Introduction to medical biochemistry one

lesson objectives.

By the end of the lesson the learner should be able to:

I. define biochemistry
II. state the importance of biochemistry in relation to clinical medicine
III. understand the scope of biochemistry one.
IV. Explain the type of chemical bonds

What is biochemistry?

It is a branch of science that combines the science of matter (chemistry) and the science of living matter (biology) that is bio-chem.

This is a branch of science that deals with the study of the chemical processes in the living body. It mainly deals with studying how chemical reactions and chemical structures give rise to life and its processes. It deals with molecules and cells and how they interact with each other.

The chemical structures studied include carbohydrates, fats, proteins, vitamins, enzymes etc.

Biochemists seek to understand the molecular structures, mechanisms and chemical processes in living organisms.

Importance of biochemistry

Understanding biochemistry is important because it helps clinicians in diagnosing various diseases through the estimation of biomolecules like enzymes, hormones, lipids and proteins in the body. Their levels increase or decrease depending on the condition of the body. This in turn helps to understand the root cause of various diseases and taking the right treatment strategies.

People take a lot of supplements like minerals, vitamins and proteins to improve their health. Proper intake of these is well understood by studying medical biochemistry.

We study biochemistry to gain knowledge of the normal body processes and therefore be in a better position to understand any abnormalities in the body. Our understanding of these would help us diagnose and treat diseases.

It helps us to gain knowledge of drug development, therapies and diagnostic tools.

Helps us to gain knowledge relevant in research of both drugs and diseases

Helps us understand better chemical structures and processes in the body

Help us understand the pathology of various diseases in the body such as diabetes, hypertension etc.

In addition, biochemistry help to explain all diseases in molecular terms.

What do we study in biochemistry?

We study biomolecules and there are about five major classes i.e. carbohydrates, vitamins, proteins, nucleic acids and lipids

Major chemical processes in the body e.g. cell development, enzyme activity, transport mechanisms like nerve transmission etc.

Nutrition and metabolism of minerals and vitamins in the body

Biochemical sequences in the body and how they interact with each other in order for cell to survive under various conditions.

Biochemistry knowledge is required in order to diagnose and treat diseases which is the reason as to why it forms one of the units in clinical medicine

Nature of biomolecules

Most biomolecules are made up of six compounds namely carbon, hydrogen oxygen nitrogen phosphorous and Sulphur. Basically, all organisms have similar biochemical pathways and share the same genetic codes

About 31 chemical elements occur naturally in plants and animals

Chemical bonds

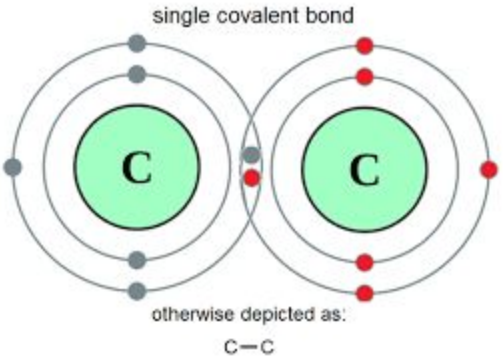
Matter is made up of ions, atoms, molecules elements and compounds.

Discuss the terms as applied in chemistry.

Atoms and molecules are held together in elements and compounds by linkages known as chemical bonds.?

When the atoms combine in chemical reactions, they do so by either gaining or losing electrons to achieve the stability of the noble gases in terms of electron configuration. This is known as the octet-duet rule and ensures that an electron configuration with the right number of electrons is achieved i.e. 2 or 8 electrons on the outermost energy level.

Atoms are held together by single, double or triple bonds. A single bond involves a single shared electron as exists in the hydrogen molecule.



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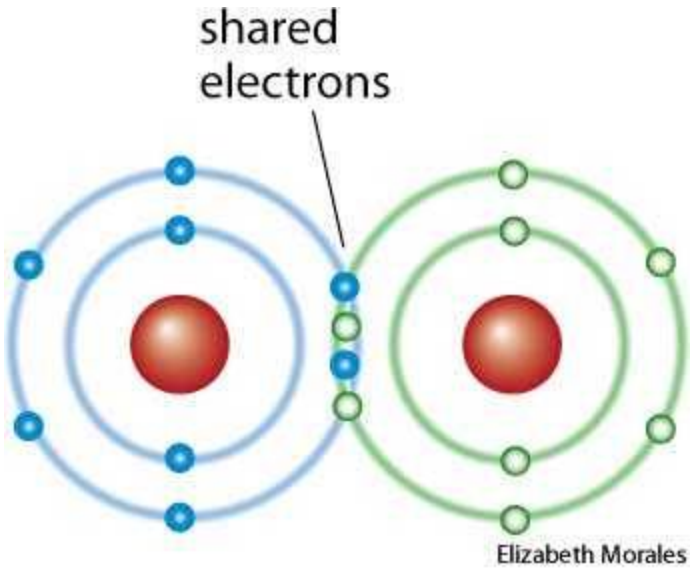
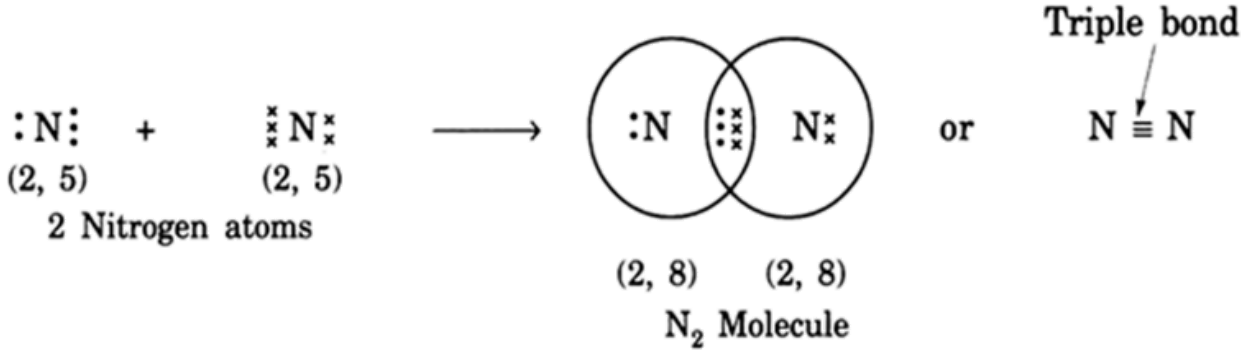
Atoms may similarly be held by a double bond as exists in the oxygen molecule where the oxygen atoms share two electrons in their structure.

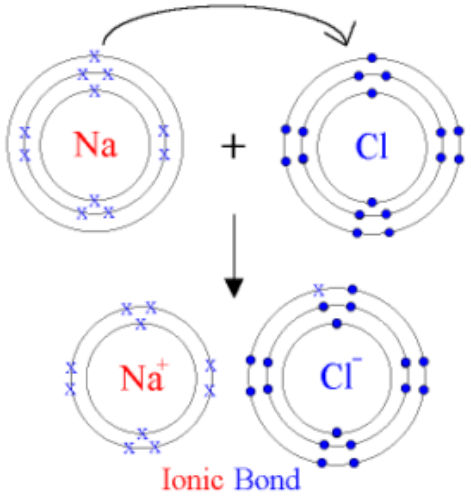


A triple bond is formed when atoms share three electrons as is present in the nitrogen molecule.

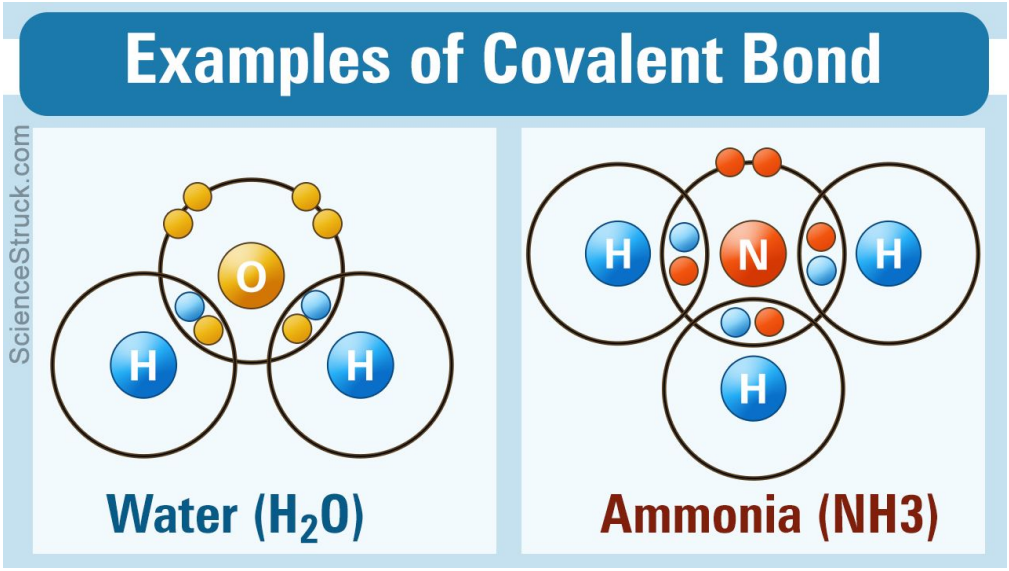


This sharing of electrons is known as **covalent** bonding and occurs in nonmetals. In this type of bond none of the elements wants to lose or gain any electron and therefore they share the electrons. Each pair of the shared electron constitute one chemical bond

Ionic bonds are formed when there is transfer of electrons between metals to non-metals. This is the case between sodium and chlorine in sodium chloride (common salt).



Polar bond if formed when there is **unequal** sharing of electrons. In this bond the electrons are not shared equally. This is the bond that exists in the water molecule. In a polar bond, one of the atoms is held closer than the other because of the unequal sharing of electrons.



Electronegativity is the ability of an atom in a molecule to attract electrons to itself. Polar bonds have atoms that have differences in electronegativity.

The electrons that have participated in the formation of the bond are known as **bonding electrons**.

The electrons that have not been shared or transferred are known as the **non-bonding** electrons.

It is important to note that the strength of the bond increases with the number of bonding electrons as the atoms are held much stronger together.

Biochemical basis of life

Water being a polar molecule is able to form hydrogen bonds which has led to its many properties. This has made water a solvent that is able to dissolve both ionic and polar molecules.

Carbon on the other hand has the ability to bond with many elements such as hydrogen, oxygen, sulfur and nitrogen to form molecules of life al so known as macromolecules. The function of these macromolecules depends on their chemical structure.

Carbohydrates is the main source of energy for both plants and animals but is also a structural component.

Lipids on their part are used as a form of stored energy and important in formation of membranes.

Nucleic acids are the carriers of genetic information.

Proteins have several functions including regulation of cell processes, building body tissues, transportation of substances in the body as well as fighting diseases in the body.

The chemical reactions involve changes in the bonds within the molecules and is usually accompanied with both gain and loss of energy.

Enzymes speed up the rate at which the reactions are taking place in the body without them being used up in the reactions they catalyze. Its good to note that rate of enzyme activities is affected by the temperature, PH. and some regulatory molecules.

Review questions

1. Explain the role of biochemistry in clinical medicine
2. Explain the what is meant by chemical bonds and discuss three types of chemical bonds
3. Discuss the polar bond in a water molecule and explain why water is regarded as a universal solvent
4. Explain what is meant by electronegativity in relation to a water molecule

2. DISCUSS THE REGULATION OF WATER INTAKE IN THE BODY.

Fluid can enter the body as performed water, ingested food and drink, as metatabolic water that is produced as a by-product of aerobic respiration and dehydration synthesis.

Body water homeostasis is regulated mainly through ingested fluids, which, in turn, depends on thirst.

Thirst is the basic urge that drives an organism to ingest water. This sensation is created by the hypothalamus which is the thirst center of the human body.

An osmoreceptor is sensory receptors that detects changes in osmotic pressure and is primarily found in the hypothalamus of most homoeothermic organisms.Osmoreceptors detect changes in plasma osmolarity.

When the osmoreceptors detect high plasma osmolarity, they send signals to the hypothalamus, which creates the biological sensation of thirst.Osmoreceptors also stimulate vasopressin hormone secretion, which starts the events that will reduce plasma osmolarity to normal levels

Thirst can be induced through the hormone angiotensin involved in the rennin-angiostensin system. The system is a complex homeostatic pathway that deals with blood volume as well as plasma osmolarity and blood pressure.

The osmoreceptors on the walls of the ascending loop of henle,the macula densa cells,stimulates the juxtaglomerular apparatus instead of the hypothalamus. When the macula densa cells are stimulated by high osmolarity, the juxtaglomerular releases rennin into the blood stream hence causing an action on the hypothalamus to cause the sensation of thirst.

MOSES NZAI KATANA,D/CM/20010/2080,MOMBASA CAMPUS.

3.EXPLAIN WHAT IS MEANT BY OSMOLALITY.

Osmolality is an estimation of the osmolar concentration of plasma and is proportional to the number of particles per kilogram of solvent.Osmolality is mostly found in fluids from cells including the Extracellular fluids and the Intracellular fluids of the cell.plasma osmolality acts as a guide to the intracellular osmolality.

The normal osmolality of the extracellular fluid is 280 to 295mOsmol/kg.

4.GIVE THE DIFFERENCES BETWEEN OSMOLALITY AND OSMOLARITY.

1.Osmolarity deals with the concentration of an osmotic solution,while Osmolality deals with the concentration of particles in a fluid.

2.Its easier to determine osmolality than osmolarity.

3.Osmolality is used to determine medical conditions like diabetes,shock and dehydration,while osmolarity is used for the detection of the concentration of dissolved particles in urine.

4.Osmolarityis expressed as osm/L while osmolality is expressed as osm/kg.

5.Osmolality is the number of osmoles of solute in a kilogram of a solvent whereas Osmolarity is the number of osmolesof solute in a litre of a solution.

MINERAL METABOLISM

Macroelements are elements needed at high concentrations. Example, Sodium, Potassium, Calcium, Magnesium and Chloride.

Sodium and Potassium: They are important in cell physiology, muscle physiology, transmission of messages and other biological processes.

Sodium is the principal cation of extra cellular fluid. It is commonly found in all types of foods. Recommended dietary allowance (RDA) is 5-10 gm. It is excreted in the urine. The concentrations are maintained by Aldosterone hormone.

Serum Sodium normal levels 135-145 Mmol/l

Potassium is intracellular cation; daily requirement is 1 gm/day. Its excretion is through kidney, linked to sodium excretion.

Since both are widely distributed, deficiency of the two elements is rarely found.

Functions:

• Sodium maintains osmotic pressure of extra cellular fluid (ECF) balance.

• supports the neuro muscular excitability

• Sodium is exchanged with Hydrogen in renal tubules to acidify urine.

• Sodium pump keeps sodium in far higher concentration outside the cell.

• Sodium and Potassium maintain the degree of hydration of plasma proteins, and there by viscosity of blood.

• Potassium is critically important for the functioning of cardiac muscle.

Hypernatremia: It occurs nearly always due to water deficiencies rather than Na+ excess. Increased sodium is found in ECF. It may be due to increased sodium in the body, decreased body water. It is usually seen in patients with dehydration, on steroid therapy or excess sodium intake.

Hyponatremia: It is common in patients who are in diuretics or excessive sweating, kidney disease, diarrhea and congestive heart failure.

Hyperkalemia is found in patients who are on excess intake orally or given intravenous drip. Other causes are decreased excretion by the kidney, diseases like Anuria, tissue damage or Diabetes Mellitus.

Hypokalemia: Low potassium is not due to dietary deficiency but due to conditions like vomiting, diarrhea. Habitual users of laxatives are prone to the condition.

Calcium and Phosphate: Major parts (90%) of them are found in the form of crystal lattice in the bone. The rest is found in the soft tissues, teeth and ECF.

Sources: Milk, milk products, green leafy vegetables are rich in calcium.

Phosphate is widely distributed in nature.

Calcium: RDA 500mg for adults and 1200mg for children, 1500mg for post-menopausal women. People, who get enough sunlight, exercise regularly, on high protein diet, require 300-400mgs per day.

Absorption: It is influenced by

• Acidic pH solubilizes Calcium salts, promote absorption.

• High protein diet favors absorption

• Certain plant products, high fiber diet, oxalates interfere with absorption.

• Vitamin D promotes absorption.

• PTH, Calcitonin favors absorption while Glucocorticoids decrease intestinal transport.

• Normal blood concentration is maintained at 9-11 mg %.

Functions:

• Calcification of bones and teeth. Bone formation requires Calcium continuously.

• It is important for blood coagulation

• Neuromuscular transmission.

• Muscle contraction

• Acts as secondary messenger in hormone action.

Clinical conditions: Hyper- calcemia; may be due to hyper parathyroidism, endocrine causes, renal failure and malignancies.

Hypo- calcemia (below 8.5mg %) due to

• Inadequate dietary intake.

• Hypoalbuminemia

• Hypo parathyroidism

• Renal disease/ failure

• Vitamin D deficiency

Chronic deficiency leads to loss of bone mass (bone resorption) and osteoporosis, bone fractures

Phosphorus:

Dietary sources are cheese, milk, nuts. Eggs and organ meats.

Absorption and regulation is similar to that of Calcium.

Functions

• Constituent of bone and teeth

• Needed for the synthesis of energy rich molecules like ATP and Creatine phosphate.

• It forms Phosphate buffer in blood.

• Constituent of phospholipids, biomolecules and coenzymes.

Trace elements

Daily requirements of some elements is very low and such elements are known as trace elements.

Iron

Iron In body is found in Haemoglobin, Myoglobin, ferritin, hemosiderin, transferrin and enzymes like cytochromes etc.

Sources are meat, fish, eggs, cereals like wheat, green leafy vegetables.

Absorption is through intestinal mucosa.

Requires acidic pH of stomach. Ascorbic acid and Ceruloplasmin promotes absorption.

It combines with intracellular binding protein Apoferritin to form ferritin. Almost 300 ferric ions can bind to one molecule of apoferritin..

For transport, free iron binds to Apo transferrin, in blood to form **transferrin**. It is the major transport form of iron. It also prevents toxicity of free iron.

Excessive binding of iron causes denaturation of ferritin molecule. It undergoes aggregation, to form hemosiderin. Mobilization of iron from hemosiderin is very slow. Thus there is accumulation of hemosiderin and the condition is called **hemosiderosis**.

Massive deposits of hemosiderin in tissues lead to **hemachromatosis**. If this takes place in liver, it causes cirrhosis. In pancreas, it damages β cells, result in Bronze diabetes. The skin of the patient has bronze coloration. Oxidative damage to cardiac muscle is a biggest concern.

Iron is stored in liver, spleen and bone marrow.

Deficiency.

Deficiency leads to Iron deficiency anaemia which is a type of hypochromic microcytic anaemia. It is associated with low hemoglobin and low ferritin levels.

Copper

Human beings contain around 100 mgs of copper. Liver, brain, kidney and heart are rich in copper. Free copper is 4%, 96 % is bound to Ceruloplasmin in body.

Sources: cereals, legumes, raisins, nuts etc

Functions:

• Cofactor of enzymes like cytochrome oxidase, dopamine decarboxylase, tyrosinase, Cytochrome .C oxidase and superoxide dismutase and monoamine oxidases are dependent on copper. Tyrosine oxidase is important for collagen metabolism

Copper deficiency:

• Failure of melanin formation because tyrosine oxidase becomes inactive.

Menke's disease or **Kinky** hair syndrome: It is a fatal sex linked recessive disorder in which there is cerebral and cerebellar degeneration, connective tissue abnormalities and kinky hair.

• Both serum [Copper] and [Ceruloplasmin] is low.

• Absorption of copper from the intestine is grossly impaired, but treatment with parenteral copper has not proved successful.

• It is X- linked disorder. Patient has normal absorption of copper but transport across the serosal aspect of mucosal membrane is defective. Patient suffers from mental retardation.

Wilson's disease: It is an Autosomal, recessive disorder. There is a decrease in the biliary excretion of copper. Blood and tissue copper is high in these patients. It leads to retention of copper, followed by hepato-lenticular degeneration. Ceruloplasmin synthesis is incomplete in the liver. Patient suffers from progressive hepatic cirrhosis and finally liver failure.

There is dysfunction of lenticular region of brain

Defective tubular reabsorption in kidney leads to aminoacidurias.

Copper deposition in the eye, as golden brown or green ring around the cornea.

Patients are treated with Pencillamine, which binds to tissue copper and mobilizes it.

Magnesium:

It is an intracellular ion, essential for life.

Sources: Widely distributed in vegetables, chlorophyll, cereals, beans, potatoes, cheese and animal tissues.

Maximum concentration is found in bones, little in Extra-cellular fluid (ECF) and soft tissues.

2/3 of magnesium in blood is in ionic form, rest is bound to protein.

It is absorbed from the small bowel.

It is excreted through feaces, urine and sweat.

Functions:

• Role in enzyme action. It is a cofactor for peptidases, ribonucleases, glycolytic enzymes etc.

• Its action is similar to that of calcium in neuromuscular irritability.

• High levels depress nerve conduction, low levels may cause Tetany.

• Major part is found in bones. In teeth, it is present as dentin and enamel.

• Magnesium deficiency occurs rarely in man.

Fluorine

It is solely derived from water, tea, and fish. Daily intake should not be more than 3mg. Excess is toxic, lethal dose is 2.5 gm. It is absorbed by diffusion from intestine. Mostly it is found in the bones and teeth. It is eliminated in the urine.

Functions:

• Fluorine is important for teeth development and prevention of Dental Caries.

• High consumption, leads to high concentration of Fluorine in enamel and dentine.

• It decreases calcium deposition.

• Teeth acquires mottling of enamel, teeth develop pits and discoloration.

• Bones contain traces of fluorine. Small quantities of it promotes bone development, increases retention of calcium and phosphate, prevent osteoporosis

• High level of fluoride in bone causes abnormal rise in calcium deposition, increases bone density Flurosis is due to toxicity of fluoride. Excess can be due to high dietary intake, contaminated water or inhalation of fluorine.

• It damages mitochondria

• Inhibit enzymes which depend on Mg, like Succinic dehydrogenase.

• Protein synthesis decreases in muscle, heart, kidney, lungs, pancreas and spleen.

• Collagen synthesis is adversely affected.

Iodine

Sources: Vegetables, fruits obtained from sea shore, sea fish are rich in iodine. It is absorbed from small intestines and transported as protein complex in plasma.

Deficiency causes goiter

Zinc

Sources are liver, milk, fish, dairy products, cereals, legumes, pulses, oil seeds, yeast and spinach etc.

It is absorbed in duodenum and ileum.

Absorption of Zinc from the intestine appear to be controlled in a manner similar to Iron. It is transported bound to a protein (α2-macroglobulin and transferrin)

It is excreted in urine and feaces.

Diets rich in calcium, phosphates interfere with Zn absorption.

RDA is 15-20mgs for adult, 3-15mgs for infants and children

It is bound as complex of protein Metallothionein. The sulfur groups of the protein chelate zinc.

The body does not store Zinc to any appreciable extent in any organ, urinary excretion is fairly constant at 10 μmol/day.

Functions:

• Zinc is important for the activity of a number of enzymes like

Carbonic anhydrase, Alkaline phosphatase, Alcohol dehydrogenase Porphobilinogn synthase Leucine aminopeptidase, Carboxy peptidase, Aldolase in glycolysis DNA, RNA polymerases as zinc has crucial role in DNA.

• Release of vitamin A from liver requires Zinc. Retenene reductase (zinc enzyme) participates in the regeneration of rhodopsin (visual cycle).

• Insulin is secreted, stored as a complex of Zinc

• It is important for wound healing.

Deficiency of Zinc: Patients requiring total parenteral nutrition, pregnancy, lactation, old age and alcoholics have been reported as being associated with increased incidence of Zinc deficiency.

It is usually associated with protein energy malnutrition (PEM)

It is caused by diuretics, chelating agents and anti-cancer drug treatment

• Results in dwarfism and hypogonadism

• Delayed sexual development

• It decreases spermatogenesis in males and irregular menstrual cycles in females.

• It stimulates ribonuclease activity; thereby it affects the synthesis of mononucleotides and nucleic acids.

• Hepatosplenomegaly

• Severe Zinc deficiency can lead to a postular skin rash, loss of body hair, diarrhea and mood change.

Selenium

Selenium is rich in liver, kidney, finger nails. Usually plant products are good sources than animal based diet.

It is absorbed from duodenum, transported as selenomethionine. It forms a complex with plasma proteins for transport. In tissues, free selenium is released.

It is excreted in urine.

Functions:

• Glutathione peroxidase is a selenium dependent enzyme. The enzyme has a role in oxidative damage by free radicals. The enzyme is critically important for the membrane stability of Red blood cells.

• Selenium has sparing action on vitamin E, by three ways. It promotes digestion, absorption of lipids and vitamin E. It is a part of glutathione peroxidase, prevents peroxidation of PUFA in the membranes. This in turn reduces the requirement of vitamin E. It helps in the retention of vitamin E in the blood.

• It is a cofactor for an enzyme involved in the synthesis of thyroid hormone.

Deficiency of selenium:

• Liver cirrhosis

• Pancreatic degeneration

• Myopathy, infertility

• Failure of growth

Toxicity: - Selenium toxicity is called Selenosis -Toxic dose is 900micro gram/day - It is present in metal polishes and anti-rust compounds

- The Toxicity symptoms are Hair loss, falling of nails, diarrhea, weight loss and gas leaky odor in breath (due to the presence of dimethyl selenide in expired air).

Halogenated aromatic hydrocarbons are useful in the treatment of Selenosis.

MINERALS (MACROELEMENTS)

Macroelement	Role	Source	Deficiency
Phosphorus	Composition of bones and teeth, maintenance of normal blood acidity	Meats, fish, milk, grains, eggs, nuts, seeds, legumes	Bone demineralization, problems with sensitivity (tingling, stinging), cardiac, respiratory, and neurological problems
Potassium	Metabolism, blood pressure regulation, nerve conduction, muscular contraction	Vegetables, fruit, dairy products, legumes	Neuromuscular and cardiac problems, confusion
Calcium	Composition of bones, muscular contraction, nerve conduction, blood clotting	Dairy products, canned fish, leafy vegetables	Tetanus, neurological problems, osteoporosis
Magnesium	Metabolism, muscular contraction, blood clotting, health of bones and teeth	Whole grains, legumes, nuts, artichokes	Depression, confusion, cramps, numbness, cardiac problems, loss of appetite, tetanus
Sodium	Composition of fluids (plasma, tears, sweat), nerve conduction	Table salt, soy sauce	Digestive and neurological problems, muscle cramps
Chlorine	Composition of gastric juice	Salt	Digestive problems, muscle cramps, apathy
Sulfur	Metabolism, immune system, composition of bones and teeth	Grains, milk, eggs, legumes	Metabolism problems, vulnerability to infections

Table 1 Functions of Trace Elements and Symptoms of Their Deficiency and Excess States

Trace element	Enzymes containing the elements and active forms	Physiological functions	Symptoms of deficiency state	Symptoms of excess state
Zinc	Carbonic anhydrase Peptidase Alcohol dehydrogenase Alkaline phosphatase Polymerase Zinc finger etc.	Protein metabolism Lipid metabolism Carbohydrate metabolism Bone metabolism	Major symptoms: Gradually exacerbating eruptions, first affecting the face and perineum Associated symptoms: Stomatitis, glossitis, alopecia, nail changes, abdominal symptoms (diarrhea, vomiting), fever Delayed wound healing, dwarfism Growth retardation, negative N balance, Immunosuppression, Mental symptoms (depression), Taste disorder, anorexia	Acute: Relative Fe-Cu deficiency, nausea, vomiting, abdominal pain, melena, hyperamylasemia, somnolence, hypotension, lung edema, diarrhea, jaundice, oliguria Chronic: Reduced reproductive function, dwarfism, taste disorder, hyposmia, anemia
Copper	Ceruloplasmin Monoamine oxidase Cytochrome oxidase Ascorbic acid oxidase Dopamine β-hydroxylase Superoxide dismutase etc.	Hemopoiesis Bone metabolism Connective tissue metabolism	Anemia Leukopenia Neutropenia Disturbed maturation of myeloleukocytes Bone changes (children): Reduced osseous age, irregular/spurring metaphysis, bone radiolucency, bone cortex thinning	Nausea, vomiting, heartburn, diarrhea, jaundice, hemoglobinuria, hematuria, oliguria, anuria, hypotension, coma, melena
Chromium	Glucose tolerance factor	Carbohydrate metabolism Cholesterol metabolism Connective tissue metabolism Protein metabolism	Abnormal glucose tolerance Reduced respiratory quotient Weight loss Peripheral neuropathy Increased serum free fatty acids Abnormal nitrogen balance Metabolic consciousness disturbance	Nausea, vomiting, peptic ulcer, CNS disorder, Liver/kidney dysfunction, growth retardation
Selenium	Glutathione peroxidase (GSH-Px) 5′-deiodinase (type I) Various selenoproteins	Antioxidant action T4→T3 conversion Reduced carcinogenicity action	Myalgia (lower extremities) Cardiomyopathy (myocardial cell collapse, fibrosis) Nail bed whitening	Selenosis (alopecia, nail detachment, CNS disorder)
Manganese	Arginase Pyruvate carboxylase Superoxide dismutase Glycosyltransferase	Bone metabolism Carbohydrate metabolism Lipid metabolism Reproduction Immunity	Reduced serum cholesterol Reduced coagulation Hair reddening Dermatitis (miliaria crystallina) Growth retardation Increased radiolucency at the epiphyses of long bones	Parkinsonian syndrome Early chronic: Impotence, loss of vigor, somnolence, anorexia, edema, myalgia, headache, excitation, fatigue Advanced stage: Extrapyramidal disorder
Molybdenum	Xanthine oxidase Xanthine dehydrogenase Aldehyde oxidase Nitrous acid oxidase	Amino acid metabolism Uric acid metabolism Sulfuric acid/sulfurous acid metabolism	Tachycardia Polypnea Night blindness Scotoma Irritability Somnolence Disorientation Coma	Hyperuricemia, gout
Cobalt	Vitamin B_{12}	Hemopoiesis	Pernicious anemia Methylmalonic acidemia	Cobalt poisoning
Iodine	Thyroid hormone	Tissue metabolism	Goiter, hypothyroidism	Goiter, hypothyroidism

(Summary of many reports)

Table 3 Daily Dietary Requirements of Trace Elements in Adult Japanese Males (body weight: 50kg)

Trace element	Mean daily intake	"No adverse effects" level (NOAEL)	"Lowest adverse effect" level (LOAEL)	Effective replenishment/ pharmacological dose	Recommended dietary allowance (RDA)	Reference dose (RfD)	RfD/ RDA
Zinc	7~11mg	30mg*	600mg	~200mg (immune functions, etc.)	9.6mg	30mg	3
Copper	1~4mg	9mg*	10mg	—	1.8mg	9mg	5
Chromium (III)	28~62μg	1,000μg*	—	150~1,000μg (diabetes mellitus, etc.)	35μg	250μg	7
Selenium	41~168μg	400μg	750μg*	~200μg (cancer prevention, etc.)	55μg	250μg	4.5
Manganese	3~4mg	10mg*	—	—	4mg	10mg	2.5
Molybdenum	135~215μg	350μg	7mg*	—	30μg	250μg	8
Iodine	200~30,000μg	3,000μg*	23,000μg	—	150μg	3,000μg	20
Arsenic	10~34μg	40μg*	700μg	—	10–34μg	140μg	4

*Basis for calculation of RfD
• The mean daily intake is approximately equal to the RDA.
• RfD/RDA indicates the safety margin between daily requirements and toxic levels, and is not very large.
(Quoted from Wada, O.: Usefulness and safety of trace chemicals. *Proceedings of Trace Nutrients Research* 2001; 18: 1–10.)