PHARMACOLOGY

Pharmacology of Bone

Skye McKennon, PharmD. BCPS, ACSM-GEI

Presentation date

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

DISCLOSURE

None

OBJECTIVES

1. Identify the appropriate drugs and drug classes for managing osteopenia and osteoporosis.
2. Explain the mechanism of action of drug classes for managing osteoporosis and correlate with underlying pathophysiology
3. Describe adverse effects and contraindications to drug classes for managing patients with osteopenia and osteoporosis.
4. Describe the clinically important drug interactions of each drug class for managing patients with osteopenia and osteoporosis.

INTERACTIVE LEARNING

State the role of the following hormones on bone mineral homeostasis:

- 1,25dihydroxyvitamin D
- Parathyroid hormone (PTH)
- Calcitonin

BONE REMODELING

OsteoBLASTS sense micro fractures → osteoBLASTS secrete RANKL

- RANK and RANKL are members of tumor necrosis factor superfamily of ligands/receptors
- Essential for function of bone-resorbing osteoCLASTS

RANKL interacts with receptor (RANK) on osteoCLASTS and osteoCLAST precursors

- Results in activation, migration, differentiation, and fusion of hematopoietic cells
- Begins process of bone resorption

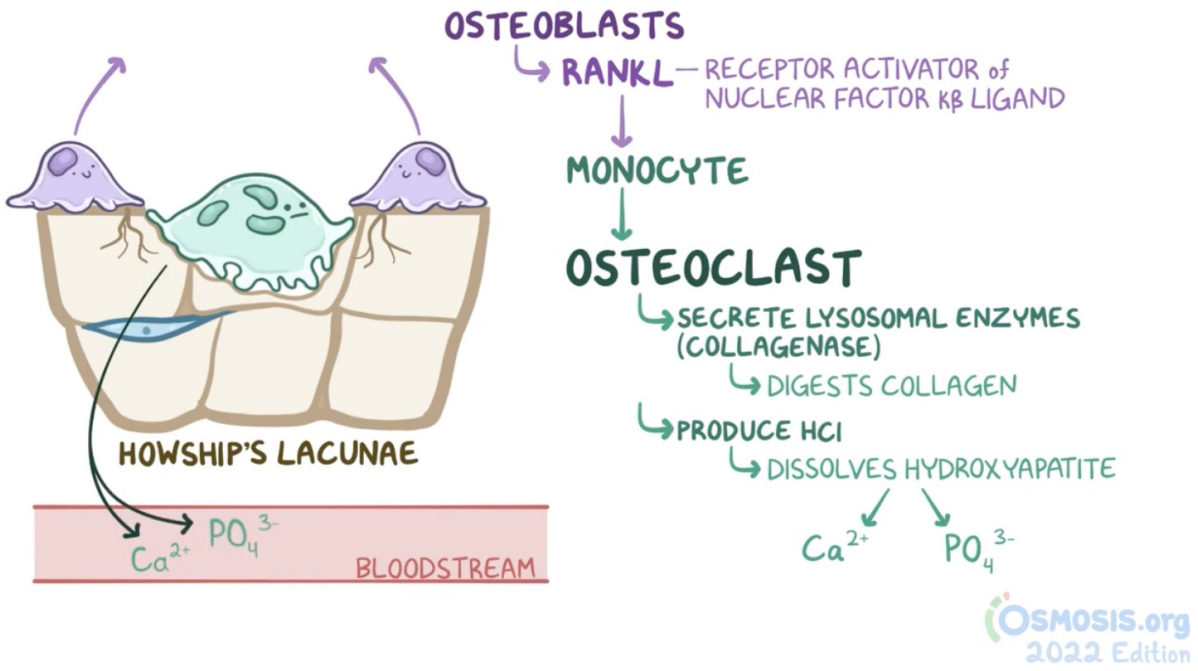
BONE REMODELING

OsteoCLASTS secrete collagenase

Collagenase digests collagen protein in the organic matrix → drills pits on the bone surface

OsteoCLASTS produce HCl → dissolves hydroxyapatite into soluble calcium and phosphate ions → calcium and phosphate ions released in blood stream

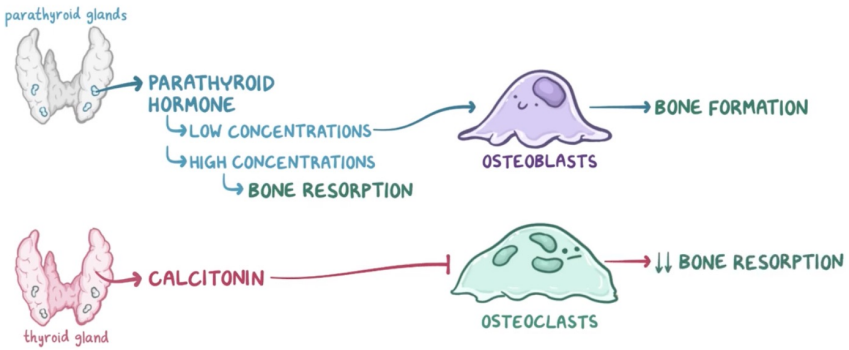
BONE REMODELING



HORMONAL CONTROL

Osteoblasts and osteoclasts are controlled by

- Parathyroid hormone (released by the parathyroid glands)
  - Low concentrations stimulate osteoBLASTS → bone formation
  - High concentrations stimulates bone resorption
- Calcitonin (released by the thyroid gland)
  - Inhibits osteoCLAST activity → decreasing bone resorption



HORMONAL CONTROL

1,25dihydroxyvitamin D (produced by the kidney and under control of parathyroid hormone [PTH] and fibroblast growth factor 23 [FGF23])

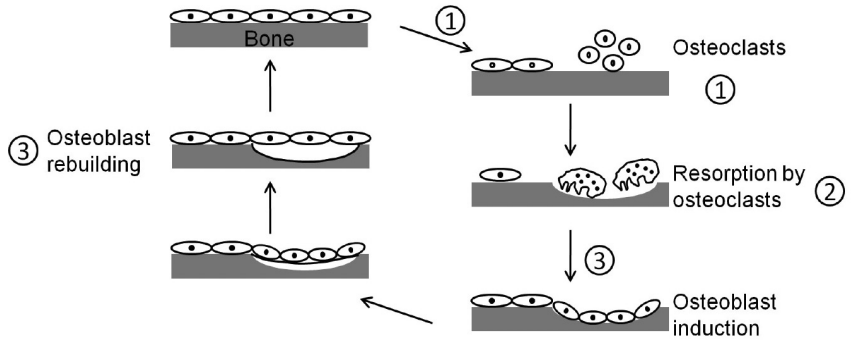
- Stimulates intestinal uptake of calcium and phosphate, and, in those with vitamin D deficiency, promotes bone formation

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Osteoporosis resulting from age or after menopause occurs because resorption exceeds formation

Drugs (i.e., glucocorticoids) and diseases can decrease bone mass

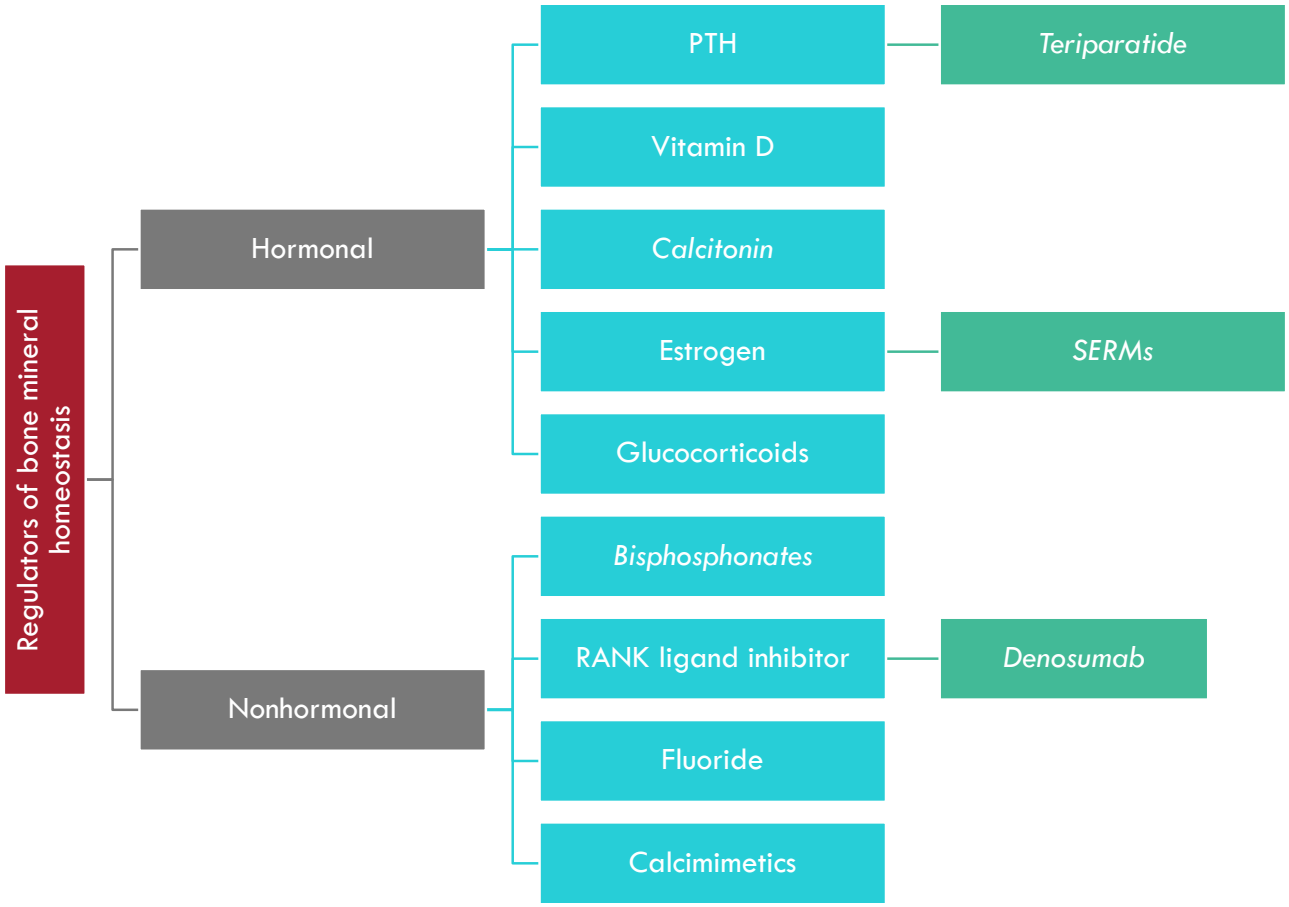
- In these cases, osteoporosis and the contributing disorder should be treated



GENERAL APPROACH TO TREATMENT

A bone-healthy lifestyle throughout life beginning at birth

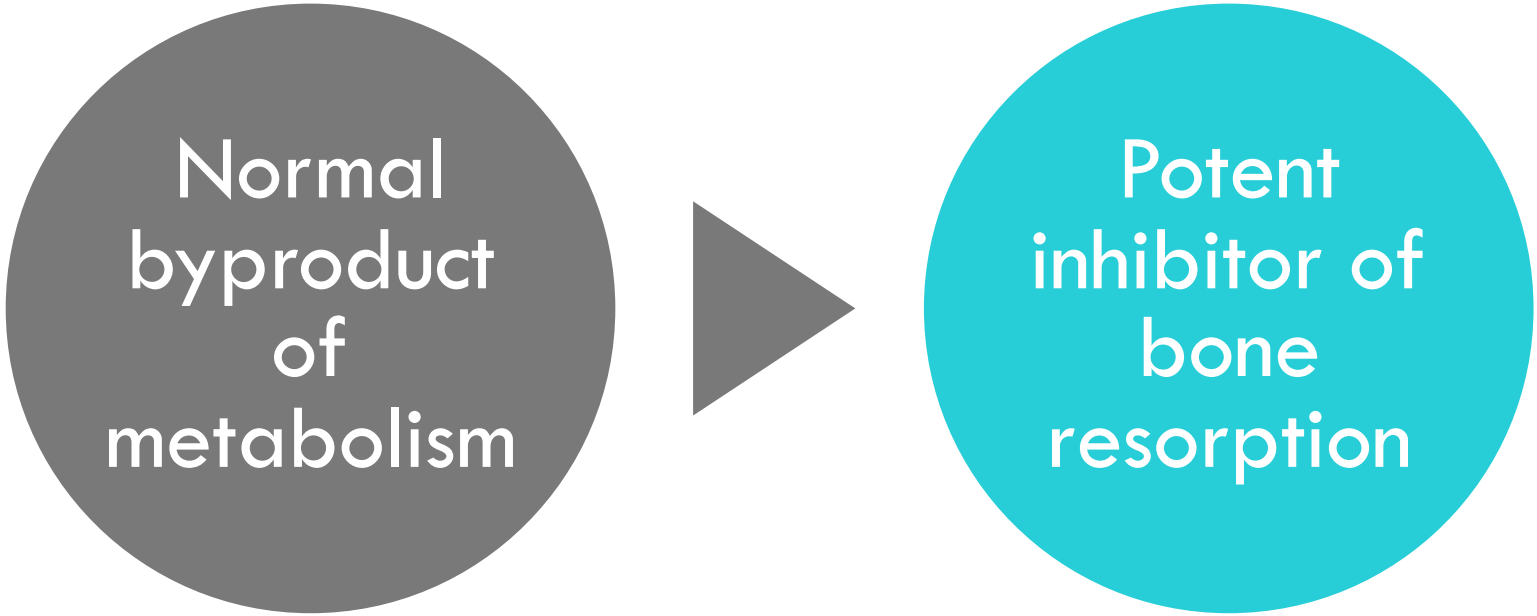
1. Nonpharmacologic options include diet changes (adequate calcium and vitamin D), social habit changes (smoking cessation and minimal alcohol), exercise, and fall prevention
2. Pharmacologic prevention and treatment is used when nonpharmacologic interventions are insufficient
   - Targeted toward both prevention of bone loss and treatment of established osteoporosis (increasing bone mass and reducing fractures)


Regulators of bone mineral homeostasis
Hormonal
Nonhormonal
PTH
Teriparatide
Vitamin D
Calcitonin
Estrogen
SERMs
Glucocorticoids
Bisphosphonates
RANK ligand inhibitor
Denosumab
Fluoride
Calcimimetics

BISPHOSPHONATES

Pharmacology of Bone

PYROPHOSPHATE



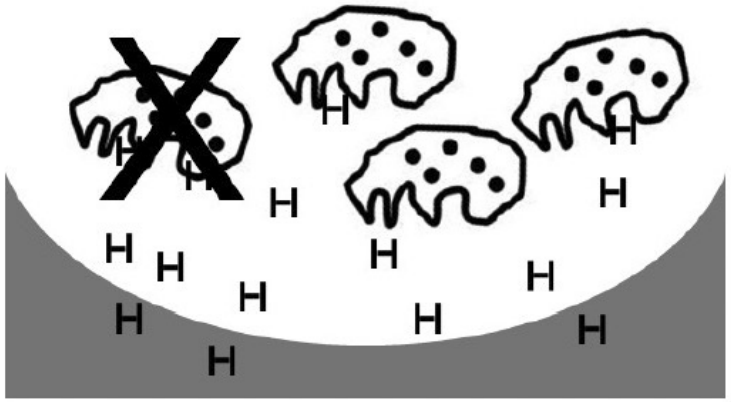
BISPHOSPHONATE MECHANISM OF ACTION

Bisphosphonates are analogs of pyrophosphate

Mimic endogenous pyrophosphate (potent inhibitor of bone resorption) and bind to hydroxyapatite (mineralized form of calcium found in bones)

When osteoCLASTS breakdown bone, also take in bisphosphonate

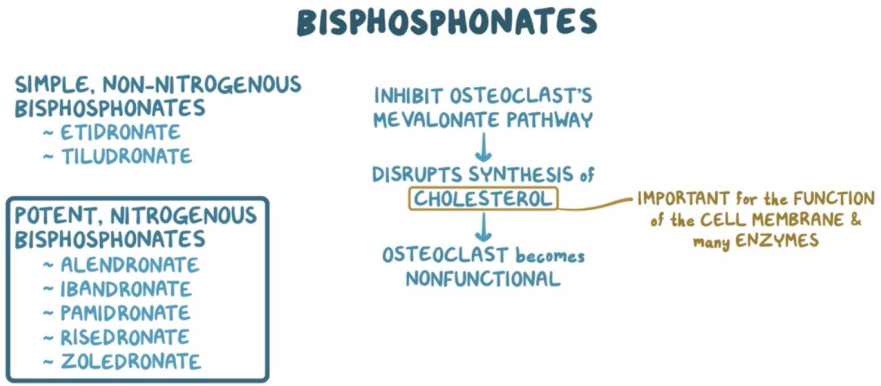
- Bisphosphonates are released upon bone remodeling
- Released bisphosphonate internalized by the phagocytic osteoclast inducing apoptosis



BISPHOSPHONATE MECHANISM OF ACTION

Inhibit osteoclast mevalonate pathway

Disrupts the synthesis of cholesterol → cell membrane dysfunction → osteoclast becoming nonfunctional



BISPHOSPHONATES (-DRONATE)

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Alendronate (Fosamax) Ibandronate (Boniva) Risedronate (Actonel) Zoledronate (Reclast)	Patients unable to stand or sit upright (oral drugs) Patients with severe renal dysfunction (excreted by the kidney)	**GI (heartburn, esophageal irritation, esophagitis, abdominal pain, diarrhea)** Severe bone, joint and/or muscle pain Hypocalcemia **Osteonecrosis of the jaw**	Avoid use of parathyroid hormone (interferes with normalization of blood calcium concentrations) May enhance hypocalcemic effects of other drugs

Pamidronate and zoledronic acid are parenteral and are used for hypercalcemia.

INTERACTIVE LEARNING

Oral bisphosphonates have special administration instructions. What is the rationale between each of the following instructions:

- Each oral tablet should be taken with at least 4 ounces of plain tap water

- Each oral tablet should be taken at least 30 minutes before consuming any food or any other supplement or medication

- Patient should remain upright (either sitting or standing) for at least 30 minutes after bisphosphonate administration

CLINICAL USE & ADME

Osteoporosis

Paget disease

Not well absorbed from the GI tract; absorption worsens in presence of food

Bind to bone, thus having a lasting effect from a single dose

- Basis of the once weekly or once yearly dosing options
- Half-life of alendronate in bone has been measured to be at least 10 years

ORAL DOSING SPECIAL CONSIDERATIONS

Oral bisphosphonates must be administered carefully to optimize the clinical benefit and minimize the risk of adverse GI effects

- Each oral tablet should be taken with at least 4 ounces of plain tap water at least 30 minutes before consuming any food or any other supplement or medication
- Patient should remain upright (either sitting or standing) for at least 30 minutes after bisphosphonate administration

DENOSUMAB

Pharmacology of Bone

RECEPTOR ACTIVATOR OF NUCLEAR FACTOR KAPPA-B (RANK) LIGAND (RANKL)

Member of tumor necrosis factor superfamily of ligands/receptors

- Essential for function of bone-resorbing osteoCLASTS

RANKL interacts with receptor (RANK) on osteoCLASTS and osteoCLAST precursors

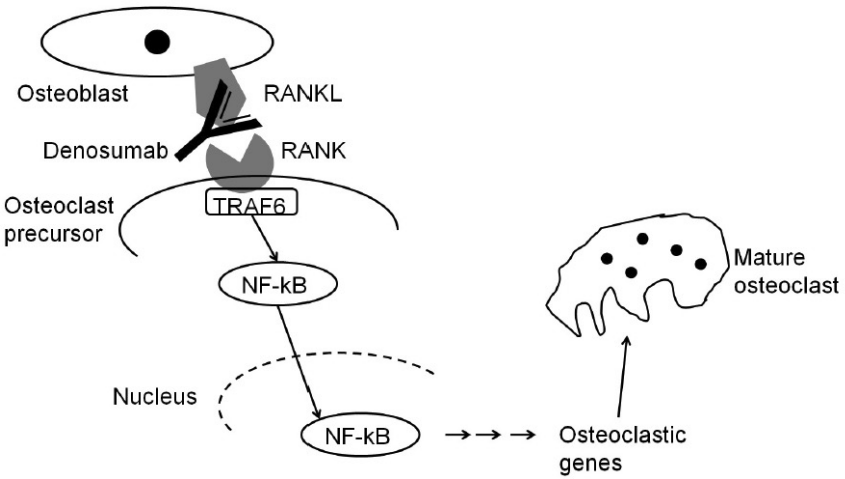
- Results in activation, migration, differentiation, and fusion of hematopoietic cells
- Begins process of bone resorption

DENOSUMAB MECHANISM OF ACTION

Denosumab is a human monoclonal antibody

Blocks RANKL and prevents it binding to its receptor (RANK) on the surface of osteoclasts

- Prevents activation and maturation of osteoclasts



DENOSUMAB

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Denosumab (Prolia) 💉	Patients with hypocalcemia; correct hypocalcemia prior to starting therapy and monitor mineral levels	Skin rash (eczema) Infections **Osteonecrosis of the jaw** Atypical fractures and delayed fracture healing	Increased immunosuppression with other immunosuppressants (i.e., corticosteroids, chemotherapy, methotrexate)

CLINICAL USE & ADME

Osteoporosis/bone loss

Other

- Bone metastases from solid tumors
- Giant cell turnover of bone
- Hypercalcemia of malignancy
- Multiple myeloma

Given subcutaneously every 6 months

PARATHYROID HORMONE

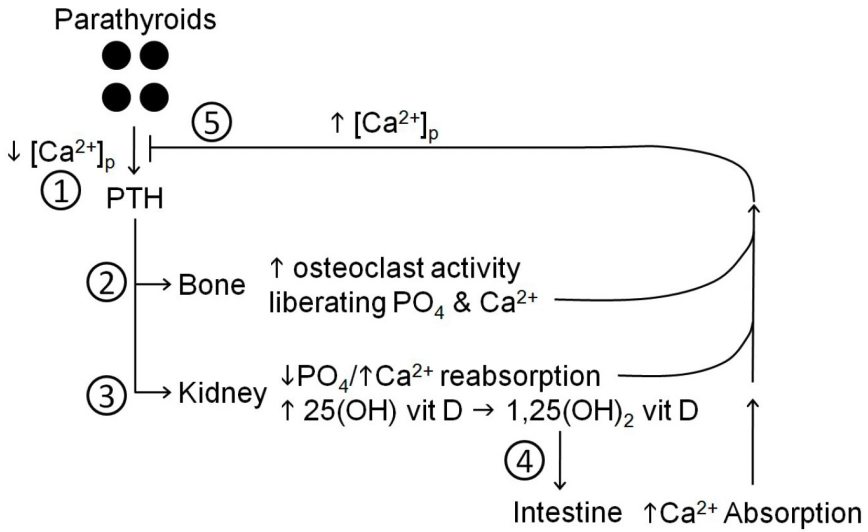
Pharmacology of Bone

ENDOGENOUS PARATHYROID HORMONE (PTH)

↓ plasma calcium is primary stimulus for PTH secretion from parathyroid glands

PTH ↑ plasma calcium via its effects on bone, kidney, intestines

Net effect of ↑ PTH concentrations is increased bone resorption, hypercalcemia, and hyperphosphatemia



EXOGENOUS PARATHYROID HORMONE MOA

Recombinant parathyroid hormone

Stimulates the formation of NEW bone and increases bone mass

Low intermittent doses of PTH produce **a net increase in bone formation**
This is the basis for the use of exogenous PTH (1-34)

EXOGENOUS PARATHYROID HORMONE - TERIPARATIDE

Contains the first 34 amino acids in human parathyroid hormone

- Although hyperparathyroidism leads to bone loss, therapeutic doses (for shorter periods of time) conversely improve bone mineral density
- Only approved osteoporosis medication that works by **stimulating bone formation**

PARATHYROID HORMONE - TERIPARATIDE

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Teriparatide (Forteo) 💉 Abaloparatide (Tymlos) 💉	Should not be used in patients at an increased risk of osteosarcoma (e.g., patients with Paget's disease of the bone, unexplained elevations in alkaline phosphatase, history of previous skeletal radiation therapy)	**Hypercalcemia** Worsening nephrolithiasis Orthostatic hypotension Nausea Pain Joint aches	When used with bisphosphonates, may interfere with normalization of blood calcium concentrations
Boxed Warning for teriparatide: Potential osteosarcoma risk			

CLINICAL USE

Osteoporosis

Only approved osteoporosis class that that works by stimulating bone formation

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

INTERACTIVE LEARNING

3. Write down the abbreviated mechanism of action for:

Bisphosphonates

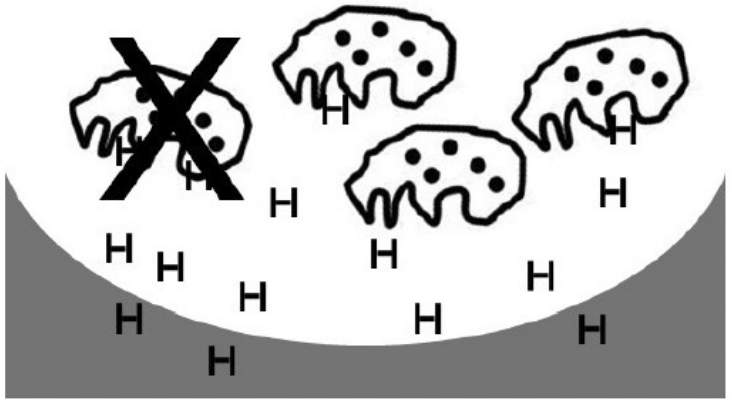
Denosumab

Teriparatide

BISPHOSPHATE MECHANISM OF ACTION

Bisphosphonates mimic endogenous pyrophosphate and bind to hydroxyapatite

- They are released upon remodeling
- The released bisphosphonate is internalized by the phagocytic osteoclast inducing apoptosis

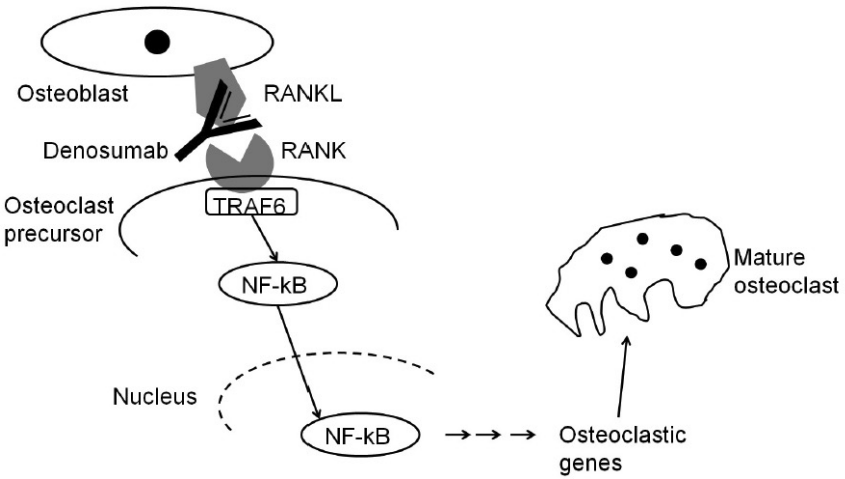


DENOSUMAB MECHANISM OF ACTION

RANKL produced by osteoblasts binds to RANK on the surface of osteoclast precursors and recruits the adaptor protein TRAF6, leading to NF-kB activation and translocation to the nucleus

NF-kB increases c-Fos expression and c-Fos interacts with NFATc1 to trigger the transcription of osteoclastogenic genes leading to mature osteoclasts

Denosumab blocks RANKL and decreases osteoclast production



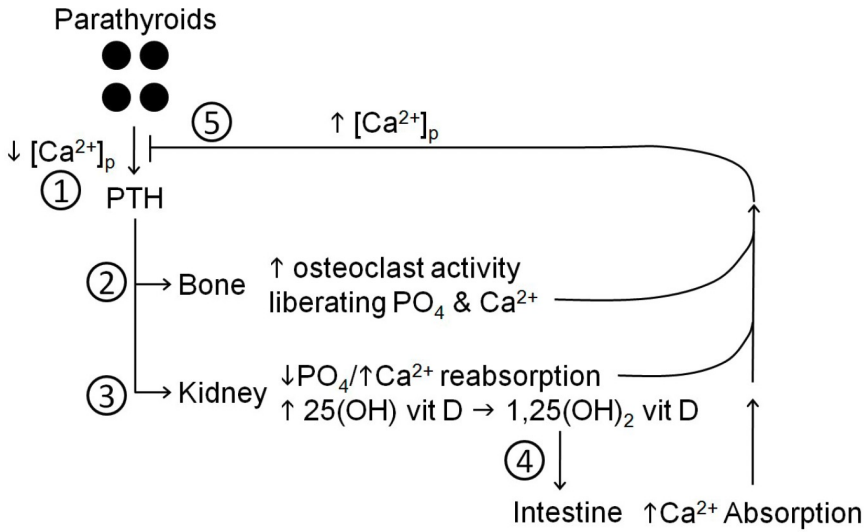
PARATHYROID HORMONE

Decreased plasma calcium is the primary stimulus for PTH secretion from the parathyroid glands

- PTH raises plasma calcium via its effects on bone, kidney and, indirectly, intestines

The net effect of high PTH concentrations is increased bone resorption, hypercalcemia, and hyperphosphatemia

Low intermittent doses of PTH produce a net increase in bone formation
This is the basis for the use of exogenous PTH (1-34)



SELECTIVE ESTROGEN RECEPTOR MODULATORS

Pharmacology of Bone

ACTIVE LEARNING

If estrogen deficiency significantly increases a patient's risk for osteoporosis and fractures, why do we not use exogenous estrogen as treatment for osteoporosis?

SERM MOA

Interact selectively with estrogen receptors (agonist and antagonist properties)

Estrogen receptor **agonist/antagonist**

- **Acts as an antagonist (antiestrogen) in the breast and uterus**
- **Agonist in bone, liver**

Antiestrogen in breast (reduces the risk of breast cancer)

Like estrogen, the selective estrogen receptor modulators (SERMs) can increase the risk for thromboembolism

Recall, estrogen receptors are steroid receptors and belong to the nuclear receptor structural family

SERMS (RALOXIFENE)

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Raloxifene (Evista)	Women with a history of or current venous thromboembolic disorders Women who are pregnant or plan to become pregnant in the immediate future.	**Increased risk of thromboembolic events** (promotes synthesis of clotting factors) Hot flashes (due to blocking effects of estrogen) Teratogenic	Avoid with ospemifene Bile acid sequestrants decrease absorption of raloxifene Raloxifene decreases absorption of levothyroxine

CLINICAL USE

Prevention of postmenopausal osteoporosis

Osteoporosis treatment

CALCITONIN

Pharmacology of Bone

CALCITONIN MOA

Calcitonin is most potent peptide inhibitor of osteoCLAST-mediated bone resorption

Calcitonin acts through the calcitonin receptor

- G-protein coupled receptor linked to Gs and Gq
- Regulates calcium levels by inhibiting osteoCLASTIC activity (breakdown of bone)

Exogenous calcitonin can be used in established osteoporosis, but studies have not shown a clear benefit to its use

Exogenous calcitonin must be administered subcutaneously or by nasal spray

- May have some analgesic action, which may be of benefit in patients with fractures

CALCITONIN

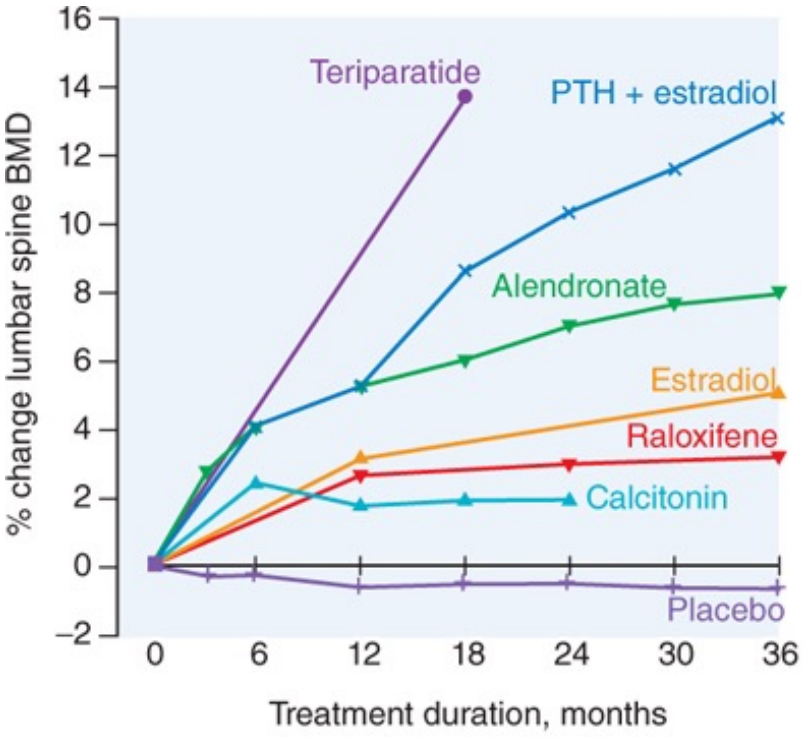
Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Calcitonin (salmon) (Miacalcin)	Hypersensitivity to salmon Cautions: Hypocalcemia Malignancy	Nasal include rhinitis and epistaxis Parenteral include flushing, nausea, and local irritation at injection site	May ↓ lithium concentrations May diminish the therapeutic effect of Sincalide Calcitonin may enhance the hypocalcemic effect of Zoledronic Acid.

CLINICAL USE

Osteoporosis treatment (postmenopausal)

Paget's disease

Hypercalcemia



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

ACTIVE LEARNING

Why does teriparatide increase lumbar spine BMD more than other agents?

REFERENCE LIST

Agents That Affect Bone Mineral Homeostasis. In: Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. eds. Katzung & Trevor's Pharmacology: Examination & Board Review, 13e. McGraw Hill; 2021. Accessed September 30, 2022.
https://accessmedicine.mhmedical.com/content.aspx?bookid=3058&sectionid=255306902

Bikle DD. Agents That Affect Bone Mineral Homeostasis. In: Katzung BG, Vanderah TW. eds. Basic & Clinical Pharmacology, 15e. McGraw Hill; 2021. Accessed September 30, 2022.
https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250601489

Drugs Used in Osteoporosis. In: Stringer JL. eds. Basic Concepts in Pharmacology: What You Need to Know for Each Drug Class, 5e. McGraw Hill; 2017. Accessed September 30, 2022.
https://accessmedicine.mhmedical.com/content.aspx?bookid=2147&sectionid=161352648

Nolin TD, Friedman PA. Agents Affecting Mineral Ion Homeostasis and Bone Turnover. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e. McGraw Hill; 2017. Accessed September 27, 2022.
https://accessmedicine.mhmedical.com/content.aspx?bookid=2189&sectionid=172483095

Raffa RB, Rawls SA, Portyansky B, et al. Drugs Used in Disorders of the Endocrine System. In: Netter's Illustrated Pharmacology, Chapter 5, 129-167.

WASHINGTON STATE UNIVERSITY
Elson S. Floyd
College of Medicine

ANY QUESTIONS?