
Osteoporosis treatment

WHEN WE DO PREVENTION?

- T-score ≤ –1.5 in a patient with risk factors or previous fracture
- T-score ≤ –2 with no risk factors

WHEN WE DO TREATMENT?

- Postmenopausal women (and men ≥50 y/o) with a history of hip or vertebral fracture

- Osteoporosis (T-score ≤-2.5)

- Osteopenia (T-score between -1.0 and -2.5) as well as one of the following risk factors:

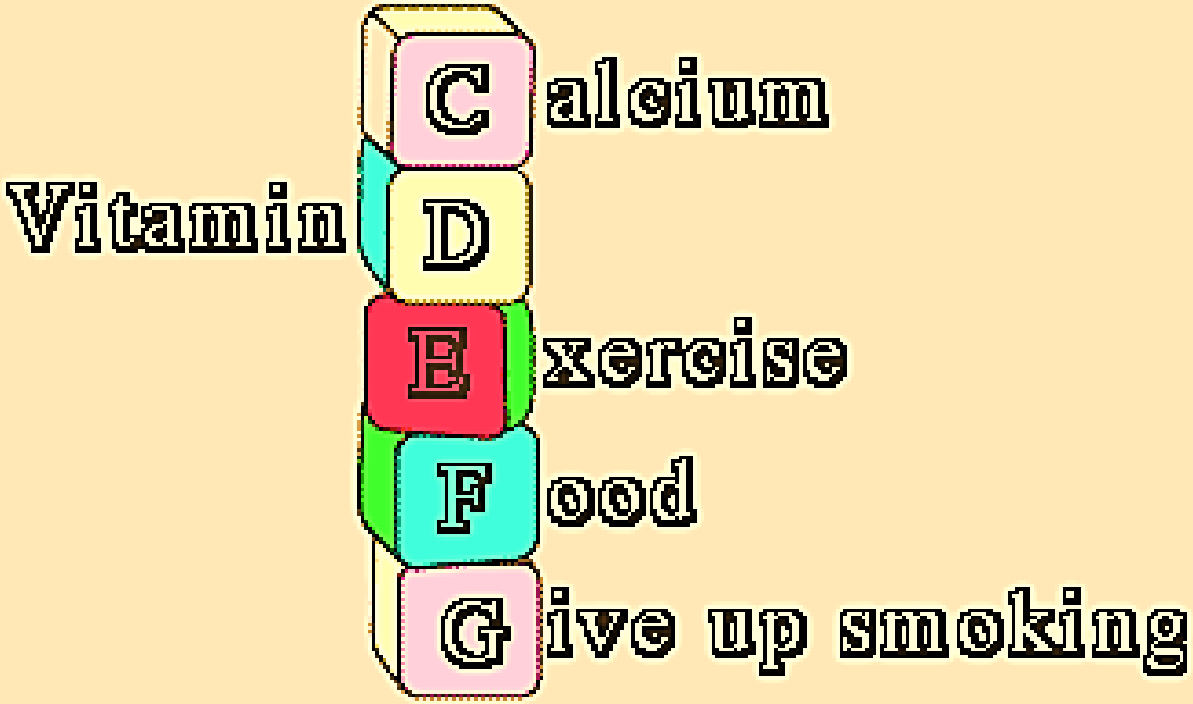
  Secondary causes associated with high risk of fracture, such as glucocorticoid use or total immobilization.

  Previous history of fracture with minimal force

  Estimated 10-year risk of hip or osteoporosis-related fracture ≥3 or ≥20 % respectively

NOF's New Clinician's Guide to Prevention and Treatment of Osteoporosis

OSTEOPOROSIS PREVENTION



- Premenopausal women and <50 Y/O men should consume at least 1000 mg of calcium per day

- Postmenopausal women & > 50 Y/O men should consume 1200 to 1500 mg of calcium per day

Most people should consume 800-1000 IU of vitamin D each day

The safe upper limit for vit. D is unclear but is > 2000 IU daily

Protein supplements:

- Protein supplements may be recommended in some people to ensure sufficient protein intake

- This may be particularly important if you have already had an osteoporotic fracture.

Alcohol, caffeine, and salt intake :

- Drinking alcohol ≥ 3 drink/day can increase the risk of fracture
- It is not clear if restricting caffeine or salt is helpful

Exercise :

- Weight-bearing exercises can improve bone mass in premenopausal women
- Most experts recommend exercising for at least 30 minutes three times per week
- The benefits of exercise are quickly lost if you stop exercising.

Stop smoking:

cigarettes is known to speed bone loss.

Preventing falls:

- Remove loose rugs and electrical cords or any other loose items
- Ensure that there is adequate lighting in all areas
- Avoid walking on ice, wet or polished floors, or other potentially slippery surfaces.
- Avoid walking in unfamiliar areas outside

DRUGS

Bone Forming:

- Synthetic PTH
- Fluoride
- Anabolic agents

Resorption Preventing:

- Estrogen & Analogs
- Calcitonin
- Bisphosphonate

Bisphosphonates

	Potency
❖First generation :	
➢ Etidronate	1
➢ Clodronate	10
❖Second generation :	
➢ Tiludronate	10
➢ Pamidronate	100
➢ Alendronate	100-1000
❖Third generation :	
➢ Risedronate	1000-10,000
➢ Ibandronate	1000-10,000
➢ Zolendronate	100,000

Adverse Events

- Heartburn, reflux, esophagitis, and ulcers
- Flu-like symptoms
- Hypocalcemia
- Ocular side effects: pain, blurred vision, conjunctivitis, uveitis, and scleritis
- Musculoskeletal pain
- Osteonecrosis of the jaw
- Atrial fibrillation
- "frozen bone“
- Esophageal cancer

Alendronate

- Increased femoral neck and spine BMD
- Reduced the risk of vertebral, hip and wrist fracture
- Weekly administration of alendronate is as effective as daily dosing
- There is currently no consensus on how long to continue bisphosphonate therapy

Calcitonin

- Mechanism :
  - Reduce osteoclastic bone resorption
  - Analgesic effect
- Dosage :
  - 50 to 100 units daily by injection
  - 200 units (one to two puff) daily intranasally

- 36% ↓ in vertebral fractures over 5 years with intranasal form

Estrogen-like" medications selective estrogen receptor modulators (SERMs)

- Raloxifen (Evista®
- Lasofoxifene

Parathyroid hormone (PTH)

- Stimulates both bone resorption and new bone formation.
- Intermittent administration stimulates formation more than resorption
- There is preclinical evidence of malignant bone tumors in animal models
- We have qualitative changes in trabecular micro architecture

COMBINATION THERAPY?

Other Treatments

- Strontium ranelate

- Vitamin K:
  Phytonadione,Menaquinone,Menatetrenone
- Denosumab
- Tibolone
- Folate/vitamin B12
- Growth factors:
  Growth hormone (GH)
  Insulin-like growth factor-I (IGF-I)
- Androgens
- Isoflavones:(a type of phytoestrogen)
- Fluoride

Denosumab (Prolia®)

- An antibody directed against a factor (RANKL)
- Denosumab improves BMD and reduces fracture in postmenopausal women with osteoporosis
- It is administered as an injection under the skin once every 6 months.
- side effects : osteonecrosis
  Skin infections (cellulitis) and eczema
  Mild transient lowering of blood calcium
- No long-term safety data
- Usually reserved for patients who are intolerant of or unresponsive to other therapies or severe osteoporosis

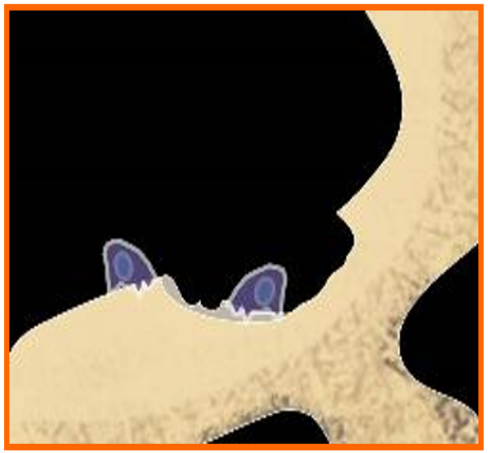
Emerging Therapies

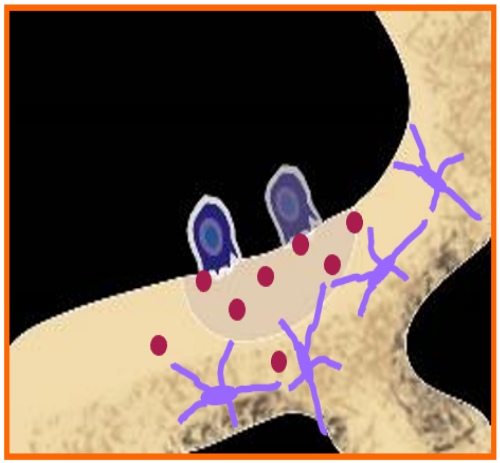
- Oral calcium sensing receptor antagonists
- Antibodies that target molecules:
(Sclerostin and Dkk1 inhibitors) involved in Wnt signaling pathway
- Integrin antagonists
- Cathepsin-K inhibitors:
Odanacatib(increased risk of stroke)
- Glucagon-like peptide 2

New drug treatments in development

Romosozumab: *'Bone-forming' human sclerostin monoclonal antibody - inhibits sclerostin*

- Sclerostin is produced by osteocytes & stops bone formation
- Romosozumab binds onto sclerostin & reduces its action





Sclerostin produced by osteocytes to stop bone formation

So by inhibiting sclerostin:

- bone formation increases
- bone breakdown decreases

Drugs: New drug treatments in development

Abaloparatide : *Parathyroid hormone related protein*

- Daily self-administered subcutaneous injection
- (A skin patch version for short term wear also planned)
- Similar vertebral fracture reductions to teriparatide but greater non-vertebral fracture reductions
- Similar safety profile to teriparatide
- Submitted to & approved by FDA for treatment of osteoporosis in postmenopausal women

AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

No prior fragility fractures or moderate fracture risk**

- Alendronate, denosumab, risedronate, zoledronic acid***
- **Alternate therapy:** Ibandronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

Prior fragility fractures or indicators of higher fracture risk**

- Denosumab, teriparatide, zoledronic acid***
- **Alternate therapy:** Alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Teriparatide for up to 2 years

Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.

** Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

*** Medications are listed alphabetically.

**** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.

Choice Of Drug

First-line for postmenopausal osteoporosis:

Bisphosphonates : Alendronate

Risedronate

In gastrointestinal intolerance:

IV Zoledronic acid

IV Ibandronate

For women with osteoporosis and increased risk of invasive breast cancer:

Raloxifene

Choice of drug

For women with severe osteoporosis T score<-3.5 or any T score with fragility fx :

Denosumab
Teriparatide
Abaloparatide

MONITORING THE RESPONSE TO THERAPY

The least significant change (LSC) CI=95%:

Change that is 2.8 times the precision error for:

- ✓ Each measured site
- ✓ Is expressed as an absolute value (g/cm2)

MONITORING THE RESPONSE TO THERAPY

Time interval for repeating DEXA :

When the expected amount of change in BMD ≥LSC

Knowledge of this change is likely to influence clinical management

Proper time for each drug: the time that 50%of patient have changing in BMD > LSC

Routin time interval: every 2 years

MONITORING THE RESPONSE TO THERAPY

Shorter time interval for repeating DXA:

- High dose corticostroids
- Mens
- Premenopausal women
- Vit. D deficiency
- Hypogonadism
- Bedridden patients
- Organ transplantation

MONITORING THE RESPONSE TO THERAPY

Skeletal site to monitor :

- ✓ one that responds quickly to therapy or lack of therapy
- ✓ Has a low LSC
- ✓ Usually this is the lumbar spine
- ✓ If the lumbar spine is not evaluable → total proximal femur

MONITORING THE RESPONSE TO THERAPY

Interpretation of BMD changes:

- ✓ Stability or ↑ in BMD is an acceptable response
- ✓ Loss of BMD > LSC is cause for clinical concern:

  Poor adherence to therapy?
  Previously unrecognized disease or disorde?
  Inadequate gastrointestinal absorption?
  Inadequate intake of calcium and vitamin D?

- ✓ If patient is well and taking the drug & supplements correctly, the correct action is **controversial**

MONITORING THE RESPONSE TO THERAPY

- Changes in the LSC**< %3-6 at the hip** and **<%2-4 at the lumbar spine** from test to test may be due to the precision error of the testing itself

MONITORING THE RESPONSE TO THERAPY

For patients suspected to drug malabsorption or noncompliance:

- Fasting urinary NTX or serum CTX before and 3 to 6 months after starting antiresorptive therapy
- Goal: ↓ %50 (NTX) or ↓ %30 (CTX)
- This approach is not useful with recombinant PTH