Therapy of Osteoporosis

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Therapy of Osteoporosis

- **Osteoporosis is a bone disorder characterized by: low bone density, impaired bone architecture, and compromised bone strength, that predispose to an increased fracture risk.**
- **Osteoporosis is a major public health threat, 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.

Medical Conditions Associated with Osteoporosis

1. Ovarian failure.
2. Testosterone deficiency.
3. Hyperthyroidism.
4. Cushing's syndrome.
5. Diabetes Mellitus.
6. Primary hyperparathyroidism
7. Anorexia nervosa.
8. Malabsorption.
9. Chronic liver disease and primary biliary cirrhosis.
10. Hypercalciuria.
11. Chronic kidney disease
12. Malignancies
13. Others.

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Drug	Comments
Anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)	↓ BMD and ↑ fracture risk; increased vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Canagliflozin (sodium-glucose co-transport (SGLT-2) inhibitors)	↓ BMD and ↑ fracture risk
Furosemide	↑ fracture risk; increased calcium elimination by the kidney
Glucocorticoids (long-term oral therapy)	↓ BMD and ↑ fracture risk; increased bone resorption and decreased bone formation; Dose- and duration-dependent

BMD = bone mineral density

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Drug	Comments
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
Proton pump inhibitor therapy (long-term therapy)	↓ BMD and ↑ fracture risk; possible calcium malabsorption secondary to acid Suppression. (calcium, vitamin B12, iron & magnesium absorption may be reduced)
Selective serotonin reuptake inhibitors	↓ BMD and ↑ fracture risk; decreased osteoblast activity
Thiazolidinediones (pioglitazone and rosiglitazone)	↓ BMD and ↑ fracture risk; inhibit osteoblast differentiation and activate osteoclast differentiation
BMD = bone mineral density	

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.**
- **Strontium (Sr) ranelate may be used for prevention of osteoporosis. It both increases deposition of new bone by osteoblasts and reduces the resorption of bone by osteoclasts.**

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 the highest amount of calcium per serving and are available in low-fat options.**

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. **Estrogen agonists/antagonists (known previously as selective estrogen receptor modulators or SERMs)**
5. **Tissue selective estrogen complexes**
6. **Calcitonin**
7. **Denosumab**
8. **Estrogen**
9. **Testosterone**

Antiresorptive Therapies

Calcium Supplementation:

- **Adequate calcium intake is part of osteoporosis prevention and treatment.**
- **It should be combined with vitamin D, especially when osteoporosis medications are taken.**
- **It produces a small increase in BMD.**
- **It prevents fractures when combined with vitamin D.**

Antiresorptive Therapies

Adverse Effects:

1. **Constipation: can be treated with increased water intake, dietary fiber, and exercise.**
2. **Calcium carbonate can create gas and cause stomach upset. Calcium citrate has fewer GI adverse effects.**
3. **May increase kidney stones (?).**

- **Calcium intake should be less than 1500 mg daily, and preferably achieved through diet.**

Antiresorptive Therapies

Drug Interactions:

- **Proton pump inhibitors can decrease absorption from the carbonate product, because it requires acid for disintegration.**
- **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

Vitamin D ranges:

1. **30 to 100 ng/mL (sufficient)**
2. **20 and 29 ng/mL (insufficient)**
3. **< 20 ng/mL (deficient).**

- **Depend on the assay method and (??).**

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.**
- **Vitamin D can enhance the absorption of aluminum; therefore aluminum-containing products should be avoided to prevent aluminum toxicity.**

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 block prenylation and inhibit GTP-signaling proteins, which lead to decreased osteoclast maturation, number, recruitment, bone adhesion, and life span.**

Bisphosphonates

- **They retard formation and dissolution of hydroxyapatite crystals within and outside the skeletal system.**
- **They localize to regions of bone resorption and so exert their greatest effects on osteoclasts.**

Bisphosphonates

Efficacy:

- **Reduce fracture risk and increases BMD.**
- **The effect is dose-dependent and greatest in the first 12 months of therapy.**
- **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.**
- **Switching to a different bisphosphonate or less frequent administration might resolve GI problems.**
- **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. **Acute phase reactions (fever, flu-like symptoms, myalgias, and arthralgias) are typically associated with intravenous administration, but rarely with daily, weekly or monthly oral bisphosphonates. This reaction usually diminishes with subsequent administration.**

Bisphosphonates

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

- **More commonly in patients with cancer, receiving higher-dose intravenous bisphosphonates, and glucocorticoids; and in those having diabetes mellitus.**
- **Risk factors include maxillary or mandibular bone surgery and poor oral hygiene.**

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 should not take bisphosphonates.**

Bisphosphonates

Administration:

- **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

- **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.**
- **If a patient misses a monthly dose: if the next month's dose is > 7 days away, take the missed dose on the morning you remember. Then resume your normal schedule. If the next dose is < 6 days away, wait until the next scheduled dose.**
- **Before intravenous bisphosphonates are used, the patient's serum calcium concentration must be normalized.**

Bisphosphonates

- **Creatinine clearance should be monitored before each dose of zoledronic acid.**
- **The intravenous products need to be administered by a healthcare provider.**
- **The quarterly ibandronate injection is given intravenously over 15 to 30 seconds.**
- **The injection can also be diluted with dextrose 5% in water or normal saline and used 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.**
- **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.**

Antiresorptive Therapies

- **Following subcutaneous injection, rapid suppression of bone turnover occurs within 12 hours.**

Pharmacokinetics:

- **Peak concentration is ~ 10 days.**
- **The half-life is ~ 25 days and the concentration slowly declines over a period of 4 to 5 months.**
- **The drug does NOT accumulate with repeated dosing at 6-month intervals.**
- **No dosage adjustment is necessary in renal impairment.**

Antiresorptive Therapies

Efficacy:

- **Over 3 years, it significantly decreased vertebral fractures, non-vertebral fractures, and hip fractures in postmenopausal women with low bone density.**
- **The 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. **Bone turnover suppression.**
3. **Serious infections including skin infections.**
4. **Muscle, bone, and joint pain and atypical fractures.**
5. **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.**

Antiresorptive Therapies

Mixed Estrogen Agonists/Antagonists:

Raloxifene:

- **is a second-generation mixed estrogen agonist/antagonist used for:**

1. **prevention and treatment of postmenopausal osteoporosis**
2. **reducing the risk of invasive breast cancer in postmenopausal women with and without osteoporosis.**

- **No benefit on cardiovascular disease.**

Antiresorptive Therapies

Pharmacology:

- **Raloxifene is an agonist at bone estrogen receptors and antagonist at breast estrogen receptors; it has minimal effect on the uterus.**
- **Bazedoxifene is an agonist at bone, and antagonist at the uterus and breast, with no breast cancer prevention effects.**
- **After raloxifene discontinuation, the effect is lost, with bone loss returning to age- or disease-related rates.**

Antiresorptive Therapies

Adverse Events:

1. **Hot flushes are common with raloxifene but not with bazedoxifene.**
2. **Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these adverse events.**
3. **Leg cramps and muscle spasms are also common.**
4. **Thromboembolic events are uncommon, but can be fatal.**

Antiresorptive Therapies

Potential Drug Interactions:

1. **Raloxifene is highly protein bound (95%), and may have binding interactions with highly protein bound drugs (warfarin).**
2. **Cholestyramine can decrease raloxifene absorption.**
3. **Rifampin, phenytoin, carbamazepine, and phenobarbital can decrease bazedoxifene levels by inducing intestinal and liver uridine diphosphate glucuronosyltransferases.**
4. **Estrogen metabolism is decreased with CYP3A4 inhibitors.**

Antiresorptive Therapies

Contraindications:

1. **active or history of venous thromboembolic disease.**
2. **pregnancy, or childbearing potential.**
3. **known coronary artery disease.**
4. **peripheral vascular disease.**
5. **atrial fibrillation.**
6. **prior history of cerebrovascular accidents.**

Anabolic Therapies

Teriparatide:

- **It is a recombinant human product representing the first 34 amino acids in human PTH.**
- **It increases bone formation, bone remodeling rate, and osteoblast number and activity.**
- **It inhibits osteoblast apoptosis.**
- **Both bone mass and architecture are improved.**

Anabolic Therapies

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, multiple risk factors for fracture, very low bone density, or have failed or are intolerant of previous bisphosphonate therapy.**

Anabolic Therapies

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

Administration:

- **Daily subcutaneous injection with site rotation.**
- **The administration of the first dose should take place with the patient either sitting or lying down to avoid orthostatic hypotension.**
- **Duration of therapy is 18 to 24 months.**

Anabolic Therapies

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.**

Glucocorticoid-Induced Osteoporosis

- **Current and prior glucocorticoid use is the most common cause of drug-induced osteoporosis.**
- **Trabecular bone is affected more than cortical bone.**
- **The pathophysiology of glucocorticoid bone loss is multifactorial:**

1. **They decrease bone formation through decreased proliferation and differentiation and enhanced apoptosis of osteoblasts.**
2. **They increase apoptosis of osteocytes.**

Glucocorticoid-Induced Osteoporosis

3. They increase bone resorption by increasing RANKL.
4. They can reduce estrogen and testosterone concentrations.
5. Negative calcium balance: decreased calcium absorption and increased urinary calcium excretion via alterations in calcium transporters.
6. The underlying disease requiring this medication also can affect bone metabolism negatively.

Glucocorticoid-Induced Osteoporosis

- **All patients using glucocorticoids should practice a bone-healthy lifestyle.**
- **All patients starting or receiving glucocorticoid therapy (any dose or duration) should ingest 1,200 to 1,500 mg elemental calcium and 800 to 1,200 units of vitamin D daily or more to achieve therapeutic 25-(OH) VD concentration.**
- **Glucocorticoids should be used at the lowest dose and for the shortest duration possible.**
- **After discontinuation, fracture risk is still higher than never users.**

Glucocorticoid-Induced Osteoporosis

Treatment:

- **Alendronate, risedronate, zoledronic acid, and teriparatide can be used.**
- **Raloxifene and denosumab may decrease bone loss from glucocorticoids.**
- **Bisphosphonate drug holiday is generally NOT considered in this condition.**