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Osteoporosis Management

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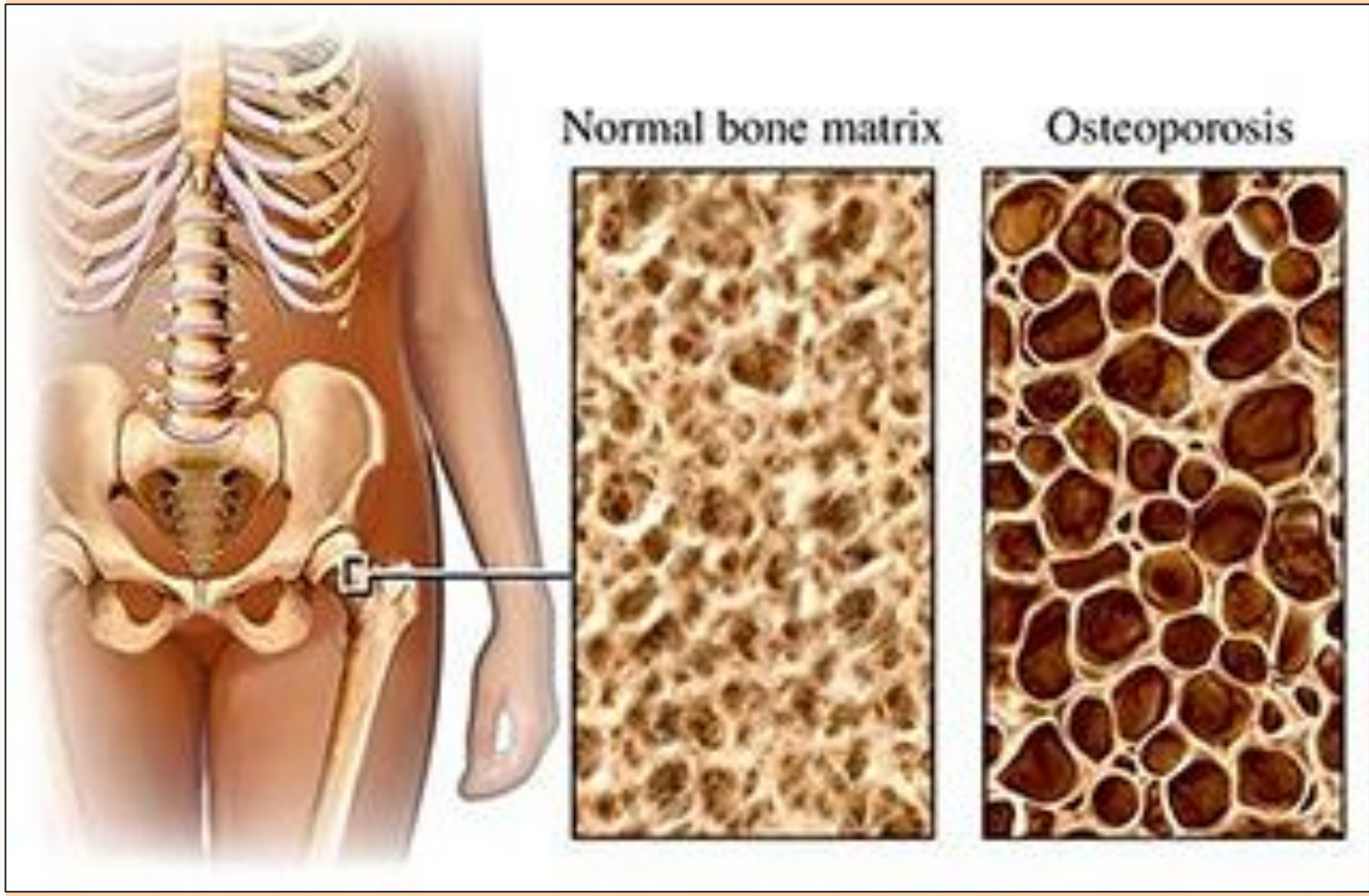
10/15/2025



Disclosures

The planner, speaker and CME Committee members have no relevant financial relationship(s) with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients to disclose.

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Cultural and Linguistic Barriers

- Compliance with medications and follow up may be limited by language barriers
- Language barriers may complicate safely communicating and understanding instructions
- Patients may not feel comfortable calling to discuss any questions (for example when seeing concerning ads about their medications on TV or the internet) due to perceived language barrier

Objectives

- Define Osteoporosis
- Identify secondary causes
- Review available treatment options tailored to your patients
- Learn to manage Steroid-Induced Osteoporosis
- Learn how to monitor treatment and when to change therapy

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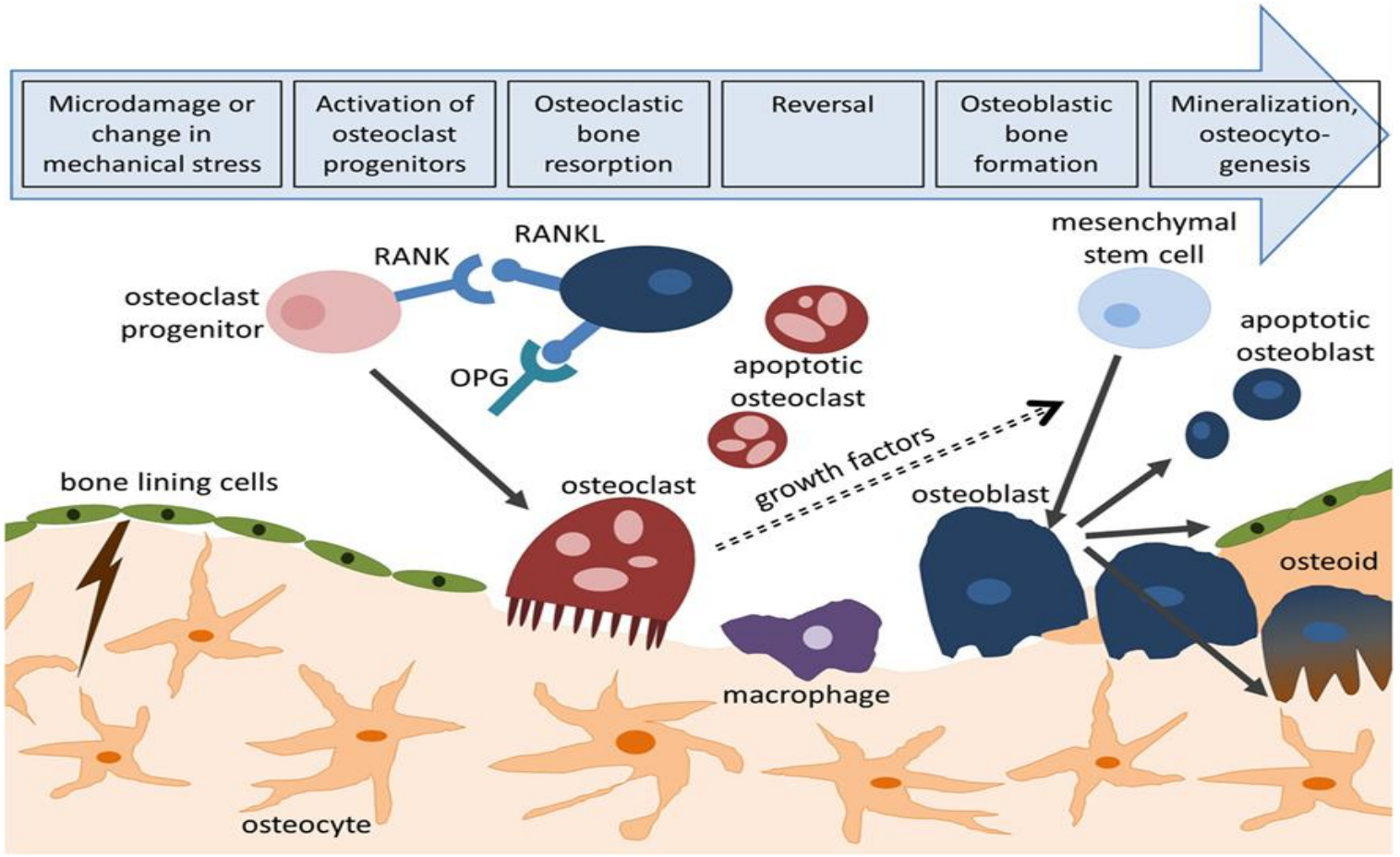
Bone Physiology



Wittkowske C, et al. In Vitro **Bone Cell Models: Impact of Fluid Shear Stress on Bone Formation.** Front. Bioeng. Biotechnol., 15 November 2016

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Epidemiology and Statistics

- According to NOF, 9.9 million people in US have osteoporosis and 43.1 million have low BMD
- 2 million fractures, 432,000 hospital admissions, 2.5 million doctor's visits, and ~180,000 SNF admissions annually due to osteoporosis
- 5.1% men and 24.5% women over 65yo have OP
- Mortality rates during hospitalization for hip fx 1-10% and 12-37% at 1yr
- ~20% patients with hip fx require long-term SNF, only 40% fully return to independent baseline functionality
- Vertebral fx can be a/w pain, disability, deformity, and mortality, and increase risk of future vertebral fx 5x and non-vertebral fx 2-3x
- Only ~1/4 women >67yo w/ OP-related fx had DXA or OP tx w/in 6mo of fx

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Definition of Osteoporosis: WHO Classification

- Osteoporosis:
  1. Postmenopausal women and men >50yrs old w/ T<-2.5
  2. T-score -1-2.5 w/ FRAX score 10yr risk major osteoporotic fracture >20% or hip fracture >3%
  3. Presence of fragility fracture (even with normal BMD)

- Diagnosis is made by site of lowest T-score

- Osteopenia: T-score -1-2.5 without significant FRAX score

- Risk of new vertebral fracture increases ~2x per SD decrease in BMD

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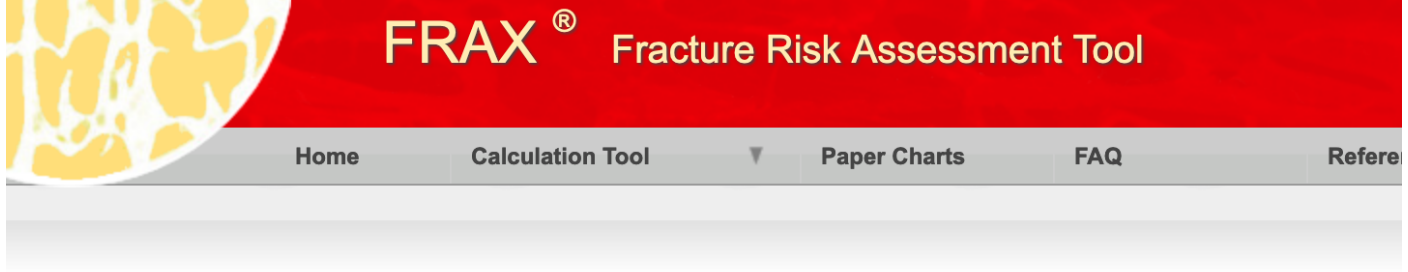

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ● No ○ Yes
6. Parent Fractured Hip ● No ○ Yes
7. Current Smoking ● No ○ Yes
8. Glucocorticoids ● No ○ Yes
9. Rheumatoid arthritis ● No ○ Yes
10. Secondary osteoporosis ● No ○ Yes
11. Alcohol 3 or more units/day ● No ○ Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear Calculate

http://www.shef.ac.uk/FRAX/

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Imaging

DXA SCAN

- T-score compares BMD to healthy young adult population (use in postmenopausal women and men >50)
- Z-score compares BMD to average for age, sex and size to identify secondary causes of OP (use in premenopausal women and men <50)
- compare BMD's not T-score between studies ideally done on same machine

Trabecular bone score (TBS): used to measure "quality" of the bone (microarchitecture)

Vertebral imaging: vertebral fracture assessment (VFA) or lateral thoracic and lumbar spine X-ray

- Consider in women >70, men >80 w/ T<-1
- Consider in women 65-69 and men 70-79 w/ T<-1.5
- Consider in postmenopausal women and men >50 w/ fragility fracture, >1.5in height loss, recent or current long-term GC
- Repeat testing if new vertebral fx, height loss, back pain, change in posture, and prior to taking drug holiday to r/o new fractures

Definition of Fragility Fracture

Clinical osteoporosis if presence of fracture in the spine, hip, wrist, humerus, ribs, pelvis (EVEN with normal DXA) following minor trauma or occurring spontaneously

Fractures of the skull, C-spine, hands, feet and ankles or stress fractures are NOT fragility fractures

Whom to screen?

NOF: women >65 and men >70, younger women and men 50-69 w/ risk factors, anyone with fracture after 50yo, anyone with condition or taking med (ie. GC >5mg prednisone x >3mo) a/w bone loss

AACE: women >65, adult w/ fragility fracture, younger postmenopausal women w/ risk factures

USPSTF: women >65 and younger women w/ risk factors

NAMS: women >65, postmenopausal women w/ risk factors and medical causes of bone loss or w/ fragility fracture

Other causes of fractures

Malignancy – e.g., multiple myeloma (lytic lesions) or prostate cancer (blastic lesions)

Paget's disease

Osteomalacia – mineralization defect causing diffuse bone pain

Trauma/repetitive stress

Infections – e.g., tuberculosis (Pott's disease)

Risk Factors for Osteoporosis

Prior fracture

FHx osteoporosis and fractures (hip)

Age

Low body weight

Caucasian

Alcohol abuse

Smoking

Rheumatoid arthritis

Medications: glucocorticoids, heparin, anticonvulsants, aromatase inhibitors, chemotherapy, immunosuppressants (cyclosporine), GnRH agonists and antagonists (Lupron), PPI, depot medroxyprogesterone, pioglitazone, Invokana, SSRI

Secondary Endocrine Causes of Osteoporosis

Hyperparathyroidism (preferentially affects wrist)

Hyperthyroidism

Cushing syndrome

Acromegaly

Primary or Secondary Hypogonadism (ie. Amenorrhea, POI, premature menopause, testosterone deficiency)

Hyperprolactinemia

Diabetes Mellitus (esp type 1)

Secondary Non-Endocrine Causes of Osteoporosis

Malabsorption
Inflammatory Bowel Disease
Cirrhosis
Multiple Myeloma
Alcoholism
Medications: ie. Glucocorticoids
Immobilization
Idiopathic hypercalciuria
Vitamin D deficiency
Rheumatoid arthritis
Hemochromatosis
Eating disorders

Renal Osteodystrophy

Difficult to distinguish between osteoporosis and CKD-metabolic bone disease

r/o adynamic bone disease: low PTHi<100 and high BSAP>42

Bone biopsy is gold standard

Few treatment options when GFR<35 and prolia can cause hypocalcemia; especially in severe renal dysfunction

Laboratory Evaluation

CMP

Vitamin D

TSH

CBC

Testosterone in young men

If clinical suspicion or low Z-score <2SD below age-matched subjects requires further eval for secondary causes:

- PTHi, LNSC, E2, LH, FSH, celiac Ab, 24hr urine calcium

- Alcohol and smoking cessation
- Weight bearing exercise (at least 30min 3x/wk)
- Goal calcium intake 1200mg through diet (plus supplement if needed)
- Goal vitamin D 25OH >30 (at least 600-800IU/day)
- Fall prevention

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Treatment

Anti-resorptive agents: slow bone breakdown

Bisphosphonates, denosumab, calcitonin, HRT, SERMs

Anabolic agents: build new bone

PTH (teriparatide), PTHrP (abaloparatide)

Anti-resorptive + anabolic agent

Romosozumab

PO Bisphosphonates

(Alendronate, Risedronate, Ibandronate)

- Take on empty stomach 30-60 minutes before eating with 8 ounces of water, and stay upright for 30 minutes
- Side effect: reflux, abdominal pain, esophagitis, hypocalcemia, ONJ, atypical femoral fractures
- Contraindicated CrCl <35
- Consider drug holiday after 5 years
- Price: ~$8/mo (~$100/yr)

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PO Bisphosphonates

Alendronate (Fosamax): daily, weekly

- Approved in women, men, and steroid-induced OP
- reduces the spine and hip fx by ~50% over 3 years if h/o prior vertebral fx or osteoporosis at hip, and reduces vertebral fx 48% over 3 years if no h/o prior vertebral fx
- Overall 4-8% improved BMD at spine and 3-4% at hip

Ibandronate (Boniva): monthly

- Only reduces vertebral fracture risk, only women
- reduces vertebral fx by ~50% over 3 years, and 4-8% improved BMD at spine

Risedronate (Actonel): daily, weekly, twice monthly

- Approved in women, men, and steroid-induced OP
- reduces vertebral fx by 41-49% and nonvertebral fx by 36% over 3 years, especially if h/o prior vertebral fx
- Overall 4-8% improved BMD at spine and 3-4% at hip

IV Bisphosphonate:

Zoledronic Acid (RECLAST)

Administered at infusion center over a 15 minutes IV infusion

Consider drug holiday after 3 years

Side effects: arthralgias/myalgias, flu-like symptoms, hypocalcemia (replete vitamin D and calcium before infusion), ONJ, atypical femoral fractures

Contraindicated CrCl <35

Price: ~$1500/dose (yr)

*reduces vertebral fx by 70% (esp at 1yr), hip fx by 41%, and nonvertebral fx by 25% over 3 yrs
Improves BMD by 7% at spine and 6% at hip

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Denosumab

(Prolia, Jubbonti)

- Activates RANKL inhibitor (osteoblasts) to decrease binding to RANK receptor on osteoclasts→decrease bone turnover
- SQ injection Q6 months
- Side effects: arthralgias/myalgias, malignancy, hypocalcemia, infection (cellulitis), ONJ, atypical femoral fractures, malignancy (nonsignificant increase in breast, pancreatic, GI, ovarian and uterine tumors)
- Okay in renal disease
- NO DRUG HOLIDAY!!! due to rebound increased risk vertebral fractures with discontinuation (from 1.2 to 7.1 per 100 participant-yrs even after 2 doses (lasts 2yrs)
- Price ~$1400/dose ($2800/yr)

*reduces vertebral fx by ~68%, hip fx by ~40%, and nonvertebral fx by ~20% over 3 yrs
Increases BMD by 9.2% at spine and 6% at total hip

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Teriparatide (Forteo)

Abaloparatide (Tymlos)

- Anabolic agent: PTHi or PTHrp analogs
- Indicated for severe osteoporosis (T<-3.5, or <-2.5 w/ fragility fracture
- Daily SQ injection
- Side effect: transient hypercalcemia (hypercalciuria) or increased uric acid, arthralgia, nausea, pain, transient orthostatic hypotension
- Black box warning: increased risk osteosarcoma in rats (avoid use if increased baseline osteosarcoma risk including primary hyperparathyroidism, Paget disease, elevated alk phos, prior XRT)
- Maximum 2 year use (then switch to bisphosphonate or denosumab)
- Price: ~$4200/mo ($50,000/yr)

*In median 19mo, reduced vertebral fx 65% and nonvertebral fx 53%
Improves BMD by 10-14% at spine and 4-6% at hip

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Romosozumab (Evenity)

Monoclonal Ab binds Sclerostin (osteocyte secreted Wnt pathway inhibitor) increases bone formation and decreases resorption

SQ injection monthly x1yr

Black box warning: increased risk of MI, stroke and CV death (do not start if MI or CVA w/in 12mo)

Side effects: arthralgia, risk of MI, CVA and CV death, hypocalcemia (1mo after), ONJ, atypical femoral fractures

Price: $1,825/dose ($21,900/yr)

*At 12 mo, reduced risk vertebral fx by 73%, reduced clinical fx by 36%, but no sig change in nonvertebral fx c/w placebo.
At 24 mo, vertebral fx were reduced by 75% when transition from romosozumab (vs placebo) to denosumab

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Other treatments

HRT (Estrogen, Testosterone)

- If primary ovarian insufficiency or hypogonadism

Raloxifene (Evista)

- SERM (Estrogen agonist/antagonist)
- Less effective antiresorptive effects than bisphosphonates
- Doesn’t improve hip fracture risk
- Consider if can’t tolerate bisphosphonates or denosumab, or increased risk invasive breast cancer
- Side effects: hot flashes, arthralgias/myalgias, VTE and CVA risk

Calcitonin: daily nasal spray, not very effective

Treating Osteoporosis in men

Treat hypogonadism w/ testosterone first (if no C/I)

PO Alendronate or Risedronate

IV Zoledronic Acid

Teriparatide/Abaloparatide

Denosumab (improves BMD, but not shown to reduce fracture risk in men except those with prostate cancer on androgen deprivation therapy)

Treat or prevent Steroid-Induced Osteoporosis

Alendronate

Risedronate

(preferred)

Zoledronic acid

Denosumab

Teriparatide

Raloxifene

Table 1. Fracture risk categories in GC-treated patients

	Adults ≥40 years of age	Adults <40 years of age
High fracture risk	Prior osteoporotic fracture(s) Hip or spine bone mineral density T score ≤−2.5 in men age ≥50 years and postmenopausal women FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ ≥20% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture(s)
Moderate fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ 10–19% FRAX* (GC-adjusted†) 10-year risk of hip fracture >1% and <3%	Hip or spine bone mineral density Z score <−3 **or** rapid bone loss (≥10% at the hip or spine over 1 year) **and** Continuing GC treatment at ≥7.5 mg/day for ≥6 months
Low fracture risk	FRAX* (GC-adjusted†) 10-year risk of major osteoporotic fracture‡ <10% FRAX* (GC-adjusted†) 10-year risk of hip fracture ≤1%	None of above risk factors other than GC treatment

* https//www.shef.ac.uk/FRAX/tool.jsp.
† Increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if glucocorticoid (GC) treatment is >7.5 mg/day (e.g., if hip fracture risk is 2.0%, increase to 2.4%).
‡ Major osteoporotic fracture includes fractures of the spine (clinical), hip, wrist, or humerus.

Highest rate of bone loss in first 3-6mo of GC tx, especially at spine

Inhibit osteoblasts and enhance osteoclasts and decreases bone quality

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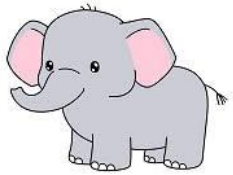
Osteonecrosis of the jaw (ONJ)



- Symptoms: pain, swelling, infection, exposed bone
- Risk 1:10,0000-1:100,000 patient years for PO bisphosphonates
- Risk factors: cancer tx w/ high dose IV bisphosphonates (dose and duration), dental extractions, implants or ill-fitting dentures, periodontal disease, smoking, glucocorticoids
- If dental procedure planned, delay initiating bisphosphonate for few months for healing (controversial whether to hold if already taking it; consider stop 2mo before invasive dental procedure if on tx >4yrs or on GC and restart when bone is healed)

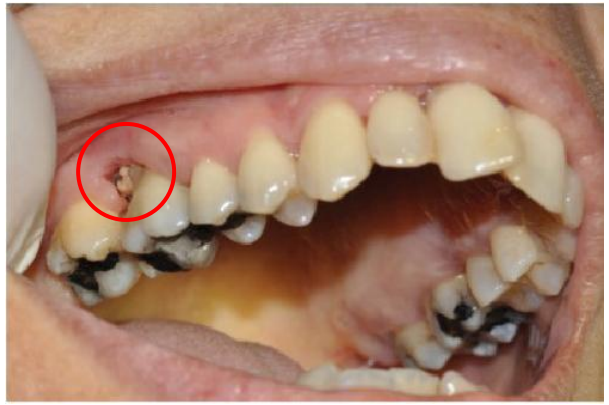


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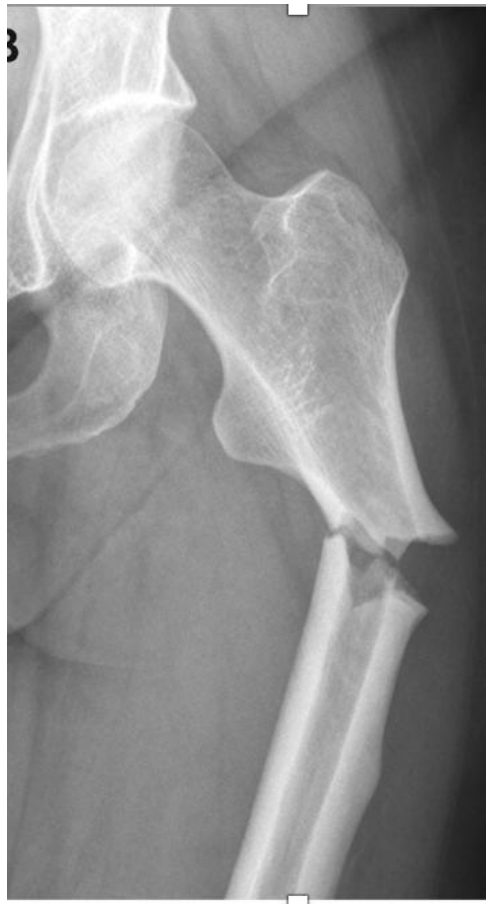
Image courtesy of Dr Ourania Nicolatou-Galitis National & Kapodistrian University of Athens, Greece. Published in Ecancermedicalscience 2018DOI:10.3332/2cancer.2018.ed77

Atypical femoral fractures

- Symptoms: dull aching pain in groin or thigh
- Associated with median 7yrs bisphosphonate tx
- Risk: 3.2-50 cases per100,000 patient-years, with longer use (> 5 years) increasing the risk to about 100 per 100,000 patient-years.
- Risk declines significantly after stopping bisphosphonate
- Risk of contralateral fracture increases significantly
- MOA: prolonged tx can over suppress bone turnover and increase fragility
- Subtrochanteric (femoral, transverse) fx: considered stress or insufficiency fractures



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Monitoring therapy

DXA

- Q1-2yrs on therapy
- BMD that is stable or improving→ effective response
- IOF 2012 criteria for failure of treatment:
  - BMD worsening >LSC (ie. >3%) and/or no sig decrease in bone turnover markers
  - 1 fragility fracture (w/ no decrease in bone turnover markers and/or decreased BMD)
  - >2 fragility fractures

Bone turnover markers:

- Controversial use
- Can check baseline fasting urine NTX or serum CTX and monitor Q3-6 months after tx and if 50% decrease in NTX or 30% decrease in CTX, then tx is effective and pt is compliant

When to refer to endocrinology?

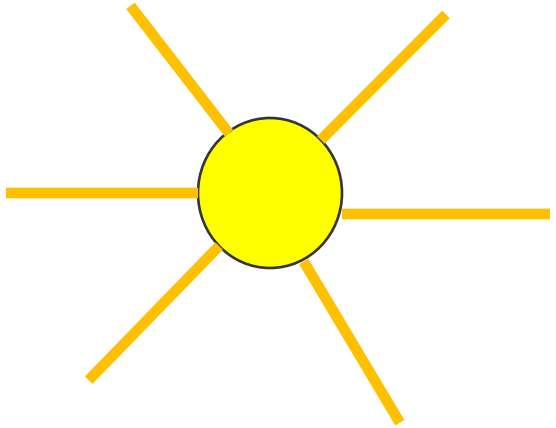
- Intolerance or contraindication to PO bisphosphonates
- Fails initial treatment
- Severe osteoporosis T>-3.5 and/or multiple fragility fractures
- Want to start Denosumab or Zoledronic acid or Teriparatide/Abaloparatide, or Romosozumab

Changing therapy

- If fails or intolerant to PO bisphosphonates, can switch to IV zoledronic acid (or denosumab)
- Denosumab→Teriparatide switch is bad!!! (bone turnover markers increase 400x)
- Denosumab→Zoledronic acid switch (administer at 9mo instead of 6mo due to low turnover markers)
- After 2yrs teriparatide/abaloparatide can switch to PO or IV bisphosphonate, denosumab, or raloxifene (last resort)
- Can start treatment 6-12wks after fracture (won't delay healing)

Take home points

- Screen women >65 and men >70, younger women and men 50-69 w/ risk factors, anyone with fracture after 50yo, if taking meds a/w bone loss
- Fragility fx in spine, hip, wrist, humerus, ribs, pelvis is osteoporosis (EVEN with normal DXA)
- Unchanged BMD is not a sign of treatment failure (compare BMD not T-scores)
- Start with PO bisphosphonate unless C/I
- Ibandronate, Raloxifene don’t improve hip BMD
- If treatment failure, switch to Zoledronic acid, Denosumab, Teriparatide/Abaloparatide or Romosozumab
- Consider drug holiday after 5yrs PO bisphosphonate, and 3yrs IV bisphosphonate, and no holiday for denosumab!
- Anabolic drugs needs to be followed by an antiresorptive drug



Thank You for joining this tour de force!

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National Osteoporosis Foundation (NOF)

Center for Disease Control (cdc.gov)