Lec. 3: Drugs Affecting Bone Metabolism

م.د شيرين محمد مكي الحسيني

Bone metabolism

is a continual cycle of bone growth and resorption that is carefully orchestrated by the dynamic relationship between osteoclasts, osteoblasts and an array of hormonal and regulatory influences.

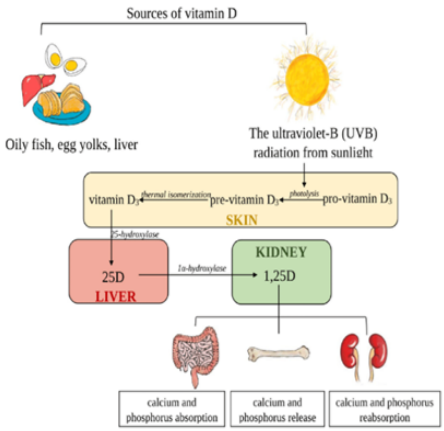
Disturbances to this delicate equilibrium where resorption is greater than growth can weaken the skeletal architecture and put one at risk for the development of chronic and debilitating diseases such as Osteoporosis.

- Bone modeling describes the process whereby bones are shaped or reshaped by the independent action of osteoblast and osteoclasts which are not necessarily coupled on time or site considrations. Bone modeling defines skeletal development and growth but continues throughout life.
- Bone remodeling is a process where osteoclasts and osteoblasts work sequentially in the same bone remodeling unit. After the attainment of peak bone mass, bone remodeling is balanced and bone mass is stable for one or two decades until age-related bone loss begins. Age-related bone loss is caused by increases in resorptive activity and reduced bone formation.

MAJOR REQUIREMENTS AND REGULATORS FOR BONE METABOLISM

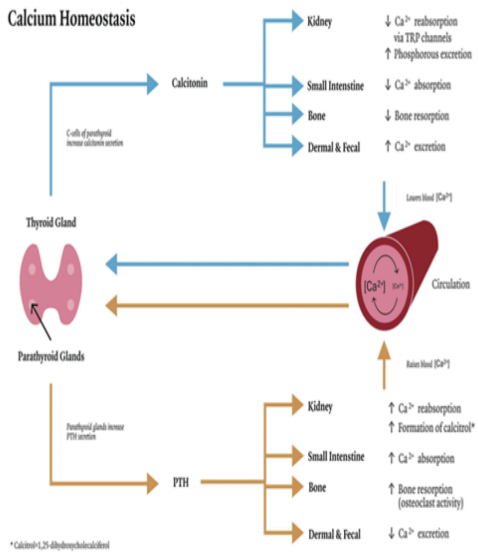
1-

Vitamin D and Calcium: vitamin D is found as either cholcalciferol (D3) or ergosterol (D2), which is derived from planets, both must be hydroxylated renally by 1-alpha-hydroxylase,to yield the biologically active form (1,25-dihydroxycholecalciferol =(calcitriol)).



2- PARATHYROID HORMON (PTH) AND CALCITONIN:

Reduced circulating calcium will stimulate PTH release, while elevated circulating calcium will stimulate calcitonin release from the parathyroid gland.



Physiologic mechanisms of calcium homeostasis. Calcium is raised via the release of parathyroid hormone (PTH). PTH secretion increases Ca 2+ absorption in the kidneys and small intestine and decreases excretion through dermal and fecal routes. PTH enhances the formation of calcitriol in the kidneys in concert with insulin-like growth factor 1. Bone resorption is increased. Calcium is lowered via calcitonin secretion from C cells of the parathyroid. Calcitonin downregulates Ca 2+ absorption in the kidneys and small intestine, and increases dermal and fecal excretion of Ca 2+ . Bone resorption is decreased. TRP: transient receptor potential.

Bone Diseases

- Osteoporosis, Paget disease, and Osteomalacia are disorders of the bone.
- **Osteoporosis is characterized by progressive loss of bone** mass **and skeletal fragility.**
- Patients with osteoporosis have an increased risk of fractures, which can cause significant morbidity.
- **Osteoporosis occurs most frequently in postmenopausal women and older adults of both sexes.**

Paget disease

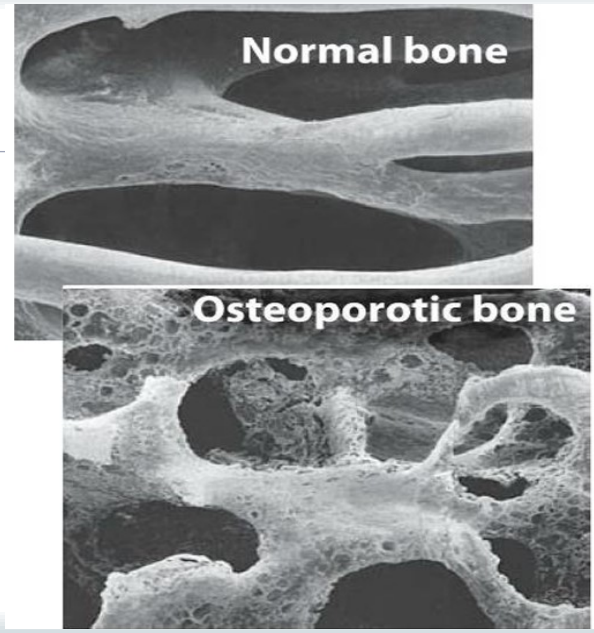
- Paget disease is a disorder of bone remodeling that results in disorganized bone formation and enlarged or misshapen bones.
- Unlike osteoporosis, Paget disease is usually limited to one or a few bones.
- Patients may experience bone pain, bone deformities, or fractures.
- Osteomalacia is softening of the bones that is most often attributed to vitamin D deficiency.
- [Note: Osteomalacia in children is referred to as rickets].

Drugs that can contribute to bone loss or increased fracture risk.

Aluminum antacids
Anticonvulsants (e.g., *phenytoin*)
Aromatase inhibitors
Furosemide
Glucocorticoids
Heparin
Medroxyprogesterone acetate
Proton pump inhibitors
Selective serotonin reuptake inhibitors
Thiazolidinediones
Thyroid (excessive replacement)

Bone remodeling

- Throughout life, bone undergoes continuous remodeling, with about 10% of the skeleton replaced each year.
- Bone remodeling serves to remove and replace damaged bone and to maintain calcium homeostasis.
- Osteoclasts are cells that break down bone, a process known as bone resorption.
- Following bone resorption, osteoblasts or bone-building cells synthesize new bone.
- Crystals of calcium phosphate known as hydroxyapatite are deposited in the new bone matrix during the process of bone mineralization.
- Bone loss occurs when bone resorption exceeds bone formation during the remodeling process.



Prevention of osteoporosis

- Strategies to reduce bone loss in postmenopausal women include adequate dietary intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, and avoidance of excessive alcohol intake.
- **Patients with inadequate dietary intake of calcium should receive calcium supplementation.**
- Calcium carbonate is an inexpensive and commonly used calcium supplement. It contains 40% elemental

- calcium and should be taken with meals for best absorption. Calcium citrate (21% elemental calcium) is better tolerated and may be taken with or without food.
- **Adverse effects of calcium supplementation include gas and bloating. Calcium may interfere with absorption of iron preparations, thyroid replacement, and fluoroquinolone and tetracycline antibiotics, and administration of these drugs should be separated by several hours.**
- Vitamin D is essential for absorption of calcium and bone health, and older patients are often at risk for vitamin D deficiency. Supplementation with vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) is used for treatment.

Treatment of osteoporosis

- Pharmacologic therapy for osteoporosis is warranted in postmenopausal women and men aged 50 years or over who have a previous osteoporotic fracture, a bone mineral density that is 2.5 standard deviations or more below that of a healthy young adult, or a low bone mass (osteopenia) with a high probability of future fractures.

Bisphosphonates

- Bisphosphonates including alendronate, risedronate, and zoledronic acid are preferred agents for treatment of postmenopausal osteoporosis.
- These bisphosphonates, along with etidronate, ibandronate, pamidronate, and tiludronate, comprise an important drug group used for the treatment of bone disorders such as osteoporosis and Paget disease, as well as for treatment of bone metastases and hypercalcemia of malignancy.

- **Mechanism of action:** Bisphosphonates bind to hydroxyapatite crystals in the bone and decrease osteoclastic bone resorption, resulting in a small increase in bone mass and a decreased risk of fractures in patients with osteoporosis.
- **The beneficial effects of alendronate persist over several years of therapy, but discontinuation results in a gradual loss of effects.**

- **Pharmacokinetics:** The oral bisphosphonates alendronate, risedronate, and ibandronate are dosed on a daily, weekly, or monthly basis depending on the drug.

BISPHOSPHONATE	FORMULATION	DOSING FREQUENCY*
Alendronate	Oral tablet Effervescent tablet	Daily or weekly Weekly
Ibandronate	Oral tablet Intravenous	Daily or monthly Every 3 months
Risedronate	Oral tablet Oral delayed-release tablet	Daily, weekly, or monthly Weekly
Zoledronic acid	Intravenous	Yearly

DOSING INSTRUCTIONS FOR ORAL BISPHOSPHONATES

- Take with 6 to 8 ounces of plain water only
  [Note: Take *risedronate* delayed-release tablet with at least 4 ounces of plain water]
- Take at least 30 minutes (60 minutes for *ibandronate*) BEFORE other food, drink, or medications
  [Note: Take *risedronate* delayed-release tablet immediately AFTER breakfast]
- Remain upright and do not lie down or recline for at least 30 minutes (60 minutes for *ibandronate*) after taking

- Absorption after oral administration is poor, with less than 1% of the dose absorbed.
- **Food and other medications significantly interfere with absorption of oral bisphosphonates.**
- Bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to hydroxyapatite in the bone.
- **Elimination is predominantly via the kidney, and bisphosphonates should be avoided in severe 37 renal impairment.**
- For patients unable to tolerate oral bisphosphonates, intravenous ibandronate and zoledronic acid are alternatives.

- **Adverse effects:** These include diarrhea, abdominal pain, and musculoskeletal pain. Alendronate, risedronate, and ibandronate are associated with esophagitis and esophageal ulcers.
- **To minimize esophageal irritation, patients should remain upright after taking oral bisphosphonates.**
- Although uncommon, osteonecrosis of the jaw and atypical femur fractures may occur with use of bisphosphonates.
- **The risk of atypical fractures seems to increase with long-term use of bisphosphonates. Therefore, current guidelines recommend a drug holiday for some patients after 5 years of oral bisphosphonates or 3 years of zoledronic acid. Figure below show relative potencies of the bisphosphonates.**

Bisphosphonate	Antiresorptive activity
Etidronate	1
Tiludronate	10
Pamidronate	100
Alendronate	1000
Risedronate	5000
Ibandronate	10,000
Zoledronic acid	10,000

Denosumab

- Denosumab is a monoclonal antibody that targets receptor activator of nuclear factor kappa-8 ligand and inhibits osteoclast formation and function.
- Denosumab is approved for the treatment of postmenopausal osteoporosis in women at high risk of fracture.
- It is administered via subcutaneous injection every 6 months.
- Denosumab is considered a first-line agent for osteoporosis, particularly in patients at higher risk of fractures.
- The drug has been associated with an increased risk of infections, dermatological reactions, hypocalcemia, and rarely, osteonecrosis of the jaw, and atypical fractures.

Parathyroid agents

- Teriparatide is a recombinant form of human parathyroid hormone and abaloparatide is an analog of parathyroid hormone-related peptide.
- These drugs act as agonists at the parathyroid hormone receptor, and once-daily subcutaneous administration results in stimulation of osteoblastic activity and increased bone formation and bone strength.
- By contrast, other drugs for osteoporosis inhibit bone resorption.
- These agents should be reserved for patients at high risk of fractures and those who have failed or cannot tolerate other osteoporosis therapies. Both drugs have been associated with hypercalcemia, orthostatic hypotension, and an increased risk of osteosarcoma in rats. Cumulative lifetime use of either agent for more than 2 years is not recommended.

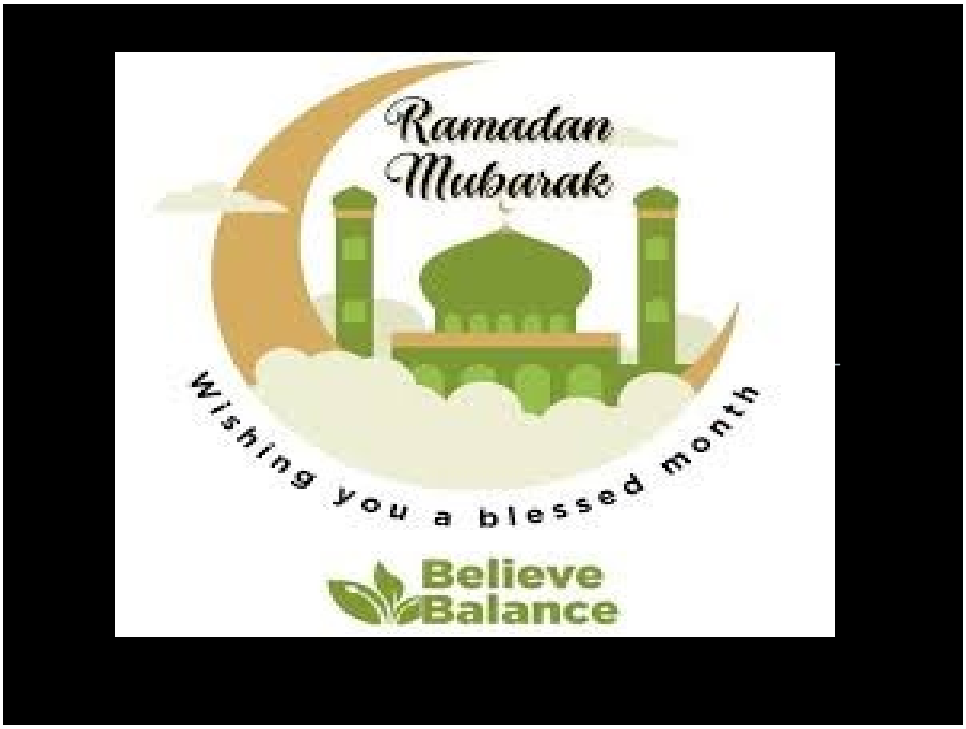
Selective estrogen receptor modulators

- Lower estrogen levels after menopause promote proliferation and activation of osteoclasts, and bone mass can decline rapidly.
- Estrogen replacement is effective for the prevention of postmenopausal bone loss.
- However, since estrogen may increase the risk of endometrial cancer, breast cancer, stroke, venous thromboembolism, and coronary events, it is no longer recommended as a preventive therapy for osteoporosis.
- Raloxifene is a selective estrogen receptor modulator approved for the prevention and treatment of osteoporosis.

- It has estrogen-like effects on bone and estrogen antagonist effects on breast and endometrial tissue.
- **Therefore, raloxifene increases bone density without increasing the risk of endometrial cancer, raloxifene should be used as an alternative to bisphosphonates or denosumab in the treatment of postmenopausal osteoporosis.**
- Adverse effects include hot flashes, leg cramps, and increased risk of venous thromboembolism.

Calcitonin

- Salmon calcitonin is indicated for the treatment of osteoporosis in women who are at least 5 years postmenopausal.
- **The drug reduces bone resorption, but it is less effective than other agents, and is no longer routinely recommended for the treatment of osteoporosis.**
- The intranasal formulation is most commonly used in osteoporosis, and adverse effects include rhinitis and other nasal symptoms.


Ramadan
Mubarak
Wishing you a blessed month
Believe
Balance