Therapy of Osteoporosis

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Therapy of Osteoporosis

- **Osteoporosis is a bone disorder characterized by: low bone mineral density, impaired bone architecture, and compromised bone strength, that predispose to an increased fracture risk.**
- **Osteoporosis is a major public health problem, with 55% of the people 50 years of age and older are expected to have this disease.**

Risk Factors of Osteoporosis

1. Female gender.
2. Advanced age.
3. Low body weight.
4. Systemic oral glucocorticoid therapy.
5. Cigarette smoking.
6. Alcohol (3 or more drinks/day).
7. Low calcium intake.
8. Low physical activity.
9. Vitamin D insufficiency and deficiency.
10. Others.

Drug-Induced Osteoporosis

1. **Glucocorticoids:**

- **Fracture risk increases before changes in BMD are detected.**
- **They decrease osteocyte and osteoblast function, and increase osteocyte and osteoblast apoptosis.**
- **They increase osteoclast proliferation while decreasing osteoclast apoptosis.**

Drug-Induced Osteoporosis

- **These medications also affect the neuroendocrine system and calcium metabolism and damage muscles.**
- **They decrease calcium absorption and increased urinary calcium excretion via alterations in calcium transporters.**
- **If you are interested, see this:**

https://www.ncbi.nlm.nih.gov/books/NBK278968/

Drug-Induced Osteoporosis

2. **Proton pump inhibitors (PPIs):**

- **Long-term PPI use is associated with a modest but consistent increase in the risk of fragility osteoporotic fractures in the hip, spine and wrist.**
- **The mechanism(s) is not clear.**
- **There is a lack of consistent effects of PPIs on bone mineral density loss.**

Drug-Induced Osteoporosis

- **PPIs increase the risk for multiple nutritional deficiencies (magnesium, iron, calcium, and vitamin B_{12}).**
- **Decreased serum magnesium reduces osteoblast activity while increasing osteoclast activity.**
- **Decreased serum calcium can induce bone resorption.**

Drug-Induced Osteoporosis

- **Low vitamin B_{12} can increase blood homocysteine, which increases pre-osteoblast cell apoptosis and osteoclastogenesis.**
- **Reductions in vitamin B_{12} can lead to peripheral neuropathy, reduced muscle strength, and increased risk for falling.**

Drug-Induced Osteoporosis

3. **Antidepressants:**

- **The mechanism by which SSRIs and SNRIs medications increase fracture risk is by increased peripheral serotonin levels.**
- **Serotonin enhances osteoclastic activity, leading to reduced bone mass and fractures.**

Drug-Induced Osteoporosis

4. **Aromatase inhibitors:**

- **They reduce peripheral estrogen levels below those attained from natural menopause, which causes accelerated bone loss and increased fracture risk.**
- **Estrogen deficiency upregulates osteoclast formation and increases the lifespan of osteoclasts, leading to increased bone loss, cortical porosity, and enlarged resorption areas.**

Drug-Induced Osteoporosis

5. **Androgen-Deprivation Therapy:**

- **GnRH therapy inhibits gonadotropins, thereby reducing testosterone and estrogens.**
- **Androgen deprivation causes an increase in interleukin-6 (IL-6), which stimulates osteoclastogenesis.**
- **Androgen receptors (ARs) on osteoblasts promote osteoblast differentiation, which decreases bone resorption.**

Other Drugs Associated with Osteoporosis

Drug	Comments
Anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)	↓ BMD 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

Desired Outcomes:

1. **The primary goal of osteoporosis care should be prevention.**
2. **Optimizing skeletal development and peak bone mass gain in childhood, adolescence, and early adulthood will reduce the future incidence of osteoporosis.**
3. **Once low bone mass or osteoporosis develops, the objective is to stabilize bone, improve bone strength and bone mass and prevent fractures.**

Prevention and Treatment

4. In patients who have already suffered osteoporotic fractures, reducing pain and deformity, improving functional capacity, improving quality of life, and reducing future falls and fractures are the main goals.

Prevention and Treatment

General approach to prevention and treatment:

A. **A bone-healthy life-style should begin at birth and continue throughout life: weight reduction, proper nutrition, moderation of alcohol intake, smoking cessation, exercise, and fall prevention.**

- **If employed early in life, it will help to optimize peak bone mass, and if continued throughout life it minimizes bone loss over time.**

Prevention and Treatment

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

C. **Prescription therapy is advised in any postmenopausal woman, or man age 50 years and older, presenting with a hip or vertebral fracture or low bone mass.**

Nonpharmacologic Therapy

Diet:

- **A diet well balanced in nutrients and minerals (without excessive protein) and limited use of salt, alcohol, and caffeine are important for bone health.**
- **Adequate amounts of calcium, vitamin D, and protein have documented impacts on bone health.**

Nonpharmacologic Therapy

- **Being thin or having anorexia nervosa decrease bone mass.**

Calcium:

- **Adequate calcium intake is necessary for calcium homeostasis throughout life, bone development during growth, and bone maintenance.**
- **Dairy products have high amount of calcium.**

Nonpharmacologic Therapy

- **Carbohydrates, fat, and lactose increase calcium absorption whereas fiber, wheat bran, phytates (beans), oxylates (spinach), high-protein diets, caffeine, and smoking decrease absorption.**
- **When diet is NOT associated with adequate intake of calcium, calcium supplements are required.**

Nonpharmacologic Therapy

Vitamin D:

- **The 3 main sources of vitamin D are sunlight (cholecalciferol and vitamin D_3), diet, and supplements.**
- **Vitamin D_3 and D_2 come from oily fish, eggs, fortified dairy products.**
- **Inadequate concentrations of 25(OH) vitamin D are common.**

Nonpharmacologic Therapy

- **Low vitamin D concentrations result from insufficient intake, dietary fat malabsorption, decreased sun exposure, decreased skin production, or decreased liver and renal metabolism of vitamin D (may be genetically determined).**
- **Endogenous synthesis of vitamin D can be decreased by Sunscreen use.**
- **Darkly pigmented skin can decrease vitamin D production.**

Nonpharmacologic Therapy

- **Seasonal variations in vitamin D concentrations are seen with troughs in late winter and peaks in late summer.**
- **Because few foods are naturally high or fortified with vitamin D, most people, especially older adults, require supplementation.**

Nonpharmacologic Therapy

Alcohol:

- **Excessive alcohol consumption increases the risk for osteoporosis and fractures.**
- **It increases bone resorption and decreases bone formation by inhibiting signaling pathways and increasing oxidative stress that results in osteoblast apoptosis.**
- **Alcoholics may have poor nutrition, decreased calcium absorption, altered vitamin D metabolism, and impaired balance resulting in falls and fractures.**

Nonpharmacologic Therapy

Caffeine (?):

- **Although results are conflicting, excessive caffeine consumption may be associated with increased calcium excretion, increased rates of bone loss, and a modestly increased risk for fracture.**

Nonpharmacologic Therapy

Smoking:

- **Smoking cessation helps to optimize peak bone mass, minimize bone loss, and reduce fracture risk.**
- **The effect is dose- and duration-dependent, but even passive smoking shows adverse effects on BMD.**
- **It reduces intestinal calcium absorption.**
- **It increases 25(OH) vitamin D catabolism.**

Nonpharmacologic Therapy

Exercise:

- **It decreases the risk of falls and fractures by stabilizing bone density and improving muscle strength, coordination, balance, and mobility.**
- **Lack of physical activity can lead to suboptimal loading/straining, decreased stimulation of bone deposition, and a subsequently reduced peak bone mass.**

Nonpharmacologic Therapy

- **All patients who are medically fit should be encouraged to perform:**

A. a moderate-intensity weight-bearing activity (walking, jogging, golf, and stair climbing) daily.

B. a resistance activity (weight machines, free weights, or elastic bands).

Pharmacologic Therapy

Drug Treatments of First Choice:

- **Biphosphonates (alendronate, risedronate, zoledronic acid), combined with adequate calcium and vitamin D intake, or denosumab are the prescription medications of choice.**
- **This is based on evidence of reduction of the risk of hip and vertebral fractures.**
- **Ibandronate, teriparatide or raloxifene are alternatives, and calcitonin is last-line therapy.**

Pharmacologic 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.**

Antiresorptive Therapies

Antiresorptive therapies include:

1. **Calcium**
2. **Vitamin D**
3. **Bisphosphonates**
4. **Denosumab**
5. **Estrogen agonists/antagonists (known previously as selective estrogen receptor modulators or SERMs)**
6. **Tissue selective estrogen complexes**
7. **Calcitonin**
8. **Estrogen**
9. **Testosterone**

Antiresorptive Therapies

Calcium Supplementation:

- It should be combined with vitamin D, especially when osteoporosis medications are taken.

Adverse Effects:

1. Constipation.
2. Gas can cause stomach upset.
3. May increase risk of kidney stones (?).

Antiresorptive Therapies

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.**

Antiresorptive Therapies

Vitamin D Supplementation:

- **Vitamin D intake is critical for intestinal calcium absorption and when combined with calcium can prevent bone loss and decrease osteoporotic fractures.**
- **Vitamin D maintenances doses (800-2,000 units daily).**
- **Serum 25(OH) vitamin D is the best indicator of total body vitamin D status.**

Antiresorptive Therapies

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.**

Antiresorptive Therapies

Bisphosphonates:

- **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.**

Bisphosphonates

Pharmacology:

- **Are analogs of pyrophosphate in which the P-O-P bond is replaced by a nonhydrolyzable P-C-P bond.**
- **Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor.**
- **They decrease osteoclast maturation, number, recruitment, bone adhesion, and life span.**

Bisphosphonates

- **They retard formation and dissolution of hydroxyapatite crystals.**
- **They localize to regions of bone resorption and so exert their greatest effects on osteoclasts in osteoporotic areas.**

Clinical Effects:

- **Reduce fracture risk and increases BMD.**
- **The effect is dose-dependent and greatest in the first year of therapy.**

Bisphosphonates

- **Weekly alendronate, weekly and monthly risedronate, and monthly oral and quarterly intravenous ibandronate therapy produce equivalent BMD changes to their respective daily regimens.**
- **After discontinuation, the increased BMD is sustained for a prolonged period of time.**

Bisphosphonates

Adverse Effects:

1. **GI complaints: heartburn and dyspepsia, esophageal erosion and ulceration, GI bleeding.**

- **GI complaints are the most common reasons for discontinuing therapy.**
- **Intravenous ibandronate and zoledronic acid can be used for patients with GI contraindications or intolerances to oral bisphosphonates.**

Bisphosphonates

2. **Injection reactions and musculoskeletal pain.**

- **If severe musculoskeletal pain occurs, the medication can be discontinued temporarily or permanently.**

3. **Fever, flu-like symptoms, myalgias, and arthralgias are typically associated with intravenous administration.**

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

Bisphosphonates

Contraindications:

1. **Patients with creatinine clearances less than 30-35 mL/min.**
2. **Patients who have serious GI upset, peptic ulcer disease or esophageal motility disorders.**
3. **Patients who are pregnant <u>should not take bisphosphonates</u>.**

Bisphosphonates

Administration:

1. **Each oral tablet should be taken with at least (~180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for ibandronate) before consuming any food, supplements (calcium and vitamin D), or drugs.**

- **The patient should remain upright (either sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration.**

Bisphosphonates

2. **A patient who misses a weekly dose can take it the next day.**

- **If more than 1 day has lapsed, that dose is skipped until the next scheduled ingestion.**

3. **A patient who misses a monthly dose:**

- **If the next month's dose is > 7 days away, take the missed dose when you remember. Then resume your normal schedule.**
- **If the next dose is < 6 days away, wait until the next scheduled dose.**

Bisphosphonates

- **Before intravenous bisphosphonates are used, the patient's serum calcium concentration must be normalized.**
- **Creatinine clearance should be monitored before each dose of zoledronic acid.**
- **The intravenous products need to be administered by a healthcare provider.**

Bisphosphonates

- **The quarterly ibandronate injection is given intravenously over 15 - 30 seconds.**
- **The injection can also be diluted with dextrose 5% in water or normal saline and infused with a syringe pump.**

Bisphosphonates

- **Once-yearly administration of zoledronic acid should be infused over at least 15 minutes with a pump.**
- **Acetaminophen can be given to decrease acute phase reactions.**
- **Although these medications are effective, adherence is poor and results in decreased effectiveness.**

Bisphosphonates

- **A drug holiday could be considered in postmenopausal women after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates.**
- **In women with a high fracture risk or lower hip BMD, continuing oral bisphosphonates for 10 years or intravenous bisphosphonates for 6 years should be considered (evidence on duration??).**
- **Other therapeutic uses include hypercalcemia associated with malignancy.**

Antiresorptive Therapies

Denosumab:

It is indicated for treatment of osteoporosis:

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 non-metastatic prostate cancer.**
3) **in women receiving adjuvant aromatase inhibitor therapy (anastrozole) for breast cancer who are at high risk of fractures.**

Antiresorptive Therapies

Pharmacology:

- **Denosumab is a fully human monoclonal antibody that binds to RANKL, blocking its ability to bind to its RANK (receptor activator of nuclear factor-κb) receptor on the surface of osteoclast precursor cells and mature osteoclasts.**

Antiresorptive Therapies

- **RANKL/RANK signaling regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling.**
- **Thus, it inhibits osteoclastogenesis and increases osteoclast apoptosis.**
- **Following subcutaneous injection, rapid suppression of bone turnover occurs within 12 hours.**

Antiresorptive Therapies

- **Its BMD effects are at least similar to weekly alendronate, and can increase BMD in patients with prior alendronate therapy.**
- **Activity dissipates with drug discontinuation.**

Antiresorptive Therapies

Adverse Effects:

1. **Dermatitis, eczema, and rashes.**
2. **Marked bone turnover suppression → Muscle, bone, and joint pain and atypical femoral fractures.**
3. **Serious infections including skin infections.**
4. **Hypocalcemia (more common in severe renal impairment).**

Antiresorptive Therapies

- **Any existing hypocalcemia should be corrected prior to use with adequate calcium and vitamin D supplements.**
- **Monitoring of serum calcium, magnesium, and phosphorus is recommended within 14 days of administration in patients having a Cl_{Cr} < 30 mL/min.**