Therapy of Osteoporosis

** Drug-Induced Osteoporosis :

الحكي مبين كثير هون بس التأثير نفسه بكل الادوية

Glucocorticoids	They decrease osteocyte and osteoblast function and number They increase osteoclast proliferation while decreasing osteoclast apoptosis. They decrease calcium absorption and increased urinary calcium excretion
Acid Suppression Therapy (PPI)	They decrease magnesium, iron, calcium, and vitamin B12 And deficiency of these elements result in reduction of osteoblast activity while increasing osteoclast activity , reducing muscle strength, and increasing risk for falling.
Antidepressants SSRIs + SNRIs	fracture risk is increased by increasing peripheral serotonin which affect bone by decreasing sympathetic tone, leading to an increase osteoclast activity and reduction of osteoblast activity.
Aromatase inhibitors	They reduce peripheral estrogen which causes accelerated bone loss and increased fracture risk.
Androgen-Deprivation Therapy	GnRH therapy inhibits gonadotropins (when they are administered continuously not in a pulsatile fashion) , thereby reducing testosterone and estrogens which causes an increase in interleukin-6 (IL-6), which stimulates osteoclastogenesis.

Other Drugs Associated with Osteoporosis

و هون نفس المبدأ

Anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)	↓ BMD (bone mineral density) and ↑ fracture risk; increased vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Furosemide	↑ fracture risk; increased calcium elimination by the kidney
Heparin (unfractionated, UFH) or low molecular weight heparin (LMWH)	↓ BMD and ↑ fracture risk (UFH >>> LMWH) with long-term use (> 6 months); decreased osteoblast formation and increased osteoclast function
Thiazolidinediones (pioglitazone and rosiglitazone)	↓ BMD and ↑ fracture risk; inhibit osteoblast differentiation and activate osteoclast differentiation
Canagliflozin (sodium-glucose co-transport 2 (SGLT-2) inhibitors)	↓ BMD and ↑ fracture risk Mechanism is controvercial

Prevention and treatment

Prevention >> **Optimizing skeletal development and peak bone mass gain** >> Nonpharmacologic Therapy >> Pharmacologic Therapy

****Adequate intake of calcium and vitamin D is the first step in prevention and treatment.**

** exercises and a diet well balanced in nutrients and minerals (**without excessive protein**) and limited use of salt, alcohol, smoking and caffeine are important for bone health.

** Carbohydrates, fat, and lactose increase calcium absorption whereas fiber, wheat bran, phytates (beans), oxylates (spinach), **high**-protein diets, caffeine, and smoking decrease absorption.

**Darkly pigmented skin can decrease vitamin D production.

Pharmacologic Therapy

Drug Treatments of First Choice:

1) **Biphosphonates** (alendronate , risedronate , zoledronic acid) combined with **adequate calcium and vitamin D** intake, or **denosumab** **are the prescription medications of choice.**
2) Ibandronate, teriparatide or raloxifene are **alternatives**, and calcitonin is **last-line therapy.**

** Prescription therapy should be considered in any **postmenopausal woman** or **man age 50 years and older** presenting with osteoporosis or low bone mass with a significant probability of hip or any other osteoporosis-related fracture.

1**- Calcium Supplementation**: It should be combined with vitamin D

Adverse Effects:

- Constipation.
- gas and cause stomach upset
- **May** increase kidney stones ?

Drug Interactions:

• Proton pump inhibitors can decrease calcium absorption.
• Fiber laxatives can decrease the absorption of calcium if given concomitantly.
• Calcium can decrease the oral absorption of some drugs including iron, tetracyclines, quinolones, **bisphosphonates**, and thyroid supplements.

لهيك ما بنعطيهم بنفس الوقت

2- Vitamin D Supplementation: Vitamin D maintenances doses (800-2,000 units daily).

Drug Interactions:

• Some drugs can induce vitamin D metabolism:rifampin, phenytoin, barbiturates, and carbamazepine.

• Vitamin D absorption can be decreased by cholestyramine, colestipol, orlistat, and mineral oil.

3- Bisphosphonates : Reduce fracture risk and increases BMD.

•Alendronate, risedronate, and intravenous zoledronic acid are indicated for postmenopausal females, males, and glucocorticoid-induced osteoporosis.

• Intravenous and oral ibandronate is indicated only for postmenopausal osteoporosis.

After discontinuation, the increased BMD is **sustained for a prolonged period of time.

Adverse Effects:

1) GI complaints: heartburn and dyspepsia, esophageal erosion and ulceration, GI bleeding, and they are the most common reasons for discontinuing therapy.

2) Injection reactions and musculoskeletal pain.

3) Fever, flu-like symptoms, myalgias, and arthralgias with IV administration (treated by acetaminophen)

4) Rarely, osteonecrosis of the jaw and atypical subtrochanteric femoral fractures

Contraindications :

-Patients with creatinine clearances less than 30- 35 mL/min.

-Patients who have serious GI upset

-Patients who are pregnant should not take bisphosphonates.

Administration:

Each oral table >> 180ml plain water >> 30 min before consuming food or ca++ or vit D>> 30 min remain upright (60 min for Ibandronate)

**Before intravenous bisphosphonates are used, the patient's serum calcium concentration must be normalized.

4) Denosumab:

Indication

1) in women and men at high risk of fractures.
2) To increase bone mass in men receiving androgen deprivation therapy [antiandrogens (flutamide), LHRH agonists (Leuprolide) for nonmetastatic prostate cancer.
3) in women receiving adjuvant aromatase inhibitor therapy (anastrozole) for breast cancer who are at high risk of fractures.

****The half-life is ~ 25 days and the concentration slowly declines over a period of 4 to 5 months.**

****No dosage adjustment is necessary in renal impairment.**

****Activity dissipates with drug discontinuation .**

Adverse Effects:

1. Dermatitis, eczema, and rashes.
2. Bone turnover suppression.
3. Serious infections including skin infections.
4. Muscle, bone, and joint pain and atypical fractures.
5. hypocalcemia

5) Mixed Estrogen Agonists/Antagonists:

• **Raloxifene** is an agonist at bone estrogen receptors and antagonist at breast estrogen receptors; it has minimal effect on the uterus.(it reduce the risk of invasive breast cancer)

• **Bazedoxifene** is an agonist at bone, and antagonist at the uterus and breast, with no breast cancer prevention effects.

Adverse Events

- Hot flushes (with raloxifene)
- Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these adverse events
- Leg cramps and muscle spasms are common / VTE are uncommon

Drug interaction

Raloxifene-Warfarin / Raloxifene-Cholestyramine / Estrogen metabolism is decreased with CYP3A4 inhibitors / Rifampin, phenytoin, carbamazepine, and phenobarbital can decrease bazedoxifene levels

Contraindications

VTE , pregnancy, Coronary artery disease , PVD ,a fib , CVA

6) Teriparatide

It is a recombinant human product representing the first 34 amino acids in human PTH.

Indications

1. Postmenopausal women at high risk of fractures.
2. Men with idiopathic or hypogonadal osteoporosis at high risk of fractures.
3. Men or women intolerant to other osteoporosis medications.
4. Patients with glucocorticoid-induced osteoporosis.
5. Patients who have a history of osteoporotic fracture

**Discontinuation of teriparatide therapy results in a decrease in BMD.

Administration

Daily subcutaneous injection with site rotation in sitting or lying down position to avoid orthostatic hypotension.

Adverse Effects:

- Transient and rare hypercalcemia (avoid in patients having hypercalcemia).
- May predispose to osteosarcoma (seen in lab animals).
- Avoid in Paget's bone disease, unexplained elevations of alkaline phosphatase, patients with open epiphyses, or patients with prior radiation therapy involving the skeleton.