TRACE ELEMENTS

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SUMMARY
Trace elements are micronutrients required in the body for its normal function especially through various enzymes, hormones, vitamins etc. where they are the important components. Prominent among them are iron, zinc, copper and cobalt. Deficiency of each one gives rise to specific clinical feature. Besides iron deficiency causing iron deficiency anemia, zinc deficiency causes ageusia and skin changes, copper deficiency hair changes, cobalt deficiency vitamin B12 deficiency and selenium deficiency cardiomyopathy.

Carbohydrates, fats and proteins are macronutrients which act as metabolic fuel in our body. Vitamins and minerals are micronutrients essential for various biochemical reactions. Minerals can be further subdivided into two groups, macro (major) and trace minerals based on their body store and daily dietary requirement.

DEFINITIONS
Macrominerals are defined as minerals that are required by adults in amounts greater than 100 mg/day. Major (macro) minerals include sodium, potassium, chloride, calcium, magnesium and phosphorus.1

Trace elements (or trace minerals) are usually defined as minerals that are required in amounts between 1 to 100 mg/day by adults. Trace mineral group includes iron, copper, and zinc.1

Ultra-trace minerals are defined as minerals that are required in amounts less than 1 mg/day. They include chromium, manganese, fluoride, iodide, cobalt, selenium, silicon, arsenic, boron, vanadium, nickel, cadmium, lithium, lead, and molybdenum.

IRON
Iron (Fe) is the most abundant trace element in our body and iron deficiency anemia is the most common micronutrient deficiency worldwide. Iron is present in hemoglobin, myoglobin, ferritin and hemosiderin and cytochrome enzymes. Hemoglobin transports oxygen to various tissues. Iron deficiency is associated with impairment in the immune function. Impairment of cell mediated immunity, reduced neutrophil, natural killer cell, myeloperoxidase and bactericidal activity in iron deficient state has been demonstrated in animal and human studies. However, cause and effect relationship between iron deficiency and infection has not been established.

Recommended dietary allowance (RDA) for men and postmenopausal women is 8mg/day, adolescents 11mg/day, premenopausal women 15 mg/day and pregnant women 30mg/day.2 Dietary form of iron are of two types- heme iron found in red meat, chicken, sea food and other animal products and non-heme iron found in dark green leafy vegetables, whole grains, nuts and dried fruits. Intestinal absorption is 15-20% for heme iron and 1-8% for non-heme iron. Absorption is increased by ascorbic acid and decreased by phytates and tannins.

Iron deficiency can be caused by increased physiological requirement, excess menstrual blood loss, poor intake, poor absorption, hookworm infestation and other infections. Iron deficiency causes hypochromic, microcytic anemia associated with easy fatigability, poor cognitive development, pica...
and occasionally dysphagia. Pallor, koilonychia and glossitis are common on physical examination. Iron overload occurs in case of high dietary intake, excessive intestinal absorption or repeated parenteral administration. Conditions associated with iron overload include hemosiderosis and hemochromatosis.

Body iron status can be assessed by estimating serum ferritin, iron, total iron binding capacity and bone marrow iron stores. Negative iron balance depletes bone marrow stores followed by serum ferritin. As deficiency worsens, serum iron falls, TIBC rises, microcytosis and hypochromasia appear on the peripheral smear.

**ZINC**

Zinc is the second most abundant trace element in the body. It is the most common catalytic metal ion in cell cytoplasm. It is a component of more than 100 enzymes like DNA polymerase, RNA polymerase, transfer RNA synthetase, reverse transcriptase, carboxic anhydrase, superoxide dismutase, alcohol dehydrogenase, thymidine kinase and alkaline phosphatase. It constitutes zinc finger proteins which are looped sequence specific DNA binding proteins those act as transcriptional mediators for nucleic acids. Zinc also plays a role in all stages of insulin metabolism. Few studies have demonstrated the beneficial effect of zinc supplementation in common cold and diarrhea in children.

RDA of zinc is 8mg/day for females and 11 mg/day for males. The highest concentration of zinc is found in choroid of eye and optic nerve followed by in muscle and bone. Liver has a small pool of 170mg which is mobilised in deficiency state. Symptoms manifest within a week of deficiency. Natural sources of zinc include meat, sea food, eggs, soya beans, peanuts, wheat bran, yeast, cheese and oysters.

Zinc deficiency is common in alcoholics and diabetics, and in malabsorption syndrome, liver and kidney diseases, burns, inflammatory bowel disease, sickle cell disease and HIV infection. Mild deficiency causes growth retardation in children. Severe deficiency leads to dwarfism and cardiomyopathy in children, teratogenicity, hypogonadism, infertility, loss of taste, poor wound healing, deformed bones, diarrhea, dermatitis, alopecia, night blindness, skin striae and nail changes. Acrodermatitis enteropathica is an inherited autosomal recessive disorder with impaired intestinal absorption and transport of zinc. Patient suffers with postural and bullous dermatitis, alopecia, growth retardation, diarrhea, secondary infection, lethargy, irritability and depression. Oral zinc supplementation leads to remission.

Copper and zinc compete for intestinal absorption. Toxicity of zinc leads to reduced copper absorption, gastritis, sweating, fever, nausea and vomiting. Plasma level of zinc is 70-120 mcg/dl. However, no single test is indicative of zinc stores in the body. Zinc in RBC and hair provides a long term assessment of body zinc status.

**COPPER**

Copper is the third largest trace element found in human body after iron and zinc. It is a component of many enzymes like cytochrome-c oxidase, superoxide dismutase, tyrosinase, dopamine beta hydroxylase ferro-oxidases and amine oxidase. Copper is involved in neurotransmitter regulation, nutrient metabolism, collagen synthesis, cellular respiration and immune function.

RDA of copper is 900mcg/day for males and females. Copper is absorbed in the small intestine by a specific transport mechanism. It is bound to ceruloplasmin in circulation. It is stored mostly in the liver and muscle. Total copper in adult human is 50-80 mg. Liver has 30-50 mcg of copper/ gram of dry tissue. Excretion is mainly through faeces, biliary and gastrointestinal secretions. Rich sources of copper include liver, shellfish, chocolate, nuts and seeds.

Copper deficiency is rare except in malnutrition, prolonged parenteral nutrition, and malabsorption disorders. Clinical features include microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, skeletal abnormalities, depigmentation of hair and skin. Menke’s and Wilson’s diseases are two major disorders of copper metabolism. Menke’s syndrome is a rare X linked recessive defect of copper absorption that has its clinical onset by 3 months of age. Patients have brittle, kinky hair, poor skin and hair pigmentation, skeletal problems, poor mental development, degenerative changes in the aorta, hypothermia and seizures.

Wilson’s or hepatolenticular degeneration is an autosomal recessive disorder due to impaired biliary copper excretion. Excess copper is deposited in the basal nuclei of brain and liver. Patient may have acute, chronic or fulminant hepatitis at presentation. Other physical signs are Kayser Fleischer ring, neurological disorder and cirrhosis of liver. Lab parameters of urinary copper >100 mcg/day, serum ceruloplasmin <20mg/l and liver copper > 250mcg/g dry weight are diagnostic of Wilson’s disease. Chelation is an effective therapy. Acute copper toxicity can cause hepatic necrosis and coma in severe cases.

Marked copper deficiency can be assessed by low serum ceruloplasmin, serum copper and RBC superoxide dismutase activity.

**CHROMIUM**

Primary function of chromium in human body is to potentiate interaction of insulin with its receptor on the cell surface. It is a constituent of glucose tolerance factor and is synergistic with insulin in promoting carbohydrate, fat and lipid metabolism. Chromium exists in trivalent state in biological system and in hexavalent state in industrial pollutants. Dietary chromium
is absorbed from the intestine, circulates in plasma bound to transferrin and is concentrated in the liver, spleen, soft tissue and bone.

RDA in males is 35mcg/day and in females 25mcg/day. Dietary sources include whole grains, meat, green beans, broccoli and spices. Chromium deficiency is seen in patients on total parenteral nutrition. Hyperglycemia, impaired glucose tolerance, neuropathy, encephalopathy, elevated plasma free fatty acid concentration and abnormalities in nitrogen metabolism have been reported in patients with chromium deficiency. However, the value of chromium supplements for diabetics is controversial.7

Industrial pollutants containing hexavalent chromium are carcinogenic. Leather tanning, dye stuff industries produce waste containing hexavalent chromium which can contaminate soil. Air-borne exposure causes contact dermatitis, skin ulcers, eczema, asthma, renal and hepatic necrosis and bronchogenic carcinoma. Plasma chromium levels are useful if the values are markedly above or below normal. Increased urinary chromium indicates recent environmental exposure to excess chromium.

MANGANESE

Manganese is located mainly in the mitochondria. It is a constituent of many important metalloenzymes like superoxide dismutase, pyruvate carboxylase, arginase and glycosyltransferase. It is absorbed in small intestine, then bound to albumin in circulation and is transported to liver and excreted in bile.

RDA in females is 1.2 mg/day and males -2.3 mg/day. Dietary sources include whole grain, nuts, leafy vegetables, soya and tea. Deficiency of manganese causes hypercholesterolemia, impaired glucose tolerance, dermatitis, changes in hair colour, skeletal abnormalities, infertility, deafness and impaired synthesis of vitamin K dependant clotting factors. Toxic exposure to manganese containing dust produces hallucinations, psychosis and neurological symptoms resembling Parkinson’s disease.8

MOLYBDENUM

Molybdenum is incorporated in many metalloenzymes like xanthine, sulfite and aldehyde oxidase. Molybdenum competes with copper at absorption sites. RDA is 45 mcg/day. Dietary sources include liver, legumes, grains and nuts. Deficiency of this trace element is extremely rare. Clinical features of deficiency include low sulfite excretion, hypercuprinemia, defective keratin formation, goiter, cretinism, hypouricemia, growth depression and neurological abnormalities.9 Excess intake leads to copper deficiency anemia, thyrotoxicosis and hyperuricemia and risk of gout.9

SELENIUM

Selenium is a component of many enzymes like glutathione peroxidase and superoxide dismutase. These impart antioxidant role to selenium as the enzymes protect against oxidative and free radical damage of cell structure. Antioxidant effect of selenium complements that of Vitamin E. Besides its antioxidant action, selenium also contributes to maintenance of normal immune function.10 It also regulates conversion of thyroxine to triiodothyronine.

RDA of selenium is 55mcg/day. Dietary sources include whole grain, egg, seafood, lean meat, garlic and mushrooms. Deficiency in endemic area causes cardiomyopathy called as Keshan’s disease in some regions of China, Kashin-Beck Disease associated with osteoarthropathy and Myxedematous Endemic Cretinism, a form of hypothyroidism with mental retardation.

Toxicity causes hair loss, nail damage, irritability, garlic odour to breath and peripheral neuropathy. Laboratory parameters to assess selenium include RBC glutathione peroxidase activity and whole blood selenium concentration.2

IODINE

Dietary Iodine is ingested as iodide. It is the basic element of thyroid hormones which are synthesized by coupling of iodinated tyrosine residues within the thyroglobulin in the follicular lumen. Proteolytic cleavage of thyroglobulin releases the thyroid hormones into circulation. Thyroid hormones play a major role in growth and metabolism.

RDA of iodine is 150mcg/day. Dietary sources include iodised salt, saltwater fish, egg, meat and milk. Maternal deficiency leads to congenital hypothyroidism, mental retardation and cretinism. Moderate deficiency in adults causes goiter. Myxedema in hypothyroid adults is characterized by hypotension and coma. Intake of large doses (>2000mcg/day)
can block thyroid hormone synthesis. 2

Iodine status of a population can be estimated by prevalence of goiter. Urinary iodide excretion can also be measured.

COBALT

Cobalt is a part of the vitamin B_{12} molecule as cobalamin and has no other known function in humans. 3 Free cobalt cannot be incorporated in body’s vitamin B_{12} pool. Hence diet has to supply body’s B_{12} needs. Dietary sources are organ meat, sea food, yoghurt etc. A deficiency in cobalt is ultimately a deficiency in vitamin B_{12}. Patient has features of anemia, anorexia and depression. Cobalt toxicity causes cardiomyopathy, heart failure, goiter, hypothyroidism, vomiting and diarrhea.

BORON

Boron has an influence in calcium and magnesium metabolism in animals and humans. 11 It is also required to convert vitamin D to its active form in the kidneys. Boron deficiency accentuates Vitamin D deficiency. Dietary sources are dried fruits, nuts, dark green leafy vegetables and grains. Supplementation of boron in the diets has been associated with raised testosterone and estradiol levels. 12 Boron deficiency may predispose to osteoporosis.

GERMANIUM

Organic germanium, bis-carboxyethylsesqui-oxide germanium (or “Ge-132”), has been shown to enhance gamma-interferon and activate macrophages and natural killer cells in experimental studies. 13 Apart from having immunostimulant effect, its deficiency may have a role

<table>
<thead>
<tr>
<th>Trace Element</th>
<th>Function</th>
<th>RDA</th>
<th>Deficiency</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Component of hemoglobin, metalloprotein, oxygen transport</td>
<td>Premenopausal:18mg/day Postmenopausal female: 8mg/day</td>
<td>Iron deficiency anemia</td>
<td>Hemosiderosis, hemochromatosis</td>
</tr>
<tr>
<td>Zinc</td>
<td>Protein synthesis, zinc finger protein, component of enzymes</td>
<td>F: 8mg/day, M:11 mg/day</td>
<td>Ageusia, Growth retardation, Dermatitis, Hypogonadism, Acrodermatitis enteropathica</td>
<td>Copper deficiency, Nausea, vomiting</td>
</tr>
<tr>
<td>Copper</td>
<td>Cellular respiration, collagen synthesis, component of enzymes, antioxidant</td>
<td>900 mg/day</td>
<td>Menke’s kinky hair syndrome, Hypochromic anemia, Skeletal defects</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Chromium</td>
<td>Glucose tolerance factor</td>
<td>F: 25mcg/day, M:35 mcg/day</td>
<td>Hyperglycemia, neuropathy, encephalopathy</td>
<td>Dermatitis, eczema, bronchogenic carcinoma</td>
</tr>
<tr>
<td>Manganese</td>
<td>Component of metalloenzymes, Manganese superoxide dismutase</td>
<td>F:1.8 mg/day M:2.3 mg/day</td>
<td>Hypocholesterolemia, Hair and nail changes, impaired clotting factors</td>
<td>Parkinsonism like features</td>
</tr>
<tr>
<td>Molybdenum</td>
<td>Cofactor for xanthine and sulfite oxidase</td>
<td>45mcg/day</td>
<td>Hypercuprinemia, Low sulfate excretion, hypouricemia</td>
<td>Risk of gout, Anemia, Thyrotoxicosis</td>
</tr>
<tr>
<td>Selenium</td>
<td>Component of glutathione peroxidase, superoxide dismutase</td>
<td>55mcg mg/day</td>
<td>Keshan’s disease, Kashin-Beck Disease Myxedematous Endemic Cretinism</td>
<td>Hair and nail loss, neuropathy, liver failure</td>
</tr>
<tr>
<td>Iodine</td>
<td>Component of thyroid hormone</td>
<td>150 mcg/day</td>
<td>Thyroiditis</td>
<td>Silicosis of lungs</td>
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<tr>
<td>Cobalt</td>
<td>Component of vitamin B_{12}</td>
<td>-</td>
<td>vitamin B12 deficiency anemia</td>
<td>Cardiomyopathy, heart failure, goiter, hypothyroidism, vomiting and diarrhea</td>
</tr>
<tr>
<td>Boron</td>
<td>calcium, magnesium, vitamin D metabolism</td>
<td>-</td>
<td>Osteoporosis, low estrogen, testosterone levels</td>
<td>-</td>
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<tr>
<td>Germanium</td>
<td>Immuno-stimulant</td>
<td>-</td>
<td>hypertension and heart disease</td>
<td>Greenish tongue, nephrotoxic</td>
</tr>
<tr>
<td>Vanadium</td>
<td>Insulin signal enhancer, lipid metabolism</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Silicon</td>
<td>Bone and connective tissue formation</td>
<td>-</td>
<td>Risk of osteoporosis</td>
<td>-</td>
</tr>
</tbody>
</table>
in causation of hypertension, hypercholesterolemia and heart disease. Dietary sources are garlic, Siberian ginseng, mushroom, and other medicinal plants.

**VANADIUM**

Vanadium has properties as an insulin signal enhancer, which increases translocation of GLUT4 to the cell membrane. Animal studies have shown that vanadium may improve insulin sensitivity, preserve pancreatic cells, and stimulate an insulin-independent phosphorylation mechanism. Vanadium deficiency has not been described in humans. Rarely, vanadium can cause nausea and greenish discoloration of the tongue. Large doses are nephrotoxic.

**SILICON**

Silicon is a constituent of certain glycosaminoglycans and polyuronides and may function as a biological crosslinking agent and thereby contributes to maintenance of architecture and resilience of connective tissue. It also improves bone health, probably by synthesis of collagen and its stabilization, and matrix mineralization. Silicon supplementation reduces absorption of toxic aluminium. Dietary sources include cereals, oat, wheat bran and vegetables. Toxic inhalation of silica causes silicosis of lungs.

**OTHER METALS**

Nickel is needed by certain enzymes used in anaerobic energy production in the cell. Cadmium is nephrotoxic in large doses. Lead and mercury are mostly known for their toxicity. Arsenic can cause acute and chronic toxicity. However, in animals, arsenic deprivation affects growth and reproduction.

**REFERENCES**


