If metal is found in excess quantities, they may be excreted via saliva. This may be reflected to diet, pollution or water. They in turn may affect the production of plaque, amount of saliva secreted, and metal concentration in saliva.[67]

Trace elements in dental caries

Of all the positive and negative interaction Fl, molybdenum, selenium and siliconium have been studied to produce cariostatic activity while interaction such as molybdenum — fluorine, molybdenum, copper, and siliconium — fluoride are primary interaction for cariostatic process. Cu acts as a caries promoting agent.[68]

Trace elements in dental soft-tissues

Epidermal parakeratosis in cheek, tongue, and esophagus is a sign of zinc deficiency. Thickening of the buccal mucosa is a common feature along with loss of filiform papillae. Deficiency of zinc could be loss of smell.[38]

Techniques to detect trace elements

Recently trace elements content of food and tissues has been created interest among research scholars. Such determinations required sensitivity and accurate methods of analysis. Most of the trace elements are estimated with a help of colorimetric and spectrographic methods of analysis.[69,70]

Atomic absorption spectrometry-based on flames arcs and sparks (flame by electrothermal):

- Emission spectroscopic methods.
- Neutron activation analysis.
- Electrochemical methods.
- Isotope dilution mass spectrometry.
- Atomic X-ray fluorescence spectroscopy.

For a single elements analysis, atomic spectroscopy and electrochemical methods are frequently applied. For multi elements tech, NAA and spectroscopic methods are used.[9]

OBSTACLES FACING ELEMENTAL ANALYSIS

The problem of analytical inaccuracy and sample contamination is the source of error in trace element studies. Accuracy in the analysis can be overcome by using properly graded instruments, avoiding operator bias, ambient temperature, and pressure. Sample contamination may occur at the collection device or storage devices or air or chemical reagents or lab instruments. The method should also include standard reference materials to avoid errors, in both sample storage and analysis.[9]

CONCLUSION

The role of copper and other trace elements in LOX and submucous fibrosis may provide vital clue for the etiopathogenesis and enable to use inhibitors of the enzyme as antifibrotic agents. The ability of LOX to function as Ras recession gene product can provide an answer to the occurrence of carcinoma. The increased levels of copper and decreased levels of zinc and iron in biopsy specimen of oral submucous fibrosis when compared to normal may be sort of interaction with the serum levels that are reversed, decreased level of copper and increased level of zinc and iron in serum specimens of oral submucous fibrosis when compared to normal subjects. It is then also possible to relate anemia, a consistent finding with these diseases. Thus the deciphered role of trace elements and interaction of metals in LOX, will enable to understand the

etiopathogenesis, provide a rapid diagnostic facility and also create effective treatment modalities.

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