8/5/23
monday

MINERALS

Inorganic substances which occur in nature & are required in small quantities for normal growth & functioning of body.

- constitute small proportion of body wt

- crucial in body fn
- mineralisation of bone
- Acid-base balance
- Neuromuscular fn
- Osmotic fn.

Classification of Minerals

- 17 organic elements
- Major elements & Trace elements
- Daily requirement less than 100 mg/day
  → Trace element
- Daily requirement more than 100 mg/day
  → major element ~~Fe~~
- Def. of trace element - small, form essential component of normal diet (Fe & I exept)
- Rubium, silver, gold, bismuth - Non-essential & contaminents.

Aluminium, lead, cadmium, mercury - Toxic & avoided.

Major	Trace	
Ca^{2+}	Iron	Flouride
Mg^{2+}	Iodine	
PO_4^{3-}	Copper	
Na^+	Manganese	
K^+	Zinc	
Cl	molybdenum	
SO_4^{2-}	Selenium	

Calcium (Ca^{2+})

- Total calcium in the human body is about 1 to 1.5kg
- 99% — bone
- 1% — extra cellular fluid

Sources of calcium

- Milk is a good source for calcium
- calcium content of cow's milk is about 100 mg/100mL
- Egg, fish and vegetables are medium sources of calcium.
- cereals (wheat, rice) contain only small amnt of calcium. But cereals are the staple diet in India. Therefore, cereals form the major sourc of Ca^{2+} in Indian diet

Daily Requirement

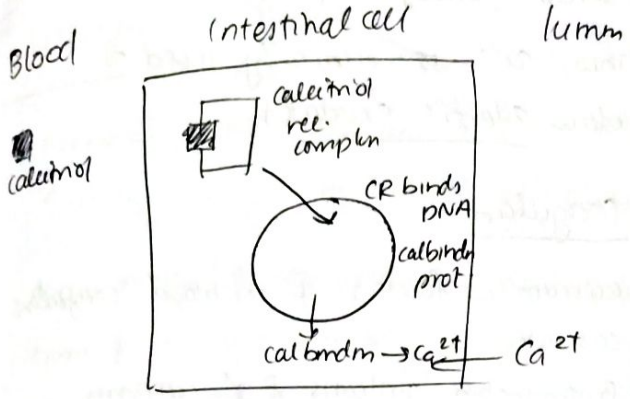
- Adult → 800mg/day
- Child → 1.2g/day
- Pregnancy & Lactation → 1.5g/day
- After 50yrs → increased need 1.5g/day & Vit D (20 Mg/day)
  → to prevent osteoporosis.

Absorption of calcium

- occurs in duodenum - 1st & 2nd part
- Absorbed against conc gradient, requires energy
- only 10% of ingested Ca is absorbed
- Excess passed out in stools.

Factors causing increased absorpn.

- Vitamin D: Calcitriol induces the synthesis of the carrier protein (calbindin) in the intestinal epithelial cells → so facilitates the absorpn of calcium.



- Parathyroid hormone increases calcium transport from the intestinal cells.
- Acidity favours the calcium absorpn.
- Amino acids: Lysine & arginine ↑ the Ca^{2+} ab.
- Lactose: ↑ calcium absorpn.

Factors causing decreased absorpn.

- Phytic a: Hexaphosphate of inositol is present in cereals.
- Oxalates: present in leafy vegetables, which causes formation of insoluble calcium oxalates.
- Malabsorpn syndromes: Here fatty acid is not absorbed, causing formation of insoluble calcium salt of fatty a.
- Phosphate: High phosphate content will cause pptn as Ca^{2+} phosphate. The optimum ratio of Ca^{2+} to PO_4^- which allows mem-absorpn is 1:2 - 2:1. Milk contains this optimum ratio.
- Alkalinity: High pH is unfavourable for calcium absorpn.

Calcium in cells

- Calcium is mainly extracellular
- Cell membrane is generally impermeable to calcium ions.
- Calcium influx into the cell is by Na^+/Ca^{2+} exchange mechanism. This mechanism is rapid, but has low affinity for calcium (NaCa Ex)
- Entry of Ca^{2+} into mitochondria is by a calcium uniport system.
- But calcium ions exit by a $Na^+ - Ca^{2+}$ antiport system, which in turn is dep. on the $Na^+ - H^+$ ATPase pump, this is called calcium pump.
- Other calcium channels are voltage operated channels (VC) & second messenger operated channels (SOC)

SH Functions of Calcium

Activation of enz

- Cal Ca^{2+} + calmodulin
  ↓
  Ca-bound calmodulin
  ↓
  Kinase → Active kinase
  ↓
  Enzyme → Phosphorylated enz-
  ↓
  Biological effect.

Mechanism of action of calmodulin

- Calmodulin can bind with 4 calcium ions → calcium binding leads to activation of enz.
- Calmodulin is part of kinase regulatory kinases
- Some other enz → activated directly by Ca^{2+} without the intervention of calmodulin.

eg: Adenyl cyclase, Phosphorylase kinase, Pyruvate kinase } Enz act by Ca^{2+}-cal complex

Muscles

- Calcium mediates excitation & contraction of m. fibres
- Upon getting the neural signal, calcium is released from sarcoplasmic reticulum.
- Calcium activates ATPase; ↑ses action of actin & myosin and facilitates excitation-contraction coupling.
- The trigger of m. contraction is the interaction of calcium with tropnin C
- Calcium ↓ses neuromuscular irritability

Nerve Conduction

- Calcium is necessary for transmission of n. impulse from presynaptic to post-synaptic region.

Secretion of Hormones

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

Second Messenger

- Calcium & cyclic AMP are second messengers of different hormones. One example is glucagon.

Vascular permeability

- Calcium decreases the passage of serum through capillaries
- Thus, Ca^{2+} is clinically used to reduce allergic exudates

Coagulation

- Calcium is factor 4 in blood coagulation cascade
- Prothrombin contains 8 γ-carboxy glutamate residues which are chelated by calcium.

Myocardium

- Ca^{2+} prolongs systole. In hypercalcemia, cardiac arrest is seen in systole

Bone & Teeth

- The bulk quantity of Ca^{2+} is used for bone & teeth formation
- Ca^{2+} along with phosphate → formation of hydroxyapatite crystals.
- Bone - reservoir of calcium.

Calpains

- Family of calcium dependent cysteine proteases (proteolytic enz.)
- Seen in mammals
- 2 main isoforms: calpain I & calpain II
- Involved: cell mobility, cell cycle progression, potentiation in neurons, cell fusion

myoblast.] calpain 3 def: limp-girdle muscular dystrophy.
calpain 10 def: Type II DM
• calpastatin: Endogenous calpain specific inhibitor

• Hyper activity of calpains → Alzheimer's d/s, cataract, MI, cerebral ischaemia

Calcium in Blood

• Normal blood calcium level is 9–11 mg/dL (10 mg/dL of Ca^{2+} = 5mEq/L)
• About 5 mg/dL of calcium is in ionized form & is metabolically active.
• Another 1 mg/dL is complexed with phosphate, bicarbonate & citrate. These two forms are diffusible from blood to tissues.
• About 4 mg/dL of calcium is bound to proteins in blood & is non diffusible.

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Homeostasis of Blood Calcium

Factors affecting Blood Calcium level

1. Vit D

• cholecalciferol is synthesized from 7-dehydro-cholesterol in skin under the influence of sunlight
• It is then hydroxylated @ 25th posn in liver & further hydroxylated at the 1st posn in kidney
• The active derivative is called dihydroxycholecalciferol / calcitriol

* Vit D & Absorpn of calcium

• Calcitriol promotes the absorpn of calcium & phosphorus from the intestine
• Calcitriol enters the intestinal cell & binds to a cytoplasmic receptor (VDR). The hormone-rec. complex interacts with DNA & causes expression & consequent transcripn of sp. genes that code for calbindin.
• Due to the ↑sed availability of cal. binding protein, the absorpn of cal. is ↑sed.

Vit. D & Bone

• Vit. D is acting ind. on bone
• With Vit. D ↑sed the no: & activity of osteoblasts, the bone forming cells.
• Calcitriol stimulates osteoblasts to secrete alkaline phosphatase
• Due to this enz - the local conc. of phosphate is ↑sed
• The ionic pdt of Ca^{2+} & PO_4 Phosphate ↑ses, leading to mineralisn

Vit. D & Renal Tubules

• Calcitriol ↑ses the reabsorpn of Ca^{2+} & Phosphorus by renal tubules, therefore, both minerals are conserved (PTH conserves only Ca^{2+})

↳ ↳

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Mineracls (cont)

(2) Parathyroid Hormones

- Hormone secreted by 4 parathyroid glands embedded in thyroid tissue
- chief cells → of gland → PTH secrete
- Secreted as prepro-PTH with 115 a.a → broken down to form mature PTH
- Storage of PTH → 1 hr
- The 1st 35 a.a of PTH are biologically active
- Control of release of the hormone is by -ve feedback by the ionized Ca^{2+} in serum.
- The release of hormone is mediated by cyclic AMP
- The normal PTH level in serum is 10-60 ng/L
- In 1° hyperparathyroidism this is used to 100ns/L

* Mechanism of Action of Parathyroid Hormones

- PTH activates adenylyl cyclase with consequent ↑ in intracellular calcium one.
- A kinase is activated & enz. systems are activated.
- Has 3 major incl. sites of act.
- Bone, kidney, intestine → ↑ serum Ca^{2+} level

1. PTH & bones:

- In the bone, PTH causes demineralisation/decalcification
- Induces pyrophosphatase in osteoclasts
- The no: of osteoclasts are also ↑sed → osteoclasts release lactate which solubilizes calcium.
- Also causes secretion of collagenase from osteoclasts → loss of matrix & resorption
- As a result mucopolysaccharides & hydroxyproline → excreted in urine.

2. PTH & kidney

- In kidney, PTH causes decreased renal excretion of calcium &
- ↑sed excretion of phosphates
- Maintained by ↑sed reabsorption of Ca^{2+} from renal tubules.

3. PTH & intestines (indirect effect)

- PTH stimulates 1-hydroxylation of 25-hydroxycalciferol in kidney to produce calcitriol.
- This indirectly ↑ses calcium absorption from intestine.

(3) Calcitonin

- It is secreted by the thyroid parafollicular or clear cells.

• calcitonin is a polypeptide

• calcitonin secretn is stimulated by serum calcium, gastrin, glucagon & biological amines.

• calcitonin ↓ses serum calcium level

• It inhibits resorptn of bone. It ↓ses the activity of osteoclasts and ↑ses that of osteoblasts.

• calcitonin & PTH are directly antagonistic

• The PTH & calcitonin together promote the bone growth & remodelling

• calcitonin level is ↑sed in medullary carcinoma of thyroid & ∴ is a tumor marker

Calcitonin & Calcitriol

• calcitonn → peptide hormone from thyroid gland → ↓s blood Ca^{2+}

• calcitriol → active form of vit D.

(4) Phosphorus

• Effect of phosphorus on calcium:

- There is a reciprocal relationship of Ca^{2+} with phosphorus. The ionic pdt of Ca^{2+} & phosphorus in serum is kept as a constant.

- In normal adults, calcium = 10mg/dL x phosphorus 4 mg/dL; so ionic pdt is 40.

- In children, ionic pdt of calcium & phosphorus in blood is about 50 (instead of 40 in normal adults)

(5) Serum Protein

• In hypoalbuminemia (eg: nephrosis, malnutrin), the total calcium is ↓sed

• In such cases, the metabolically active ionized form is normal, & so there will be no def. manifestn.

	Vit. D	PTH	Calcitonin
Blood calcium	↑	drastically ↑	decreased
Mam action	absorptn from gut	demineralisation	opposes demineralisn
Ca^{2+} absorptn from gut	↑	↑ (indirect)	—
Bone resorptn	↓	↑	↓
Def. manifestn	Rickets	tetany	—
Use in rickets	drug of choice	contraindicated	theoretically beneficial
Effects of excess	Hypercalcemia +	Hypercalcemia ++	Hypocalcemia

⑥ Alkalosis & Acidosis

- Alkalosis favours binding of more calcium with proteins, with consequent lowering of ionized calcium
- Here total calcium level is normal, but calcium def. may be manifested
- Acidosis favours ionizm of calcium

⑦ Renal Threshold

- The renal threshold for calcium in blood is 10 mg/dl
- When injected IV → most of calcium is rapidly excreted.

[Ca^{2+} homeostasis → X- Essay]

Hypercalcemia

causes

1. Hyperparathyroidism
2. Multiple myeloma
3. Paget's d/s
4. Metastatic carcinoma of bone
5. Hyrotoxicosis, Addison's d/s
6. Benign familial hypercalcemia
7. Dehydra
8. Prolonged immobiliza
9. Tuberculosis, leprosy, sarcoidosis
10. Milk-alkali syndrome
11. Drugs
    - Thiazide diuretics
    - Excess vitamin D or vit A
    - Excess Ca^{2+} given IV
    - Lithium, Theophylline

Symptoms

- Polyuria & polydipsia (ADH antagonism)
- Confu, depres, psychosis
- Osteoporosis & pathological fracture
- Renal stones
- Ectopic calcifican & pancreatitis
- Serum alkaline phosphatase may be ↑sed

Management of hypercalcem.

- Adequate hydran, IV normal saline
- Furosemide IV to promote Ca^{2+} excre
- Steroids, if there is calcitriol excess
- Definitive Rx for the underlying disorder

Hypocalcemia

causes

1. Def. of vit D.
   - ↓sed exposure to sunlight
   - Malabsorpn, dietary def., Hepatic d/s
   - ↓sed renal synthesis of calcitriol
   - Nephrotic syndrome (binding protein lost)
   - Anticonvulsant therapy
2. Def. of parathyroid
   - Hypoparathyroidism (1°, 2°)

3. ↑sed calcitonin

- Medullary carcinoma of thyroid

~~Causes of hyp~~

4. Def. of calcium

- Intestinal malabsorp,
- Acute pancreatitis
- Alkalosis ↓sing ionized Ca^{2+}

5. Def. of magnesium

6. ↑ in phosphorus level

- Renal failure
- phosphate infusion
- Renal tubular acidosis.

Symptoms

1. Muscle cramps
2. Paresthesia, especially in fingers
3. Neuromuscular irritability, muscle twitching
4. Tetany (Chvostek's sign, Trousseau's sign)
   ↓
   carpopedal spasm in tetany
5. Seizures
6. Bradycardia
7. prolonged QT interval

Rx

1) Oral Ca^{2+} with vit D supplementation
2) underlying cause should be treated
3) Tetany needs IV calcium (usually 10 mL 10% calcium gluconate over 10 min, followed by slow IV infusion) IV calcium should be given only very slowly.

Cont: of Vitamins

X-linked hypophosphatemic rickets (vit D resistant rickets)

- most common hypophosphatemic rickets
- x-linked dominant disorder
- defective gene is called PHEX gene (phosphate regulating gene with homology to endopeptidases on the X chromosome)
- mutation of PHEX gene lead to ↑sed level of FGF-23.

Lab findings -

Serum calcium - normal

Serum P - low.

Serum PTH - normal

Serum 1,25-$(OH)_2$ D - low or normal

Autosomal dominant hypophosphatemic rickets

mutation in gene encoding FGF 23 which prevents the degradation of FGF 23 by protease

Lab findings

same as in X linked hypophosphatemic

Autosomal recessive hypophosphatemic rickets

very rare