Calcium

- Calcium is the most abundant mineral in the human body (1.0 to 1.5 kg).

- About 99% of the total body calcium (calcium phosphate) is present in bones and teeth as insoluble and crystalline hydroxyapatite.

- The remaining 1% of the total body calcium is distributed in soft tissues, extracellular fluid and blood.

- The normal plasma total calcium level ranges from 9.0 to 11.0 mg/dL and exists in three forms namely

a) Ionised or diffusible calcium (physiologically active form in blood). Normal level of ionized calcium in plasma is 4.5 to 5.5 mg/dL.

b) Protein bound calcium (bound to plasma proteins like albumin).

c) Complexed calcium (as complex with organic acids like citrate or phosphate).

Dietary Sources of Calcium

- Milk and milk products, sea foods, eggs etc are good sources.

- Cereals, pulses, nuts, beans and leafy vegetables are other sources.

Recommended Daily Allowance (RDA)

Infants – 400 mg/day

Children – 1000 mg/day

Adults – 800 mg/day

Pregnancy and Lactation – 1200 mg/day

Absorption

Absorbed in duodenum and jejunum of small intestine through calbindin protein.

Factors Increasing Intestinal Absorption of Calcium

Lactose in diet, acidic foods, acidic pH, organic acids, vitamin D (calcitriol), parathyroid hormone (PTH), protein rich diet, lactation and pregnancy, growth hormone, ratio of calcium and phosphate (between 1:2 and 2:1).

Factors Decreasing the Intestinal Absorption of Calcium

Phytic acid in cereals, oxalates in green leafy vegetables, high fibre diet, increase in age, dietary phosphates and magnesium, fat rich diet and glucocorticoids.

Functions

1) In bones and teeth development

Along with phosphate, calcium is required for mineralization (hydroxyapatite crystals) of bones and teeth.

2) In blood coagulation

Calcium is known as factor IV in blood coagulation cascade and is involved in thrombin formation.

3) In muscle contraction

Calcium is required for excitation and contraction of smooth, skeletal and cardiac muscles.

4) In nerve conduction

Calcium is necessary for transmission of nerve impulses from pre-synaptic to post-synaptic region.

5) In generation of pacemaker potential

Calcium is required for generation of pacemaker potential in sinu-auricular node of heart. The pacemaker potential initiates the heart beat.

6) In secretion of hormones

Calcium mediates the secretion of insulin, parathyroid hormone, calcitonin, vasopressin etc.

7) For activation of enzymes

Certain enzymes like succinate dehydrogenase, pyruvate dehydrogenase, ATPase, protease, phospholipase etc are activated by calcium.

8) In vascular permeability

Calcium is required for the maintenance of membrane permeability and vascular permeability. It decreases the passage of serum through capillaries.

9) As second messenger

Calcium serves as second messenger for hormones like oxytocin, epinephrine etc.

10) Calcium is required for formation of milk in lactating mothers.

11) Calcium is required for secretion of saliva.

Regulation of Blood Calcium Level (Calcium Homeostasis)

Blood calcium level is regulated by factors like parathyroid hormone (PTH), calcitriol and calcitonin.

a) Parathyroid hormone (PTH) and calcitriol (During hypocalcemia)

- During hypocalcemia, the low level of calcium in blood stimulates the release of PTH (a protein hormone) from parathyroid glands.

- PTH increases the mobilization of calcium and phosphate from bones (bone resorption) by stimulating osteoclast activity.

- In kidney, PTH increases renal tubular reabsorption of calcium while decreasing renal excretion of it.

- In kidney, PTH also enhances the formation of calcitriol (active form of vitamin D) by activating the enzyme 25 hydroxy cholecalciferol-1-hydroxylase.

- Calcitriol increases the calcium level in blood by

1) Stimulating the absorption of calcium (and also phosphate) from intestine by inducing the synthesis of calbindin protein.

2) Stimulating the mobilization of calcium (and also phosphate) from bones (bone resorption).

3) Stimulating the renal tubular reabsorption of calcium (and also phosphate).

Thus PTH and calcitriol elevate blood level of calcium towards normal.

b) Calcitonin (During hypercalcemia)

- During hypercalcemia, the high level of calcium in blood stimulates the release of calcitonin (a protein hormone) from C-cells of thyroid gland.

- Calcitonin decreases the blood calcium level by increasing the deposition of calcium in bones (by stimulating osteoblast activity) and decreasing the mobilization of calcium from bones (by inhibiting osteoclast activity).

- Calcitonin also increases the urinary excretion of calcium.

- Thus calcitonin lowers the blood level of calcium towards normal.

- PTH and calcitonin have antagonistic actions on blood calcium level.

Deficiency Manifestations

Nutritional deficiency of vitamin D, chronic dietary deficiency of calcium or phosphate or both, calcium malabsorption, renal dysfunction, liver dysfunction and mild hypoparathyroidism cause calcium deficiency.

Deficiency diseases

1) Rickets – Characterised by incomplete mineralization of growing bones in children.

2) Osteomalacia – Characterised by demineralization of preformed bones in adults.

3) Tetany – A severe fall in plasma calcium level (<7.5 mg/dL) causes tetany.

- Is characterized by neuromuscular hyperexcitability and convulsions.

4) Blood clotting disorder

- A severe fall in plasma calcium level increases blood clotting time.

5) Osteoporosis

- Is indicated by progressive loss of bone density due to loss of organic matrix and demineralization of bone.

- Is characterized by frequent bone fractures.

- Is of two types namely-

a) Primary osteoporosis and b) Secondary osteoporosis.

Hypercalcemia

- Hyperparathyroidism, hypervitaminosis D, thyrotoxicosis etc cause hypercalcemia (12 to 20 mg/dL in blood).

- The clinical features of hypercalcemia are appetite loss, nausea, vomiting, weakness of muscles, deposition of calcium in kidney, arteries, cornea and bronchi.

- Cardiac arrhythmia, lethargy, confusion, depression and mental slowness are other clinical features.

Phosphorus

- Phosphorus is the second most abundant mineral in human body (0.7 to 1 kg phosphorus).

- About 80% of the total body phosphorus is present in bones and teeth (calcium phosphate) as insoluble and crystalline hydroxyapatite.

- The remaining 20% of the total body phosphorus is distributed in soft tissues, extracellular fluid and blood.

- The normal plasma inorganic phosphate concentration ranges from 3.0 to 4.5 mg/dL and exists in three forms namely-

a) Free inorganic phosphate

b) Protein bound phosphate

c) Phosphate complexed with cations such as Na^{2+}, Ca^{2+}, K^{+} etc.

Dietary Sources of Phosphorus

- Milk and milk products (casein is a phosphoprotein), meat, eggs etc are good sources of phosphorus.
- Cereals, pulses, nuts and leafy vegetables are other sources.

Recommended Daily Allowance (RDA)

- Infants: 400 mg/day
- Children: 1000 mg/day
- Adults: 800 mg/day

Absorption

- Dietary phosphorus (only inorganic phosphate) is absorbed in the jejunum of small intestine.

Factors Increasing the Intestinal Absorption of Phosphorus

- Calcitriol (active form of vitamin D), ratio of dietary calcium and phosphate (between 1:2 and 2:1) and parathyroid hormone.

Functions

1) Along with calcium, phosphate is required for mineralization (hydroxyapatite crystals) of bones and teeth.

2) It is required for synthesis of phospholipids, an important constituent of membrane lipids.

3) It is required for formation of various bio-organic substances like nucleic acids (DNA & RNA), co-enzymes (NAD^+, $NADP^+$, FAD, FMN, TPP, pyridoxal phosphate etc), nucleotides (UDP, CDP, AMP, ADP, GDP etc) and second messengers (cAMP and cGMP etc).

4) It is required for the production of high energy phosphates like ATP and creatine phosphate.

5) It is required in carbohydrate metabolism (like in formation of intermediates like glucose-6-phosphate).

6) It is required for the formation of phosphoproteins like casein.

7) It is required for activation and inactivation of enzymes. Eg: Pyruvate dehydrogenase.

8) Phosphate is a constituent of phosphate buffer, an important buffer system in blood.

Regulation of Blood Phosphorus Level (Phosphorus Homeostasis)

- PTH and calcitriol act together to regulate the blood phosphorus level under hypophosphatemic state.

a) Calcitriol

- In hypophosphatemia, low blood phosphate level enhances the formation of calcitriol from calcidiol by activating the enzyme 25 hydroxycholecalciferol-1-hydroxylase.

- Calcitriol increases blood phosphate level by-

1) Stimulating the absorption of phosphate (and calcium) from small intestine.

2) Stimulating the absorption of phosphate (and calcium) from bones (bone resorption).

3) Stimulating the renal tubular reabsorption of phosphate (and calcium).

- Thus calcitriol elevate the blood level of phosphorus (and calcium) towards normal.

b) Parathyroid hormone (PTH)

- PTH enhances the renal excretion of phosphate though it stimulates the renal tubular reabsorption of calcium.

- Therefore, hypersecretion of PTH produces hypercalcemia and hypophosphatemia.

- Hyposecretion of PTH produces hypocalcemia and hyperphosphatemia.

- Thus an inverse relationship exists between concentrations of calcium and phosphate in relation to PTH.

Excretion

Phosphate is excreted in urine and feces.

Phosphate Deficiency

- Hyperparathyroidism and vitamin D deficiency cause phosphate deficiency.
- Symptom of phosphate deficiency is defective mineralization of bones and teeth.

Hyperphosphatemia

- Hypoparathyroidism, severe renal failure, diabetes mellitus etc cause hyperphosphatemia.
- Retention of phosphate causes acidosis.

Fluorine (F_2)

- Fluorine is a trace element present mostly in bones and teeth.

- The concentration of fluoride (F^-) in serum is 4 μg/dL.

Sources

- Drinking water (with a fluoride concentration of 1 PPM), tea, sea fish, cheese, jowar and fluoride rich tooth paste.

Recommended Daily Allowance (RDA)

- 2 mg/day

Absorption and Excretion of Fluoride (F^-)

- Completely absorbed in small intestine.

- Mainly excreted in urine and to some extent in sweat.

Functions

- Fluoride is essential for the normal development of bones and teeth.

- In oral cavity, lactic acid is produced by anaerobic bacteria (Streptococcus mutans) by fermenting carbohydrate containing food debris adhered to teeth.

- The lactic acid reduces the pH around the teeth and causes dental caries by degrading enamel and dentine.

- Fluoride, by inhibiting enolase enzyme of glycolysis, prevents lactic acid formation. Thus fluoride prevents dental caries by inhibiting glycolysis process in anaerobic bacteria.

- Fluoride is incorporated into hydroxyapatite of dental enamel to form fluoroapatite. Fluoroapatite hardens the dental enamel and makes it acid resistant and so protects the teeth from dental caries.

- Fluoride promotes the normal development of bones by retaining calcium and phosphate as fluoroapatite which is resistant to resorption. Fluoride, along with calcium and vitamin D, is used in prevention and treatment of osteoporosis in elderly people.

Deficiency Symptoms

- Dental caries and tooth decay are found to increase in children in areas where the fluoride concentration is less than 0.5 PPM in drinking water.

Fluoride Toxicity (Fluorosis)

- Excess intake of fluoride produces fluoride toxicity which includes dental fluorosis and skeletal fluorosis.

- The normal fluoride concentration level in blood is 4 μg/dL. In fluorosis, it may go upto 50 μg/dL.

- The safety line of fluoride concentration in drinking water is about 1 PPM.

- Fluoride level more than 2 PPM leads to loss of weight, gastroenteritis and loss of appetite.

- Fluoride level more than 5 PPM leads to mottled enamel, discolouration of teeth and striations in enamel.

- Fluoride level more than 20 PPM leads to osteoporosis and brittle bone.

Dental Fluorosis

- Excess intake of fluoride (3 to 5 PPM) causes dental fluorosis in children.

- Characterised by mottled enamel and discolouration of teeth.

- Chalky white patches with yellow or brown stains develop over the surface of teeth.

- Incisors, lateral incisors and molars of permanent dentition are affected.

Skeletal Fluorosis

- Excess intake of fluoride more then 8 PPM causes skeletal fluorosis.

- Characterised by hypercalcification of bones of spine, pelvis and limb.

- Calcification of ligaments and tendons of spine and bone joints occurs.

- At advanced stage, individuals cannot perform their normal daily routine work due to stiff joints and crippled nature *(Genu valgum)*.

Non-Skeletal Fluorosis

- Soft tissues like skeletal muscle, erythrocytes, gastrointestinal mucosa, ligaments, spermatozoa etc are damaged.

Management of Fluorosis

- Should avoid fluoride rich food items like cheese, jowar, sea fish, tea etc.

- Should avoid fluoridated tooth paste.

- Should consume antioxidants like vitamin C and vitamin A.

- Should consume fluoride free water.

Iron

- Adult human body contains 3 to 5 g of iron.

- About 70% of the total body iron is present in RBCs (as component of heme in hemoglobin).

- The plasma iron concentration ranges from 60 to 170 μg/dL.

- Iron exists in two forms namely-

1) Physiologically active form - Part of hemoglobin, myoglobin, heme-enzymes, non-heme iron containing enzymes etc.

2) Storage form - It exists in storage proteins like ferritin and hemosiderin.

Food Sources

- Animal foods like liver, heart, bone marrow, muscles, spleen, beef etc are rich sources of heme iron.

- Plant foods like cereals, pulses, green leafy vegetables, banana, jaggery, nuts etc are other sources of non-heme iron.

Recommended Daily Allowance (RDA)

Children - 15 mg/day

Adult Males - 10 mg/day

Adult Females - 20 mg/day

Pregnancy and Lactation - 40 mg/day

Mechanism of Iron Absorption and Transport

- Iron in ferrous (Fe^{2+}) state can only be absorbed in duodenum and jejunum of small intestine.

- So heme iron or ferrous (Fe^{2+}), which is obtained from animal origin foods, is efficiently absorbed in the small intestine.

- Non-heme iron or ferric (Fe^{3+}), which is obtained from plant origin foods, is liberated from non-heme proteins and organic acids by the action of gastric HCl. Reducing substances (vitamin C, glutathione, cysteine etc) reduce iron from its ferric (Fe^{3+}) state to ferrous (Fe^{2+}) state in intestinal lumen.

- Ferrous (Fe^{2+}) is absorbed by intestinal mucosal cells through an energy dependent process. The mucosal cell protein named DMT-1 binds to ferrous and transports it into the mucosal cell. The unabsorbed ferrous in the intestinal lumen is excreted.

- In mucosal cells, ferrous is oxidized to ferric by the enzyme ferroxidase and binds to apoferritin (a glycoprotein) to form ferritin (a temporary storage form of iron).

- Apoferritin has a very rapid turn over. It is synthesized and degraded in intestinal mucosal cells according to the body need for iron. Amount of iron absorption in intestine is determined only by the quantity of apoferritin synthesized and not by the quantity of iron present in the intestinal

lumen. Once the apoferritin molecules available in intestinal mucosal cells are completely saturated with iron, further absorption of iron by the cells gets blocked ***(Mucosal Block Theory)***.

- In mucosal cells, ferric is slowly liberated from ferritin and reduced to ferrous by the enzyme ferroreductase.

- Iron in the ferrous state enters the blood from mucosal cells through a cell membrane transporter.

- In blood, ferrous is oxidized to ferric by ceruloplasmin (a copper containing protein). The ferric then combines with apotransferrin to form transferrin (an iron transporting protein).

- Transferrin is transported to cells of bone marrow, liver, muscles etc (for synthesis or storage).

- The transferrin is taken up by the the transferrin receptors of respective cells.

- The transferrin-receptor complex is internalized and then iron in ferric form is taken up by the cell.

Thus iron is absorbed and transported to the target tissues.

Functions of Heme and Non-Heme Iron

1) By being part of hemoglobin, iron takes part in transport of oxygen and carbondioxide. Hemoglobin also serves as buffer system in RBCs.

2) Iron is also a constituent of myoglobin which stores oxygen in muscles.

3) Iron is a component of cytochromes, Fe-S proteins and cytochrome C oxidase which take part in mitochondrial electron transport chain and oxidative phosphorylation.

4) Heme containing enzymes like catalase and glutathione peroxidase serve as antioxidant enzymes.

5) Heme containing enzyme thyroperoxidase is involved in the synthesis of thyroid hormones.

6) Iron is needed for immunocompetence of the body.

7) Iron serves as co-factor of the lysosomal enzyme myeloperoxidase which is involved in the phagocytosis of foreign particles like bacteria.

8) Iron serves as cofactor of several enzymes like xanthine oxidase, succinate dehydrogenase, aconitase etc.

Deficiency Manifestations of Iron

- Iron deficiency anemia is commonly seen in menstruating females, undetected gastrointestinal bleeding, chronic blood loss in hemorrhoids, dietary deficiency of iron, multiple pregnancies, impaired intestinal absorption of iron, achlorhydria, hookworm infection etc.

- Iron deficiency anemia is characterized by hypochromic and microcytic RBCs.

- The symptoms of iron deficiency anemia are pale face, fatigue, weakness, decreased exercise tolerance, dullness, headache, loss of appetite etc.

Iodine

- Iodine (I_2) is a trace element.

- Most of the body iodine (about 80%) is present in thyroid gland and muscles.

- The plasma iodine concentration ranges from 5 to 10 μg/dL.

Dietary Sources

- Drinking water, sea foods, vegetables and fruits grown on sea coast, iodised salt etc.

Recommended Daily Allowance (RDA)

- Adults -150 μg/day

- Adolescence and pregnancy - 200 μg/day

Absorption

- Dietary iodine (iodide or I^-) is absorbed mainly in small intestine and to a small extent through skin and lungs.

Introduction to Thyroxine Synthesis

- Thyroid hormones, T_4 (Thyroxine or Tetra iodo thyronine) and T_3 (Tri iodo thyronine) are iodinated tyrosine residues.

- Free tyrosine cannot be iodinated to thyroid hormones.

- The T_3 and T_4 are synthesized by iodination of tyrosine residues of thyroglobulin (a glycoprotein).

- Thyroglobulin, synthesized in thyroid acinar cells, is a dimeric protein with 140 tyrosine residues.

- The tyrosine residues of thyroglobulin are iodinated to T_3 and T_4 through the following steps:

1) The iodide (I^-) is transported from blood stream into acinar cells by Na^+-K^+-ATPase dependent iodide-pump. This transport of iodide against electrochemical gradient is called "iodide trapping".

2) The iodide (I^-) is then oxidized to iodinium ion (I^+) (or active iodine) by the enzyme thyroperoxidase in the presence of H_2O_2.

3) In the presence of H_2O_2 and thyroperoxidase, the iodinium ions react with tyrosine residues of thyroglobulin to yield mono iodo tyrosine (MIT) and di iodo tyrosine (DIT). About 20% of the tyrosine residues of thyroglobulin are iodinated.

4) The coupling of two molecules of DIT forms tetra iodo thyronine or thyroxine (T_4). Likewise, the coupling of one molecule of DIT and one molecule of MIT yields tri iodo thyronine (T_3). The coupling of iodotyrosines is an oxidative condensation reaction catalysed by thyroperoxidase enzyme. The T_3 and T_4 thus formed remain linked to other aminoacid residues through peptide bonds and are stored as part of thyroglobulin in thyroid follicles.

5) Whenever secretion of thyroid hormones is required, thyroglobulin undergoes proteolysis and releases free T_3 and T_4 into bloodstream. T_3 is more active than T_4 in biological function but half life is less comparatively. Under normal conditions, 99% of the hormone produced by thyroid gland is T_4.

6) The MIT and DIT are also released within thyroid glands during proteolysis of thyroglobulin. The released MIT and DIT are deiodinated by enzyme deiodinase and the liberated iodine is reutilized for synthesis of thyroid hormones.

Functions of Thyroxine

- Has calorigenic effect. Increases cellular metabolism by increasing basal metabolic rate (BMR).

- Produces hyperglycemia by stimulating glycogenolysis, gluconeogenesis and by increasing absorption of glucose from the gut.

- Enhances lipolysis in adipose tissues by stimulating the activity of triglyceride lipase.

- At physiological levels, it promotes growth and development of body by enhancing protein synthesis.

- Increases heart rate, cardiac output, respiration rate etc.

Deficiency Manifestations

Goiter – Enlarged thyroid gland and decreased synthesis of thyroid hormones.

Cretinism – Characterized by growth retardation, mental retardation and dwarfism.