College of Pharmacy
Fourth year. Clinical Pharmacy

Rheumatologic Disorders

Osteoporosis

Introduction

Osteoporosis is a bone disorder characterized **by low bone density**, **impaired bone architecture**, and **compromised bone strength** predisposing to **fracture**.

Pathophysiology

1-Bone loss occurs **when resorption exceeds formation** (when the bone resorption greatly exceeds the ability of osteoblasts to form new bone).

2-Men and women begin to lose bone mass **starting in the third or fourth decade because of reduced bone formation**. **Estrogen deficiency during menopause increases osteoclast activity,** increasing bone resorption more than formation.

3-**Men are at a lower risk for developing osteoporosis** and osteoporotic fractures. Male osteoporosis results from aging or secondary causes.

4-**Age-related osteoporosis results from** hormone, calcium, and vitamin D deficiencies; less exercise; and other factors.

5-**Drug-induced osteoporosis** may result from systemic corticosteroids, excessive thyroid hormone replacement, antiepileptic drugs (eg, phenytoin, phenobarbital), depot medroxyprogesterone acetate, and other agents.

Clinical presentation

1-**Many patients are unaware that they have osteoporosis and only present after fracture**. Fractures can occur after bending, lifting, or falling or independent of any activity.

2-The most common fractures involve **vertebrae**, **proximal femur**, and **distal radius** (wrist or Colles fracture).

3-Multiple vertebral fractures decrease height and sometimes curve the spine (**kyphosis** or **lordosis**).

4-Patients with a **nonvertebral fracture frequently present with severe pain**, swelling, and reduced function and mobility at the fracture site.

Diagnosis

1-Physical examination findings may include bone pain, postural changes (ie, kyphosis), and loss of height (>1.5 in [3.8 cm]).

2-**Bone mineral density** (BMD) is measured by dual-energy x-ray absorptiometry (**DXA) scan.**

Treatment

Goals of Treatment:

1-The primary goal of osteoporosis care is **prevention**. Optimizing peak bone mass when young reduces the future incidence of osteoporosis.

2-After low bone mass or **osteoporosis develops**, the objective is to stabilize or improve bone mass and strength and **prevent fractures**.

3-Goals in patients with **osteoporotic fractures** include **reducing pain and deformity**, improving function, reducing falls and fractures, and improving quality of life

Nonpharmacologic Therapy

1-All individuals should have **a balanced diet with adequate intake of calcium and vitamin** D. Protein is required for bone formation.

2- **Smoking cessation, and reduced alcohol and caffeine consumption** are recommended.

3-**Weight-bearing aerobic** and **strengthening exercises** can decrease risk of falls and fractures by improving muscle strength, coordination, balance, and mobility.

4-**Fall prevention programs** can decrease falls, fractures, other injuries, and nursing home and hospital admissions.

5-**Vertebroplasty** and **kyphoplasty** involve injection of cement into fractured vertebra(e) for patients with debilitating pain from compression fractures. Recent research demonstrated **only short term benefit** with no major pain relief and the potential for post-procedure complications.

Pharmacologic Therapy

General Approach

1-Combined with adequate calcium and vitamin D intakes, **alendronate**, **risedronate**, **zoledronic acid**, and d**enosumab** are the prescription **medications of choice** because they reduce both hip and vertebral fracture risks.

2-**Abaloparatide**, **bazedoxifene/conjugated equine estrogens**, **ibandronate**, **raloxifene**, **romosozumab**, and **teriparatide** are **second-line alternatives** because they decrease vertebral but not hip fracture risks.

3-**Calcitonin** is **last-line therapy**. **Estrogen** and **testosterone** are **not used for osteoporosis treatment but can have a positive bone effect when prescribed for other conditions.**

Antiresorptive Therapy

Calcium Supplementation

1-There are insufficient data to support using calcium and vitamin D supplementation to reduce fracture incidence.

2-Because the **fraction of calcium absorbed decreases with increasing dose**, maximum single doses of 600 mg or less of elemental calcium are recommended.

3-**Calcium carbonate is the salt of choice** because it contains the highest concentration of elemental calcium (40%) and is typically least expensive. **It should be ingested with meals** to enhance absorption in an acidic environment.

4-**Calcium citrate** (21% calcium) has **acid-independent absorption and need not be taken with meals.** It may have fewer GI side effects than calcium carbonate.

5-**Tricalcium phosphate** contains 38% calcium. It may be useful in **patients with hypophosphatemia that cannot be resolved with increased dietary intake.**

6-**Constipation is the most common calcium-related adverse reaction**; treat with increased water intake, dietary fiber , and exercise.

7-Calcium carbonate can sometimes cause flatulence or upset stomach. Calcium causes kidney stones rarely.

8-Calcium can **decrease the oral absorption of some drugs** including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Vitamin D Supplementation

1-Supplementation is usually provided with **daily** nonprescription cholecalciferol (**vitamin D3**) products. Higher-dose prescription ergocalciferol (**vitamin D2**) regimens given weekly, monthly, or quarterly may be used for replacement and maintenance therapy.

2-Current guidelines recommend treating patients with osteoporosis to a 25-hydroxyvitamin D concentration of at least 30 ng/mL or 30–50 ng/mL.

3-Because the **half-life of vitamin D is about 1 month**, **recheck the vitamin D concentration after about 3 months of therapy.**

4-**Medications that can induce vitamin D metabolism** include rifampin, phenytoin, barbiturates, valproic acid, and carbamazepine.

5-**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.

Bisphosphonates

1-Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor. Therapy leads to decreased osteoclast maturation, number, recruitment, and life span.

2-Incorporation into bone gives bisphosphonates **long biologic half-lives of up to 10 years**.

3-**Ibandronate is not a first-line therapy** because of the lack of hip fracture reduction data.

4-BMD increases are dose dependent **and greatest in the first 12 months of therapy**. After discontinuation, the increased BMD is sustained for a prolonged period that varies per bisphosphonate.

5-Alendronate, risedronate, and IV zoledronic acid are FDA indicated for postmenopausal, male, and glucocorticoid-induced osteoporosis. IV and oral ibandronate are indicated only for postmenopausal osteoporosis.

6-**Weekly** alendronate, weekly and **monthly** risedronate, and monthly oral and **quarterly** IV ibandronate therapy produce equivalent BMD changes to their respective daily regimens.

7-Oral bisphosphonates must be **administered correctly** to optimize clinical benefit and minimize adverse GI effects.

A-Each oral tablet should be **taken in the morning with at least 6 oz** (180 mL) of **plain water** (not coffee, juice, mineral water, or milk) **at least 30 minutes** (60 minutes for oral ibandronate) **before consuming any food**, supplements, or medications.

B-An exception is **delayed-release risedronate, which is administered immediately after breakfast** with at least 4 oz (120 mL) of plain water.

C-The patient **should remain upright** (**sitting or standing**) **for at least 30 minutes** after alendronate and risedronate and **1 hour after ibandronate** to prevent esophageal irritation and ulceration.

D-If a patient **misses a weekly dose**, it can be taken the next day. If more than 1 day has elapsed, that dose is skipped. If a patient **misses a monthly** dose, it can be taken up to 7 days before the next scheduled dose.

8-The most common bisphosphonate adverse effects include nausea, abdominal pain, and dyspepsia. **Esophageal, gastric, or duodenal irritation,** perforation, ulceration, or bleeding may occur.

9-The most common adverse effects of **IV bisphosphonates** include **fever**, **flu-like symptoms**, and **local injection-site reactions.**

10-**Rare** adverse effects include **osteonecrosis of the jaw** (**ONJ**) and subtrochanteric femoral (atypical) fractures. ONJ occurs more commonly in patients with cancer receiving higher-dose IV bisphosphonate therapy.

11-**The optimal duration of bisphosphonate therapy is unknown**. Some experts recommend considering a bisphosphonate holiday in postmenopausal women after 5 years of oral bisphosphonates or 3 years of IV bisphosphonates if no significant fracture history, hip BMD T-score is above –2.5, and fracture risk is not high.

12-In women with a high fracture risk or lower hip BMD T-scores, continuing oral bisphosphonates **for 10 years or** IV bisphosphonates for 6 years should be considered.

13-A bisphosphonate **holiday should last for ≤5 years** with BMD and patient assessment done every 2–4 years.

Denosumab

1-Denosumab is a RANK ligand inhibitor that **inhibits osteoclast formation** and **increases osteoclast apoptosis**. It is indicated for treatment of osteoporosis in women and men.

2-**Adverse reactions not associated with the injection site include** back pain, arthralgia, and infection. **ONJ** and **atypical femoral shaft fracture** occur rarely. Denosumab is **contraindicated in patients with hypocalcemia until the condition is corrected**.

Mixed Estrogen Agonists/Antagonists and Tissue-Selective Estrogen Complexes

1-**Raloxifene** is an estrogen agonist/antagonist that is **an estrogen agonist on bone receptors** but an antagonist at breast receptors, with minimal effects on the uterus.

2-It is approved for prevention and treatment of **postmenopausal osteoporosis** .

3-**Bazedoxifene** is an estrogen agonist/antagonist that is an **agonist at bone** and antagonist at the uterus and breast; however, **it has no breast cancer prevention effects**. The proprietary product **Duavee** is combined with conjugated equine estrogens (**CEE**), making it a tissue-selective estrogen complex. It **is approved for prevention of postmenopausal osteoporosis and vasomotor menstrual symptoms**.

4-The **benefit is lost after discontinuation**, and bone loss returns to age- or disease-related rates.

5-**Hot flushes are common with raloxifene** but **decreased with bazedoxifene/CEE**. Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these events.

Calcitonin

1-Calcitonin is an **endogenous hormone released from the thyroid gland** when serum calcium is elevated. **Salmon calcitonin is used** clinically because it is more potent and longer lasting than the mammalian form.

2-Calcitonin is indicated for osteoporosis treatment for women at least 5 years past menopause.

3-An FDA Advisory Committee Panel vote**d against continued use for postmenopausal osteoporosis,** but it can be used if **alternative therapies are not appropriate**. Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy.

Hormone Therapies

1-Hormone therapies (**estrogen and testosterone**) are **not recommended solely for osteoporosis** but have positive bone effects when used for other indications.

2-Estrogen therapy can be a good choice for **women going through early menopause when protection against bone loss is needed** in addition to reduction of vasomotor symptoms.

3-**Estrogen with or without a progestogen significantly decreases fracture risk and bone loss in women**. When estrogen therapy is discontinued, bone loss accelerates and fracture protection is lost.

4-**Testosterone** is used to treat hypogonadism in men, **but an osteoporosis medication should be added when risk for osteoporotic fracture is high.**

Formation Medications

Parathyroid Hormone Analogs

1-**Abaloparatide** is an analog of parathyroid hormone-related peptide (PTHrP), and **teriparatide** is an analogs of parathyroid hormone (PTH); these agents are indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture.

2-**Transient hypercalcemia** can occur and is less common with abaloparatide than teriparatide. Because of an increased incidence of **osteosarcoma in rats**, both medications contain a box warning against use in patients at increased risk for osteosarcoma; this adverse effect has not occurred in people.

3-PTH analogs should **not be used in patients with hypercalcemia**.

Formation and Antiresorptive Medication

Romosozumab

1-Romosozumab **prevent inhibition of bone formation** and **decrease bone resorption**, an activity that differentiates this medication from other anabolic therapies.

2-It indicated for postmenopausal women at high risk for fracture.

3-Romosozumab **antibodies may occur in 10%–20%** of patients but are generally **not neutralizing and do not reduce efficacy.**

4-**Serious cardiovascular events have been reported**, and the labeling contains a boxed warning of an increased risk of myocardial infarction (MI), stroke, and cardiovascular death.

5-Romosozumab should not be used within 1 year of an MI or stroke, and benefit–risk evaluation should be conducted in patients with or at risk for these conditions.

6-**Rare cases of ONJ** and atypical femoral fractures have been reported.

7-Therapy should be **limited to 12 monthly doses**. If osteoporosis therapy remains warranted, continued therapy with an antiresorptive agent should be considered.

Sequential and Combination Therapy

1-In sequential therapy, **an anabolic agent is given first to increase bone mass, followed by an antiresorptive agent**. This regimen is generally reserved for patients with severe osteoporosis because of the cost of anabolic agents.

2-Starting with an antiresorptive first and then switching to teriparatide results in lower BMD increases but may be especially useful for patients **who have fractured or continue to lose bone mass while on antiresorptive therapy.**

3-**Combination therapy is rarely used** because of no documented fracture benefit, increased cost, and potential for more adverse effects.

4-When **raloxifene is used for breast cancer prevention**, another **antiresorptive** agent is **sometimes prescribed**, especially if hip fracture risk is high.

Glucocorticoid-induced osteoporosis

1-Glucocorticoids decrease bone formation through decreased proliferation and differentiation as well as enhanced apoptosis of osteoblasts. They also increase the number of osteoclasts, increase bone resorption, decrease calcium absorption, and increase renal calcium excretion.

2-All glucocorticoid doses and formulations have been associated with increased bone loss and fractures; however, **risk is much greater with oral prednisone doses ≥5 mg daily** (or equivalent) and **oral therapy** vs inhaler or intranasal therapy.

3-Perform an initial **BMD assessment prior to or within 6 months of glucocorticoid initiation** for adults ≥40 years of age and for adults <40 years of age with a history of fragility fracture or other risk factors.

4-Repeat **BMD testing is recommended every 2–3 years** during osteoporosis therapy for those taking very high glucocorticoid doses (≥30 mg prednisone per day or a cumulative dose >5 g in the past year), or other risk factors for osteoporosis.

5-**All patients starting or receiving systemic glucocorticoid** therapy (any dose or duration) **should practice a bone-healthy lifestyle and ingest 1000–1200 mg elemental calcium and 600–800 units of vitamin D daily** to achieve therapeutic 25-hydroxyvitamin D concentrations.

6-Use **the lowest possible corticosteroid dose** and **duration**.

7-**Alendronate**, **risedronate**, **zoledronic** acid, **denosumab**, and **teriparatide** are FDA approved for glucocorticoid-induced osteoporosis.

8-**Oral bisphosphonates are recommended first-line**, although **IV bisphosphonates can be used in nonadherent** patients or those unable to take the oral preparations.

9-**Teriparatide is recommended for patients who cannot use a bisphosphonate**, and **denosumab** is recommended if neither a bisphosphonate nor teriparatide can be used.

10-Denosumab is not recommended as first-line therapy due to **limited safety data in this population.**

Evaluation of therapeutic outcomes

1-Assess **medication adherence** and **tolerability** at each visit.

2-Ask patients about **possible fracture symptoms** (eg, bone pain, disability) at each visit.

3-Obtain a central DXA BMD measurement after 1–2 years or 3–5 years after initiating a medication therapy to monitor response.

4-Repeat a central **DXA every 2 years until BMD is stable**, at which time the reassessment interval can be lengthened.

Reference

Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 11th Edition. 2021.