AGENTS THAT AFFECT BONE MINERAL HOMEOSTASIS

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Lecture Objectives

-Classify Drugs Used in Metabolic Bone Disorders
-Enlist Calcium Preparations
-Enlist Vitamin D Preparations
-Clinical Uses of Calcium and Vitamin D
-Describe Actions of Vitamin D on Intestine, Kidney and Bone
-Describe the Mechanism of Actions, Clinical Uses, and Adverse Effects of Bisphosphonates
-Describe the Mechanism of Action, Clinical Uses and Adverse Effects of Calcitonin
-Classify Drugs Used to Treat Osteoporosis
-Explain the Mechanism of Actions of SERM (Raloxifene) selective estrogen receptor modulator and RANK Ligand (Denosumab) Receptor activator of nuclear factor-kB

Introduction

- Calcium and phosphate are the major mineral constituents of bone and their homeostatic balance is carefully maintained.
- Approximately 98% of the 1-2 kg of calcium and 85% of the 1 kg of phosphorus in the human adult are found in bone, the principal reservoir for these minerals.
- Calcium and phosphate enter the body from the intestine.
- In the steady state, renal excretion of calcium and phosphate balances intestinal absorption. In general, over 98% of filtered calcium and 85% of filtered phosphate is reabsorbed

- PTH and the steroid vitamin D principally regulate calcium and phosphate homeostasis.

- Vitamin D is a prohormone rather than a true hormone

- PTH stimulates the production of the active metabolite of vitamin D, 1,25(OH)2D.

Cont…..

- 1,25(OH)2D, on the other hand, suppresses the production of PTH.
- 1,25(OH)2D stimulates the intestinal absorption of calcium and phosphate.
- 1,25(OH)2D and PTH promote both bone formation and resorption in part by stimulating the proliferation and differentiation of osteoblasts and osteoclasts.
- Both PTH and 1,25(OH)2D enhance renal retention of calcium, but PTH promotes renal phosphate excretion.

Bone remodelling

- Bone remodeling is a dynamic, lifelong process in which old bone is removed from the skeleton and new bone is added.
- It consists of two distinct stages – resorption and formation involves osteoblasts and osteoclast.
- Usually, the removal and formation of bone are in balance and maintain skeletal strength and integrity.

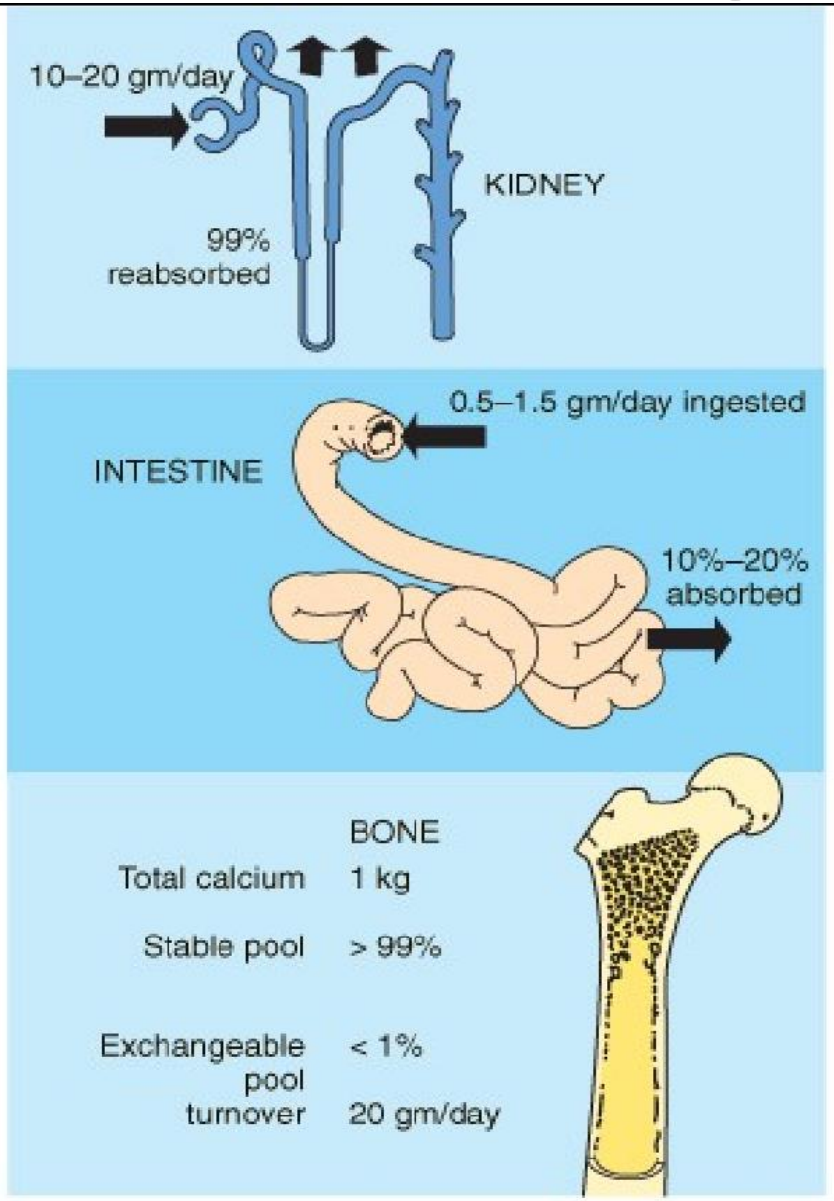
Cont.…

Osteoblasts are responsible for bone matrix synthesis. They secrete a collagen rich ground substance essential for mineralization.

- The osteoblasts also have estrogen receptors. Estrogens can actually increase the number of osteoblasts, increasing therefore collagen production

Osteoclasts play a role in controlling the extracellular concentration of calcium and phosphate, and are directly stimulated by calcitonin and inhibited by PTH .

Sites of calcium regulation



- If the plasma calcium levels become elevated, soft tissue calcification may occur; there may be decreased excitability of nervous tissue and muscle weakness, lethargy and coma.

- If plasma calcium levels become reduced, there may be paresthesia and in more severe cases, tetany and convulsions.

Calcium preparations

calcium carbonate(40%)
calcium citrate
calcium gluconate
calcium lactate
calcium chloride

- **Uses.**

  Indigestion(antacid)
  Hyperkalemia
  Hypocalcemia
  Kidney Failure
  Osteoporosis

Drugs used in Bone mineral homeostasis

A. Hormonal regulators

- Parathyroid hormone
- Vitamin D
- Calcitonin
- Glucocorticoids
- Estrogens

B. Non hormonal regulators

- Bisphosphonates
- Calcimimetics
- Plicamycin
- Thiazides
- Fluoride

A. Hormonal agents

1.Parathyroid hormone (PTH)

Example: Teriparatide inj

- Parathyroid hormone is a peptide hormone composed of 84 amino acids

- The major role for PTH is the maintenance of **normal extracellular calcium levels**

- *Stimulates intestinal absorption*
- *Decrease urinary excretion of calcium*
- *Mobilize bone to provide calcium.*

Cont…

Pharmacokinetics

- Given SC or IV once daily
- Peak concentration occurs after 30min
- Half life is 10 min after IV injection and 1 hour after SC injection.

Uses

- Anabolic effect on bone: increase in bone density, decrease in fractures
- Treatment of severe osteoporosis: when initial therapy with anti resorptive drug has not been effective

Cont….

Side effects

- Nausea, dizziness, headache, arthalgias
- Mild hypercalcaemia, transient orthostatic hypotension
- Leg cramps

Vitamin D Preparations

Ergocalciferol{vitamin D2}

Cholecalciferol(vitamin D3)

Calcitriol

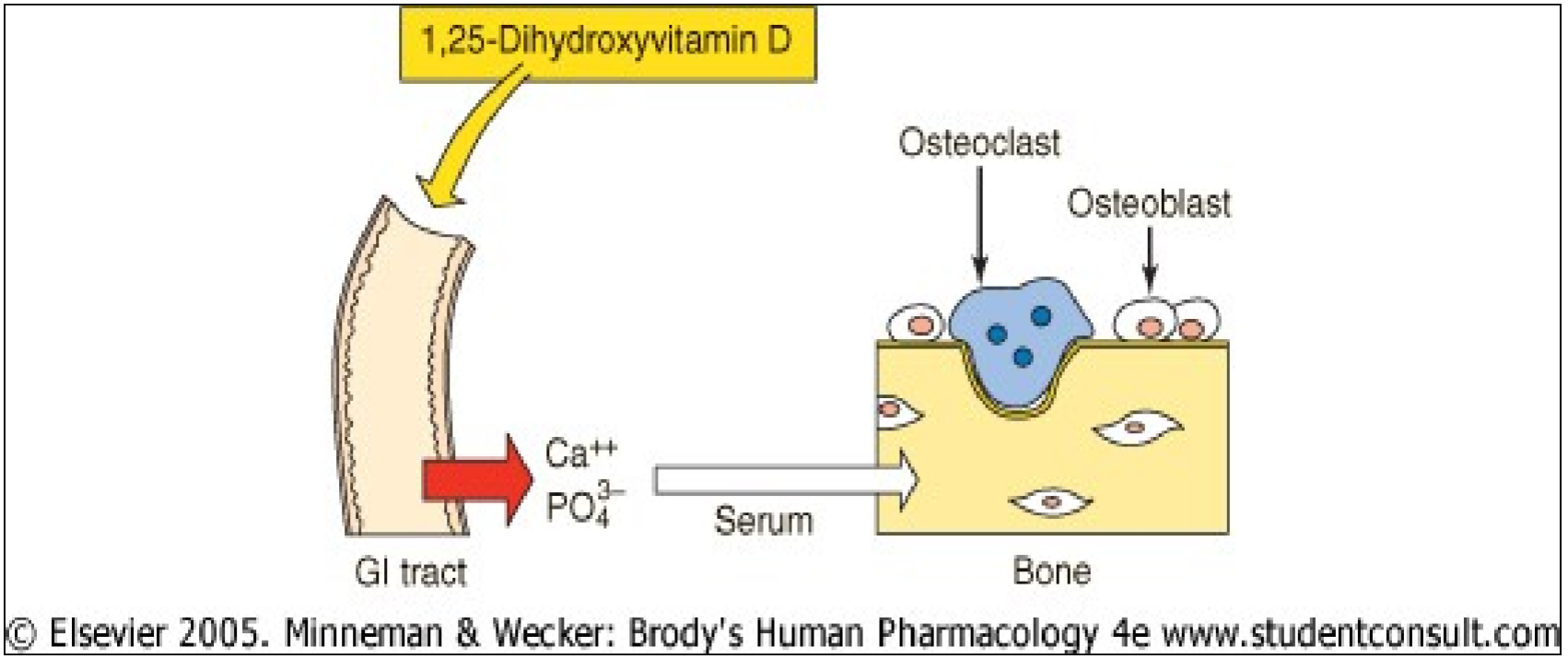
Alfacalcidol

Calcipotriol

2. Vitamin D

- **Example**: Calcitriol, Cholecalciferol.
- Vitamin D is produced in the skin from 7-dehydrocholesterol under the influence of ultraviolet irradiation.
- Vitamin D is a prohormone that serves as precursor to a number of biologically active metabolites. It is first hydroxylated in the liver to form 25-hydroxyvitamin D (25[OH]D).
- This metabolite is further converted in the kidney to a number of other forms, the best-studied of which are 1,25-dihydroxyvitamin D (1,25[OH]2D) and 24,25-dihydroxyvitamin D (24,25[OH]2D).
- Only vitamin D and 1,25(OH)2D (as calcitriol) are available for clinical use.

Mechanisms of Action of 1,25-dihydroxy vitamin D



- 1,25-dihydroxyvitamin D increases calcium and phosphate absorption from the intestine; increasing serum concentrations
- The ions deposit in bone, increasing bone mineralization

Cont ….

MoA

- **GI tract**:Increased calcium and phosphate absorption by 1,25 (OH)2D.
- **Bone**:Increased calcium and phosphate resorption and bone formation
- **Kidney**: decreases Calcium and phosphate excretion

Cont….

Pharmacokinetics

- Given orally and bind to alpha protein in the blood.
- Half life is about 22hrs.
- Eliminated through faeces.

Uses:

- Prevention and treatment of rickets, osteoporosis, otseomalacia and vitamin D deficiency
- Hypocalcaemia
- Osteodystrophy of chronic renal failure, due to decrease calcitriol generation

Cont….

Side effect

- Exess intake causes hypercalcaemia manifested by constipation, depression, weakness and fatigue
- Polyuria and polydipsia
- May lead to renal failure and kidney stones due to deposit of calcium salt in the kidney

3. Calcitonin

Examples: Calcitonin, salcatonin, procaine.

- The calcitonin is secreted by the parafollicular cells of the thyroid gland.it is a peptide hormone.

MoA

- The principal effects of calcitonin are to lower serum calcium and phosphate by actions on bone and kidney.
- Calcitonin inhibits osteoclastic bone resorption.(it slows dowen bone loss)
- In kidney it decreases the reabsorption of both calcium and phosphate in the proximal tubules.
- Secretion is always determined by calcium concentration.

Cont…..

Pharmacokinetics

- Given by SC or intranasal
- Plasma Half life is 4-12min
- Action last for several hours

Uses:

- Hypercalcaemia associated with neoplasia
- Pagets disease of bone
- Postmenopausal and corticosteriods induced osteoporosis

Cont…

Side effects

- Nausea and vomiting.
- Facial flashing.
- Tingling sensation in the hands.
- Unpleasant taste in the mouth.
- Local hypersensitivity.

4. Glucocorticoids

MOA

- Excessive glucocorticoids hormones alter bone mineral homeostasis by antagonizing vitamin D-stimulated intestinal calcium transport, by stimulating renal calcium excretion, and by blocking bone formation.

- inhibit cytokine release by cytolytic effects of some bone tumors, inhibit calcium absorption from intestine and by increasing calcium excretion in urine.

Cont…..

Uses

- Hypercalcemia due to malignancies or Vitamin D intoxication

ESTROGEN.

MoA

- Estrogens can prevent accelerated bone loss during the immediate postmenopausal period and at least transiently increase bone in the postmenopausal woman.
- Estrogens reduce the bone-resorbing action of PTH.
- Estrogen administration leads to an increased 1,25(OH)2D level in blood..
- Estrogen receptors have been found in bone, and estrogen has direct effects on bone remodeling.

Cont.…

Pharmacokinetics

- Well absorbed in Git
- Widely distributed in tissue and converted to an active metabolite in liver, lungs spleen , kidneys,
- Half life is 32 hrs
- Excretion in feaces

Uses:

- Hormone replacement therapy
- Prevention and treatment of postmenoupasal osteoporosis

Cont…..

Side effects

- Hot flashes and leg cramps
- May cause venous thromboembolism

B. Non Hormonal agents

1. Bisphosphonates

Examples:Etidronate, pamidronate(only parentral), alendronate, ibandronate, zolendronate

MoA (*inhibition of osteoclast activity*)

- Decrease activity of the osteoclast proton pump (needed to dissolve hydroxyapatite) and increases osteoclast apoptosis ("programmed cell death").
- BPs also reduces transformation of osteoclast precursor cells to mature osteoclasts.
- Bind to bone, inhibit calcium resorption

They also interfere with mevalonate pathway of cholesterol synthesis which is required for normal function of osteoclasts.

Cont….

Pharmacokinetics

- Given orally and poorly absorbed, may be given IV in malignancy.
- 50% of dose accumulates at site of bone mineralization. Free drug excreted by kidneys
- Take on empty stomach, with water, 30 minutes before other intake

Cont….

Side effects:

- GIT disturbance,(esophagitis,gastritis)
- Peptic ulcer disease
- bone pain
- osteomalacia

Uses:

- Treatment of osteoporosis
- Treatment of Paget's disease of bone
- Treatment of hypercalcemia of malignancy

  Osteolytic bone metastasis

2. Calcimimetics

Examples:Cinacalcet

MoA

- Enhances the sensitivity of the parathyroid calcium sensing receptors to the concentration of blood calcium;
- –Make it more responsive to calcium
- – Suppress PTH
- – Can decrease serum calcium and phosphate

3. Plicamycin

MoA

- Plicamycin is a cytotoxic(anti tumor) antibiotic .it produces its anticancer effects by binding to DNA and inhibiting the production of proteins necessary for sustaining the life of a cell
- Inhibits osteoclast activity,(it inhibits RNA synthesis in osteoclasts)

Preventing bone breakdown

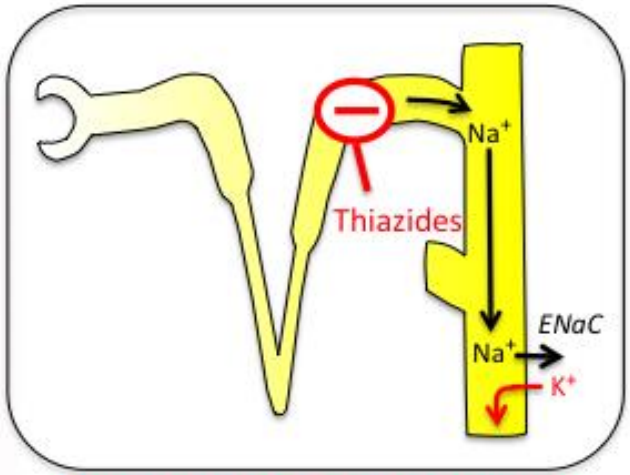
Uses

- Treat hypercalcemia
- Treat pagets disease

4. Thiazides

MOA

- The principal application of thiazides in the treatment of bone
- mineral disorders is in reducing renal calcium excretion. **By increasing calcium reabsorption from the luminal membrane into the interstitium in exchange for sodium**, thiazides reduce urine calcium levels and increase blood
- calcium.
- However, if indicated, this effect of thiazide diuretics makes thiazides useful for nephrolithiasis and osteoporosis treatment



Enhanced Na^+ delivery results in K^+ loss in the collecting duct

Urine

lumen / tubular

Distal Convoluted Tubule Cell

Blood

basolateral

Thiazide Diuretics

Na^+/Cl^- cotransporter

CLC-K

Cl^-

Na^+

Cl^-

Na^+

ATP

K^+

Lower Na_i facilitates Ca reaborption by Na/Ca exchange

Collecting duct

K^+

Ca^{2+}

TRPV5

Ca^{2+}

Na^+

parathyroid hormone

+

Na^+

loss of H^+

H^+

10% of filtered Na is normally reabsorbed in the distal convoluted tubule

Thiazide diuretics:

- Loss of Na & Water
- Hypokalemic metabolic alkalosis
- Increased Ca^{2+} reabsorption

5. Fluoride

MoA

- Stimulate osteoblast activity and increase bone formation
- Increases bone density
- Fluoride use increases incidence of fractures because of weaker bone formation

Cont…

Side effects

- GI side effects: Nausea
- Musculoskeletal pain, joint swelling
- Increased risk of fracture: Dose-related

Phosphate Binders

- These are medications that bind phosphate in the gut to prevent absorption, used in combination with calcium supplements to treat hyperphosphatemia (renal failure, hypoparathyroidism,vit D intoxication)
- High phosphate leads to elevated PTH
- High phosphate causes decreased vitamin D levels and hypocalcemia
- Should be given with meals, Include;
- Sevelemar (Renagel)
- Fosrenol (lanthanum carbonate)

Cont. . ..

Side effects

- GI discomfort
- Mild metabolic acidosis

Uses

- Secondary hyperparathyroidism

Drugs For Osteoporosis

1. Calcitriol
2. Bisphosphonates
3. Cinacalcet
4. Calcitonin
5. Estrogen
6. Calcium
7. PTH

Denosumab(RANKL) (INHIBITOR)

Receptor activator of nuclear factor-kB ligands.
It is a human monoclonal antibody that binds RANKL, preventing RANKL from activiting RANKL, its receptor on the osteoclast surface. With reduse RANK-RANKL binding, osteoclast formation, function and survival are inhabited, so bone resorption decreases and bone mass increases.

Uses;

Osteoporosis
Treatment induced bone loss
Metastases to bone
Giant cell tumor of bone

Raloxifene. SERM . selective estrogen receptor modulator

- The MOA of raloxifene occurs through binding to estrogen receptors. estrogen-agonistic effect on bone.

- During reproductive life in the female, estrogens have an important role in maintenance of bone integrity. Inhibit the cytokines that recruit osteoclast, and oppose the bone-resorbing calcium mobilising action of PTH.

Thank You