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Drugs affecting Ca^{+2} Homeostasis

Basic Pharmacology

- **Calcium** and **phosphate** are the major mineral constituents of bone.
- **Bone** is the principal reservoir for these minerals.
- There is constant **exchange** of bone mineral with that in the extracellular fluid.

Abnormalities in bone mineral homeostasis can lead to:

1-Cellular dysfunctions as tetany, coma, and muscle weakness.

2-Disturbances in structural support of the body as osteoporosis and fractures.

Calcium and phosphate enter the body by:

I- Intestinal absorption.

II-Reabsorption by the **kidney tubules**.

So, disease of the intestine or

Kidney disease as chronic renal failure

Disrupts bone mineral homeostasis.

Regulators of calcium homeostasis:

I-Hormonal

A-Primary hormones:

- **Parathyroid hormone (PTH).**
- **Vitamin D.**

B-Secondary hormones:

- **Calcitonin.**
- **Glucocorticoids.**
- **Estrogen.**
- Growth hormone.
- Insulin.
- Thyroid hormone.

Deficiency or excess of these **secondary regulators** within a physiologic range does not produce the disturbance of calcium and phosphate homeostasis that is observed with deficiency or excess of **primary regulator**.

II-Non-hormonal:

Drugs as:

- **Bisphosphonates.**
- **Diuretics**:

Loop diuretics.

Thiazide diuretics.

*Plasma Ca^{+2} concentration:

8.5-10.4 mg/dl

- 45% bound to plasma proteins

-10% complexed with inorganic anions

*Hypocalcemia: ↓ 8.5mg/dl

↑neuromuscular excitability, tetany, impaired Mineralization of the skeleton.

*Hypercalcemia: ↑ 10.5 mg/dl

Cardiac arrythmias, soft tissue calcifications

CNS abnormalities

Classification

1-Promote Ca^{+2} and bone resorption:

*Parathyroid hormone (PTH), analoges.

*Vit D, metabolites, analoges.

2-Inhibit Ca^{+2} and bone resorption:

*Bisphosphonates

*RANK ligand (RANKL) inhibitors

*Calcitonin

*Estrogens and SERMs

Parathyroid hormone *(PTH)*

PTH is a polypeptide hormone (secreted in response to low serum ionized Ca^{2+}) that regulate plasma Ca^{2+} by affecting:

I- Bone resorption and formation.

II- Renal Ca^{2+} excretion and reabsorption.

III- GIT Ca^{2+} and phosphate absorption.

The primary function of PTH is to maintain a constant concentration of **Ca^{2+}** in the extracellular fluid by:

1- ↑ **Bone** Ca^{2+} mobilization (bone resorption).

2- ↑ **Renal** Ca^{2+} absorption and ↑ Ph excretion.

3- ↑ **GIT** absorption of Ca^{2+} and phosphate.

4- ↑ Synthesis of vitamin D.

In Bone

PTH can ↑ both the rate of bone formation and bone resorption.

Mediated by cytokines as RANKL (**R**eceptor **a**ctivator of **n**uclear factor-**k**B **l**igand)

Produced by osteoblasts regulating number and activity of osteoclasts:

*Continous exposure→Bone resorption

*Pulsatile exposure→Bone formation

In the kidney

PTH increases the reabsorption of Ca+2 and Mg+2, and it increases the production of 1, 25-(OH)2 D3 from 25-(OH)D3 (1- hydroxylase step).

PTH also decreases reabsorption of phosphate, bicarbonate, sodium, and chloride.

Net results of PTH is:

- **Increased** serum calcium.
- **Decreased** serum phosphate.

so,

- If the level of **Ca^{2+} is decreased** , PTH secretion **increases**.
- If the level of **Ca^{2+} is increased**, PTH secretion **decreases**.

SO,

Sustained hypocalcemia induces

parathyroid hypertrophy and hyperplasia.

*Teriparatide

- Teriparatide is recombinant human PTH which behaves as a full PTH agonist.

- Teriparatide is administered parenterally once a day, and this intermittent exposure results in net bone formation.

- Teriparatide is used in the treatment of osteoporosis.

- Major adverse effects are hypercalcemia and hypercalciurea.

*Calcium sensor sensitizers: (calcimimetics)

- The parathyroid gland senses Ca^{+2} via the action of the protein calcium-sensing receptor (**CaSR).** Activation of CaSR reduces the amount of PTH synthesized and released by the gland.

- Cinacalcet (Sensipar) is an oral agent that acts similar to Ca^{+2} on the CaSR; this reduces serum PTH.

- Cinacalcet is approved for use in patients with hyperparathyroidism 2ry to renal disease.

- Hypocalcemia is the major adverse effect

Vitamin D

- Vitamin D is **fat soluble** vitamin.
- Produced in the **skin** from 7-dehydrocholesterol under the influence of **ultraviolet** irradiation.
- Vitamin D is also found in certain **foods**.

Function of vitamin D:

1- ↑ **GIT** absorption of Ca^{2+} and phosphate.

2- ↑ **Bone** Ca^{2+} mobilization (bone resorption).

3- ↓ **Renal** excretion of Ca^{2+} and phosphate.

-All vitamin D metabolites bind to a specific plasma-binding protein, vitamin D- binding protein.

-Vitamin D, calcifediol, and calcitriol are all administered orally;

calcitriol may be administered parenterally.

This leads to maintain Ca^{2+} and phosphate levels that essential for:

- Neuromuscular activity.
- Mineralization of bone
- Other Ca^{2+} dependent functions.

Vitamin D deficiency:

Decrease Vit D → ↓ absorption of Ca^{2+} and phosphate → ↓ blood level of Ca^{2+} → ↑ PTH secretion → Resorption of bone to correct blood Ca^{2+} level.

This results in:

Children:

Leads to failure to mineralize newly formed bone and cartilage matrix.

Causing the defect in growth known as **rickets**

Adults:

Leads to generalized accumulation of undermineralized bone matrix.

Causing **osteomalacia**.

Manifested by bone pain, tenderness and muscle weakness.

Therapeutic uses of vitamin D:

Elevate serum calcium in hypocalcemia caused by:

1-Treatment of **rickets**.

2-Treatment of **osteomalacia**.

3-Treatment of **hypoparathyroidism** with $Ca.^{+2.}$

4-Prevention and treatment of **osteoporosis**.

5-In **renal** disease.

6- Treatment of **psoriasis vulgaris** due to it inhibits epidermal proliferation (Topical Calcipotriene).

	PTH	Vitamin D
Intestine	Increased calcium and phosphate absorption (by increased $1,25(OH)_2D$ production)	Increased calcium and phosphate absorption by $1,25\ [OH]_2D$
Kidney	Decreased calcium excretion, increased phosphate excretion	Calcium and phosphate excretion may be decreased by 25(OH)D and $1,25(OH)_2D$
Bone	Calcium and phosphate resorption increased by high doses. Low doses may increase bone formation.	Increased calcium and phosphate resorption by $1,25(OH)_2D$; bone formation may be increased by $24,25(OH)_2D$
Net effect on serum levels	Serum calcium increased, serum phosphate decreased	Serum calcium and phosphate both increased

The net effect of PTH is to:

- Raise serum **calcium.**
- Reduce serum **phosphate**.

The net effect of vitamin D is to:

- Raise serum **calcium.**
- Raise serum **phosphate.**

Bisphosphonates

Analogs of pyrophosphate (P-O-P) that bind directly to hydroxyapatite crystals in bone and impair reabsorption.

First generation:

Etidronate.

Second generation:

Alendronate, Pamidronate.

Third generation:

Residronate, Zoledronate

Mechanism of action:

- The non-nitrogenous bisphosphonates such as etidronate are internalized by osteoclasts and converted into an ATP analog that cannot be hydrolyzed. This metabolite impairs various functions and induces apoptosis in osteoclasts.

- Amino bisphosphonates such as alendronate and risedronate inhibit farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway that appears to be critical for osteoclast survival.

Pharmacokinetics:

Absorption:

- Poorly absorbed orally (< 10%),

- Food, Ca++, Fe++ containing supplements & antacids containing Ca++, Mg++ or Al+3 →↓ absorption.

- To improve absorption:

 Taken in morning on empty stomach, 30 minutes before food consumption.

 Given with 250 ml of plain water to ↓ GIT irritation.

 The patient must remain upright for at least 30 minutes to avoid the risk of esophagitis

Excretion:

The remainder is excreted unchanged in the urine.

Adverse effects:

- GIT: if taken orally→ nausea, esophagitis and gastritis.

- I.V. medication → hypocalcaemia, transient fever, rash, leucopenia and myalgia.

- pamidronate→ Iritis and hearing loss

- Recently bisphosphonates are linked to a serious bone disease called osteonecrosis of the jaw & rarely subtrochanteric femur fractures in patients on long-term bisphosphonate treatment.

Therapeutic Uses:

1. Osteoporosis : The main aim of treatment is to stabilize bone metabolism, prevent bone fractures and relieve pain
2. Paget's disease: given until a therapeutic response is produced as evidenced by normalization of serum alkaline phosphatase. Patients are given a break from therapy for 3 months or until the serum alkaline phosphatase becomes elevated again and another cycle is then started.

3. Hypercalcemia: in hyperparathyroidism & in cancer patients.

4. Malignant bone disease:

-In advanced cancers that metastasize to the bone as lung cancer, breast cancer, prostate cancer, multiple myeloma and others, bone metastasis can result in severe pain, pathologic fractures and hypercalcemia.

-Intravenous bisphosphonate, particularly zoledronate (Zometa) once every 4 weeks, significantly reduces the risk of these events and reduces the incidence of bone metastasis.

Denosumab

Mechanism of action:

- Denosumab is a monoclonal antibody that blocks the action of RANKL, this reduces osteoclast proliferation and activation.

- Efficacy at reducing bone loss is comparable to that of bisphosphonates.

NB): denosumab can be used in patients with advanced renal disease, unlike the bisphosphonates, as it is:

1-Not cleared by the kidney,

2-Has the advantage in that it is readily reversible because it does not deposit in bone.

Therapeutic uses:

-Denosumab is administered subcutaneously every 6 months & is approved for the treatment

Of:

1-Post-menopausal osteoporosis

2-solid tumors (prostate and breast),:

for reducing the risk of bone loss and bone metastasis in patients with clinical trials showed that the drug was equivalent to zoledronate for this indication.

Adverse effects:

- Increased risk of infection especially cystitis is associated with the use of denosumab.
- transient hypocalcaemia , especially in patients with marked bone loss
- Because the suppression of bone turnover with denosumab is similar to that of the potent bisphosphonates, the potential risk of osteonecrosis of the jaw and subtrochanteric fractures is comparable.

II-Estrogen and SERMs

- Estrogen is often employed combined with a progestin to prevent endometrial carcinoma and to relieve menopausal symptoms such as hot flashes.
- However, concern that estrogen increases the risk of breast cancer and fails to reduce or may actually increase the development of heart disease has reduced enthusiasm for this form of therapy, at least in older individuals.

*Raloxifene

- Action:

1-Selective estrogen receptor modulator that mimics the effects of estrogen on bone.

2- Raloxifene increases bone mineral density (BMD) in postmenopausal women and decreases vertebral fractures in women with osteoporosis.

- Side effects:

1- Although raloxifene activates estrogen receptors in bone, it has antiestrogen effects in breast and uterine tissues and can cause or intensify hot flashes and other symptoms of estrogen Withdrawal in menopausal women.

2-Raloxifene increases the risk of stroke, pulmonary emboli, and deep vein

I-Calcitonin

- It is secreted by the parafollicular cells of thyroid.

- The principal effects of calcitonin are to:

Lower serum calcium and phosphate by actions on

bone and **kidney**.

I- Bone

- Calcitonin **inhibits** osteoclastic bone resorption.

- Also, it **stimulates** bone formation by osteoblast.

II-Kidney

- Calcitonin reduces both Ca^{+2} and Ph reabsorption.
- Also, inhibits reabsorption of other ions as:

Na^{+}, K^{+}, and Mg^{+2}.

Pharmacologic properties:

(1) Synthetic salmon calcitonin (Fortical, Miacalcin) is 50 to 100 times more potent than human calcitonin and has a longer half-life.

(2) Currently approved products are administered parenterally or as a nasal spray.

(3) Decreases in plasma Ca^{+2} are seen in 2 hours and persist for 6–8 hours.

Therapeutic uses:

Reduces Hypercalcemia due to:

1- Paget's disease.

3- Osteoporosis.

4- Hyperparathyroidism.

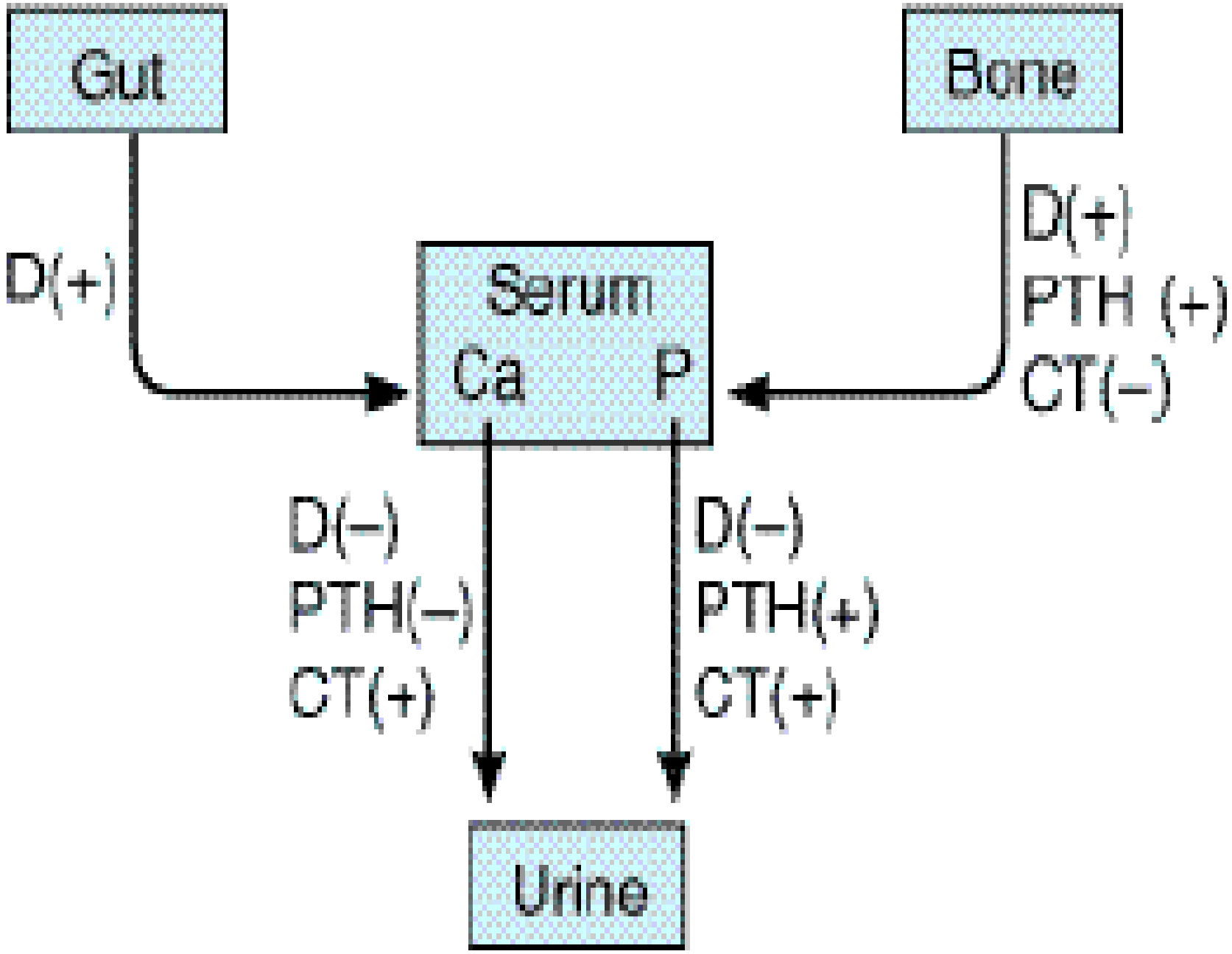
5- Vitamin D toxicity.

6- Osteolytic bone metastasis.

Side effects:

- Local hypersensitivity reactions including rashes, other allergic reactions, and nausea have been noted in patients

- A potential problem with calcitonin is a loss of effectiveness with prolonged use possibly because of the production of anticalcitonin antibodies.


Gut
Bone
D(+)
D(+)
PTH (+)
CT(–)
Serum
Ca
P
D(–)
PTH(–)
CT(+)
D(–)
PTH(+)
CT(+)
Urine

Drugs used in treatment of osteoporosis:

1-Bisphosphonates. 2-Vitamin D, Ca^{2+}.

3-Calcitonin.

4-Denosumab.

5- Estrogen, Raloxifen.

6-Teriparatide

7-Thiazide Diuretics.

Paget Disease of bone

The second most common bone disorder.

Characterized by excessive bone turnover, localized bone deformities, pain, and fractures. Its cause remains uncertain.

*The goals of treating patients with Paget disease are to control bone pain and to prevent progressive bone deformity and other manifestations of the disease.

*Calcitonin or a bisphosphonate drug such as zoledronate is usually employed for this purpose, and the combination of calcitonin and a bisphosphonate may be useful in more severe cases.

Hypocalcemia

Disorders:

Hypoparathyroidism; pseudohypoparathyroidism; renal failure; inadequate calcium intake or absorption; abnormal vitamin D metabolism, ingestion, or absorption; tissue resistance

Management:

Soluble Ca+2salts and/or vitamin D or its analogs

Hypercalcemia

Disorders:

Hyperparathyroidism, hypervitaminosis D, neoplasia, sarcoidosis, hyperthyroidism

Management (based on cause and severity):

- *Mild hypercalcemia*: dietary restriction of calcium
- *Moderate hypercalcemia*: loop diuretics and intravenous saline
- *Severe hypercalcemia*: intravenous bisphosphonates, calcitonin, glucocorticoids


Thank you
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