## Learning objectives

- Review the guidelines on the screening, treatment and monitoring of patients with osteoporosis with emphasis on the recently published ACP guidelines.
- Discuss the controversies on long-term treatment for osteoporosis and the role of drug holiday.

## Case 1

- A 53-yr-old postmenopausal, white, woman coming for evaluation of osteoporosis
- Height: 161.7 cm, weight: 57.4 kg
- Prior fx: no
- Parental hip fx: mother had hip fracture at age 75
- Current smoking: yes, 25 pack-years
- Steroid use: no
- RA: no
- Secondary osteoporosis: no
- Current calcium intake: ~ a cup of milk q day with cereal
- Walks for 30 minutes a day
- Spine BMD: -2.7
- Femoral neck BMD T-score: -2.2
- Total hip T-score: -1.9

## Case 2

- 77 yo male referred for evaluation of osteopenia
- No tobacco, no ETOH, no secondary causes for bone loss or osteoporosis, not on meds that may cause bone loss
- No h/o fracture,
- Mother had h/o hip fx
- wt=89.4 kg, ht=177.8 cm
- FN BMD (Hologic) 0.700 g/cm2 (T-score =-1.7)

## NEW ACP Guidelines in Osteoporosis

- **Recommendation 1:** *ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)*
- Criticism by the American Society for Bone and Mineral Research (ASBMR):
  - Omission of anabolic agents such as teriparatide and abaloparatide
- https://www.asbmr.org/ASBMRStatementsDetail/acp-s-new-osteoporosis-guidelines-applauded-as-mov

Ann Intern Med 2017;166:818-839

## NEW ACP Guidelines in Osteoporosis

- **Recommendation 2:** *ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)*
- Criticism by the ASBMR:
  - ACP's guideline to discontinue osteoporosis medications after five years does not take into account individual variability for treatment as some patients may require more or less than five years of treatment. Additionally, some osteoporosis medications, such as denosumab, cannot simply be discontinued without follow-up therapy, as doing so leads to negative clinical consequences.

Ann Intern Med 2017;166:818-839

## NEW ACP Guidelines in Osteoporosis

- **Recommendation 3:** *ACP recommends that clinicians offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)*

Ann Intern Med 2017;166:818-839

## NEW ACP Guidelines in Osteoporosis

- **Recommendation 4:** *ACP recommends against bone density monitoring during the 5-year pharmacologic treatment period for osteoporosis in women. (Grade: weak recommendation; low-quality evidence)*
- *ASBMR 2017 debate*: Experts question the feasibility of compliance on starting a patient on a medication but no monitoring for effectiveness will be done.

Ann Intern Med 2017;166:818-839

## NEW ACP Guidelines in Osteoporosis

- **Recommendation 5:** *ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)*

Ann Intern Med 2017;166:818-839

## NEW ACP Guidelines in Osteoporosis

- **Recommendation 6:** *ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation; low-quality evidence)*

## Difference between 2017 and 2008 guidelines

- No recommendation for any specific therapeutic agent in the 2008 guidelines.
- No specific recommendation for duration of therapy in the 2008 guidelines.
- No specific recommendation regarding follow-up bone density testing in the 2008 guidelines.
- No specific recommendation to avoid using raloxifene in 2008 guidelines.

## Osteoporosis: Epidemiology

- Affects >9.9 M of Americans, and additional 43.1 M have low BMD
  - (F Cosman, Osteoporosis International, 2014; 25(10)2359-81).
- 1:2 women >50 y.o. and 1:4 to 5 men will have an osteoporosis-related fracture

- National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis*, 2014.

## Osteoporosis: Epidemiology

- Hip fractures result in as much as 8-36% excess mortality within the first year and accounts about 70% of fracture costs
- Hip fx results in 20% long-term NH admissions and only 40% goes back to pre-fx level of independence

- National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis*, 2014

## Osteoporosis: Definitions

- A skeletal disease characterized by compromised bone strength predisposing a person to an increased risk of fracture
- Characteristics:
  - Low bone mass
  - Microarchitectural disruption
  - Increased skeletal fragility

National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis*, 2014; *NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. JAMA* 2001;285:785-95.

## Osteoporosis: Diagnosis

- Bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA scanning)

| Classification | T Score |
|---|---|
| • Normal | > -1 SD |
| • Osteopenia | > -2.5 and < -1 SD |
| • Osteoporosis | ≤-2.5 SD |
| • Severe | ≤-2.5 SD + fx |

- *The World Health Organization Assessment of Osteoporosis at the Primary Health Care Level. Summary Report of a WHO Scientific Group.* Geneva: WHO, 2007.

## Risk Factors for Low Bone Density

**Modifiable**

- Low calcium intake
- Inadequate exercise
- Low body weight
- Smoking/Drinking
- Hormone deficiency
  - Amenorrhea >1 yr
  - Menopause <age 40

**Non Modifiable**

- Increasing age
- Female gender
- White or Asian race
- Family history
- Previous fracture

## Secondary Causes of Osteoporosis

**Disease States**

- Malabsorption (Celiac)
- Chronic liver disease
- Vitamin D deficiency
- Hypogonadism
- Thyrotoxicosis
- Hypercortisolism
- Hyperparathyroidism
- Anorexia nervosa
- Multiple myeloma
- Rheumatoid arthritis
- Any disability

**Medications**

- Steroids
- Phenobarbital
- Dilantin
- Thyroid hormone excess
- Aromatase inhibitors
- Androgen deprivation
- Depo-Provera
- Thiazolidinediones

## When to Measure BMD?
## National Osteoporosis Foundation Guidelines

BMD testing should be performed:

- In women age 65 and older and men age 70 and older
- In postmenopausal women and men between age 50–69, based on risk factor profile
- In postmenopausal women and men age 50 and older who have had an adult age fracture, to diagnose and determine degree of osteoporosis

- National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis*, 2014.

## When to Measure BMD?
## US Preventive Services Guidelines

- All women ≥65 years of age
- Routine screening beginning at age 60 for women at increased risk
- USPSTF makes no recommendation for or against routine screening in postmenopausal women <60 or in women 60-64 without increased risks

US Preventive Services Task Force. *Screening for Osteoporosis*. http://www.ahrq.gov/clinic/uspstf/uspsoste.htm

## Medicare

- Individuals 65 ≥ y.o.
- Estrogen deficient women at risk for osteoporosis
- Individuals with vertebral abnormalities
- Long-term steroid Rx (daily dose of ≥ 5mg prednisone or equivalent ≥ 3 mos
- Individuals with primary hyperparathyroidism
- To monitor response or efficacy of an FDA-approved drug for osteoporosis

## BMD and Fracture Risk

- Low BMD is associated with increased fracture risk; T scores ≤-2.5 have the highest risk; cost-effective to treat
- HOWEVER, there are more patients with T scores in the osteopenic range
- Thus, the absolute number of fractures is greater in patients with osteopenia by BMD

## Fracture risk assessment

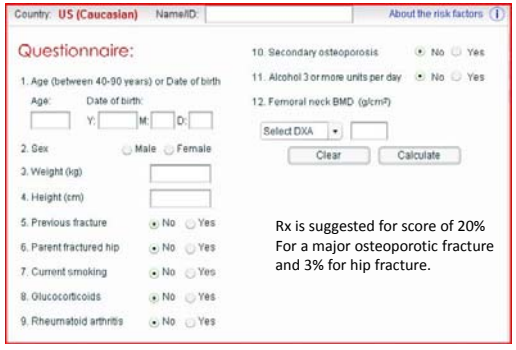
- WHO developed a Working Group on the Assessment of Osteoporosis at the Primary Health Care Level
- Aims
  - To identify and validate clinical risk factors for use in fracture risk assessment, either alone, or in combination with bone mineral density tests
  - To develop algorithms for risk assessment that were sufficiently flexible to be used in the context of many primary care settings, including those where BMD testing was not readily available

- WHO Scientific Group. *Assessment of osteoporosis at the primary health-care level. Technical report.* Sheffield, UK: WHO Collaborating Centre for Metabolic Bone Diseases, 2007:

## Fracture risk assessment tool (FRAX calculator)

- Designed to calculate the 10-year absolute fracture risk, similar to cardiac risk calculators
- FRAX should not change the recommendations for treating patients with T scores ≤-2.5
- BUT, it provides considerable help in providing a way to make more objective treatment decisions for patients with T scores between -1.0 to >-2.5
- Will allow the identification of those in this group who would benefit from treatment

## FRAX calculator




www.sheffield.ac.uk/FRAX/

## FRAX calculator

- FRAX only applies to
  - Previously untreated patients
  - Patients older than 50 years of age
- Only incorporates the femoral BMD
- Race/ethnic-specific

## Prevention and Treatment of Osteoporosis

**Non Pharmacologic**

- Calcium
- Vitamin D
- Weight bearing exercise
- Smoking cessation

**Pharmacologic**

- Bisphosphonates
- Raloxifene (SERMS)
- Calcitonin
- Denosumab
- Teriparatide hormone
- Abalopartide

## Calcium Supplementation

- Average daily dietary intake can be estimated by multiplying each dairy product serving by 300 mg and then adding 250 mg (average calcium intake from other foods)
- Recommended intake:
  - Ages 9-18: 1300 mg/day
  - Ages 19-50: 1000 mg/day
  - Ages >50:
    - women: 1200 mg/day
    - Men: 1000 mg/day till age 70 where recommended intake is 1200 mg/day

- IOM (Institute of Medicine), *Dietary Reference Intakes for Calcium and Vitamin D,* Washington, DC: The National Academies Press, 2011

## Calcium Supplementation

- Types of supplements:
  - Calcium carbonate: taken with meals to ensure an acidic stomach which enhances absorption.
  - Calcium citrate: taken with or without meals
- Diets high in fiber decrease calcium absorption due to complexing of the calcium with fiber
- Elemental calcium more important

## Calcium Supplementation: Counseling

- Reduced stomach acid will decrease the absorption of calcium carbonate preparations; consider advising all those who take acid suppression therapy to take calcium citrate
- Calcium supplements interfere with the absorption of alendronate, iron and thyroid supplements; these medications should be taken separately from calcium

## Vitamin D Supplementation

- Vitamin D enhances intestinal absorption of calcium and is important for normal mineralization of bone
- Also important for normal muscle function and balance
- Increasingly recognized that the US population is vitamin D deficient
  - Less time outdoors
  - Widespread use of sunscreen

## Vitamin D Supplementation

- Current recommended daily intake is at least 1000 IU units daily; some experts recommend as much as 2000 IU daily
- Vitamin D3 is preferred over D2
- If you chose to measure vitamin D levels, the recommended assay is 25 OH vitamin D
- Normal levels are >30 ng/dl
- For severe deficiency, consider 50,000 IU weekly for 8-12 weeks as initial therapy
  - Office of Dietary Supplements National Institutes of Health. Dietary Supplement Fact Sheet: Vitamin D, 2009. http://ods.od.nih.gov/factsheets/vitamind.asp

## Lifestyle Interventions

- Encourage decreased smoking and alcohol use
- Encourage resistance exercise, recognizing the need to adjust exercise programs for patients with concurrent disease
- For frail elderly patients, stress the importance of preventing falls
  - Home safety evaluations
  - Decreased use of mind-altering medications

## Pharmacologic Interventions

<u>Antiresorptive</u>

- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronic acid
- Raloxifene
- Denosumab
- Calcitonin*
- Estrogen*

<u>Anabolic</u>

- Teriparatide
- Abaloparatide

## Bisphosphonates: Alendronate (ALN)

- Antiresorptive agent that prevents bone loss
- Dose: 70 mg q week
- Approved for prevention and treatment
- Increases bone density at spine and hip
- Decreases spine and hip fractures by 50% over three years
  - Decrease in spine fractures noted by 12 months
  - Decrease in hip fractures noted by 18 months
- Prevents steroid-induced bone loss
  - Liberman UA et.al, NEJM. 1995; 333(22):1437-43
  - Saag KG et.al, NEJM. 1998;339(5):292-299.

## Bisphosphonates: Risedronate

- Similar to alendronate
- Approved for prevention and treatment
- Decreases spine (65%) and hip fractures (40%) over three years
  - Decrease in spine fractures noted by 12 months
- Prevents steroid-induced bone loss
- Dose: 150 mg/month, 35 mg/week, both prevention and treatment
- Same side effects as alendronate
  - McClung et.al, NEJM 2001; 344(5):333-340, Harris ST et.al, JAMA 1999;282(14):1344-52

## Bisphosphonates: Ibandronate

- Approved to treat postmenopausal osteoporosis (not prevention)
- Increases spine and hip bone density
- Reduces vertebral fractures by 62% in three years ***but has not been shown to reduce hip fractures***
- Dose: 150 mg po once monthly or 3 mg IV every three months
- Same side effects

Chesnut CH, et.al, JBMR 2004;19(8):1241-9

## Bisphosphonates: Zoledronic Acid

- Approved for prevention and treatment
- Increases spine and hip bone density
- Reduces spine and hip fractures
  - Decreases spine fractures 70% over three years
  - Decreases hip fractures 41% over three years
- Intravenous only: 5 mg IV once yearly
- Side effects: Flu symptoms for 24-28 hours; concerns about afib and osteonecrosis

Black DM, et.al, NEJM. 2007;356:1809-1822

## SERM: Raloxifene

- Estrogen agonist/antagonist
- Increases hip and spine bone density
- 50% reduction in vertebral fractures; no decrease in nonvertebral fractures
- BUT, 50% reduction in breast cancer over 5 years of treatment
- Dose: 60 mg/day
- Side effects: Hot flashes, DVT

Cummings SR et.al, 1999;281:2189-2197

## Denosumab

- Indications: postmenopausal women with osteoporosis at high risk for fracture, women on aromatase inhibitors, male osteoporosis, men on androgen deprivation therapy
- used in subjects with renal impairment
- 60 mg SQ every 6 months given by a health care personnel
- Reduces vertebral fractures by 68% and hip fractures by 40% (FREEDOM Trial)
- Side effects: back/musculoskeletal pain, high cholesterol, cystitis (5.9%), infection
- Discontinuation may result in rebound bone loss and increased fractures

  - Cummings SR, et.al, *N Engl J Med*, 2009, 361(8):756-65.
  - Aubry-Rozier B, et.al, Osteoporos Int. 2016 May;27(5):1923-5.

## Teriparatide

- Anabolic agent approved for osteoporosis
- For severe or refractory disease
- 20 mcg daily SQ injection for max 2 yrs
- Reduced vertebral fracture by 65% and nonvertebral fractures by 53%

  - Neer RM et al, *N Engl J Med*, 2001, 344(19):1434-41.

## Teriparatide:

- Should not be prescribed in patients with increased baseline risk for osteosarcoma
- Paget's Disease
- Unexplained elevation in alk phos
- Open epiphysis
- Prior external beam or implant radiation therapy involving the skeleton

## Abaloparatide

- analog of human parathyroid hormone related peptide
- stimulates osteoblast function and increased bone mass
  - (Harslof 2016; Leder 2017)
- Dose: 80 mcg q day for 2 years
- **Indications:**
  - postmenopausal women with osteoporosis at high risk for fracture
  - patients who have failed or are intolerant to other available osteoporosis therapy.

## Abaloparatide

| | Participants With Fracture, No. (%) | | | Abaloparatide vs Placebo | | |
|---|---|---|---|---|---|---|
| | Abaloparatide (n = 824) | Placebo (n = 821) | Teriparatide (n = 818) | Risk Difference (95% CI) | RR or HR (95% CI) | *P* Value |
| New vertebral fracture | 4 (0.6) | 30 (4.2) | 6 (0.8) | −3.64 (−5.42 to −2.10) | RR, 0.14 (0.05 to 0.39) | <.001 |
| Nonvertebral fracture | 18 (2.7) | 33 (4.7) | 24 (3.3) | −2.01 (−4.02 to −0.00) | HR, 0.57 (0.32 to 1.00) | .049 |

Miller PD et.al. JAMA 2016;316(7):722-733

## Choosing a Therapy

- Estrogen is very effective in preventing bone loss, but generally only used in the setting of menopausal symptoms.
- Consider raloxifene in women with osteoporosis of spine and with increased risk of breast cancer
- Bisphosphonates are the mainstay of treatment—make sure that both hip and spine are protected
- Consider denosumab for those with chronic renal disease or intolerant to BPs or treatment failure
- Teriparatide or abaloparatide for those with severe osteoporosis

## Long-term bisphosphonates

- Atypical femur fractures (AFF):
  - 3.2 to 50 cases/100,000 person-years
- Osteonecrosis of the jaw (ONJ)
  - 1/10,000 to 1/100,000 person-years

**Journal of Bone and Mineral Research 2016, 31 (1): 16–35**

## Long-term bisphosphonates:

- In 2011, the FDA recommended that physicians reassess the indication for continued BP therapy beyond 3 to 5 years but noted that in high-risk patients, drug discontinuation may not be advisable.
- Statement: “Important Limitation of Use” statement: “The optimal duration of use has not been determined. All patients on BP therapy should have the need for continued therapy re-evaluated on a periodic basis.”

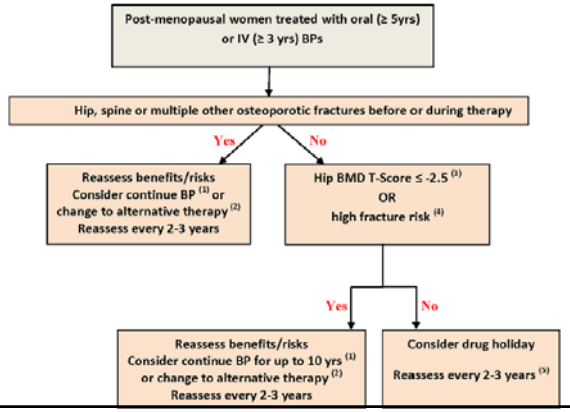
## ASBMR on long-term BPs

- The benefits of 5 years of therapy clearly outweigh the risks.
- For treatment up to 10 years with oral bisphosphonates (FLEX extension) and 6 years with IV BPs (HORIZON extension), estimates of benefits and risks are based on much weaker data.
- For patients who fracture on therapy, assess adherence and rule out secondary causes of osteoporosis.

**Adler RA et.al., Journal of Bone and Mineral Research 2016, 31 (1): 16–35**

**Management of patients on long-term bisphosphonates**

**Journal of Bone and Mineral Research 2016, 31 (1): 16–35**




## Approach to Case 1

- Optimal calcium and vitamin D
- Lifestyle modification
- Patient has osteoporosis, thus, treatment is indicated
- Bisphosphonates first line
- If patient has strong family of breast cancer, may consider raloxifene

## Approach to Case 2

- FRAX score: 14% for a major osteoporotic fx and 9.2% for a hip fracture in 10 years.
- Because FRAX is high, treatment is indicated aside from optimal calcium/vit. D and lifestyle modification
- May use bisphosphonates
- If patient has CKD: use denosumab
- In patients with history of multiple vertebral fractures: consider teriparatide or abaloparatide

## Case 3

- A 75 year old Caucasian woman was treated with ALN for osteoporosis X 10 years, without fractures during treatment. To minimize risk of ONJ and AFFs, ALN was discontinued. At the time of discontinuation of therapy T-score was -2.2 at the femoral neck site.
- Follow-up bone density testing after 3 years of drug holiday showed that T-score at the femoral neck was now -2.7, with 7.5% loss at this site. Similar losses were reported at the lumbar spine.

## Approach to Case 3

- Treatment is indicated given the significant decline in bone density.
- May try bisphosphonates again or may use non-bisphosphonates

## SUMMARY:

- Initiate therapy in those with BMD T scores ≤-2.5 or a history of fragility fracture
- Initiate treatment in postmenopausal women or men ≥ age 50 with BMD T scores between -1.0 and >-2.5 based on the FRAX scores as discussed previously

## SUMMARY:

- All patients should have lifestyle interventions when appropriate
- Calcium supplementation of 1200 mg/day
- Vitamin D supplementation of at least 1000 IU daily (Vitamin D3 preferred)
- Bisphosphonates are generally first-line drug of choice for treatment
- Consider raloxifene for women with increased risk of breast cancer
- Consider Denosumab in patients with chronic kidney disease
- Consider and anabolic agent (teriparatide and abaloparatide) in patients with severe osteoporosis

## Key References


- Nelson HD, et al. Screening for osteoporosis: an update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2010;153:99-111.
- National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis, Osteoporos Int*. 2014;25(10):2359-2381. http://www.nof.org/
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- US Preventive Services Task Force. *Screening for Osteoporosis*. http://www.ahrq.gov/clinic/uspstf/uspsoste.htm
- WHO Scientific Group. *Assessment of osteoporosis at the primary health-care level. Technical report*. Sheffield, UK: WHO Collaborating Centre for Metabolic Bone Diseases, 2007.
- WHO Fracture Risk Assessment Tool. http://www.shef.ac.uk/FRAX/index.jsp
- IOM (Institute of Medicine), *Dietary Reference Intakes for Calcium and Vitamin D,* Washington, DC: The National Academies Press, 2011