Osteoporosis

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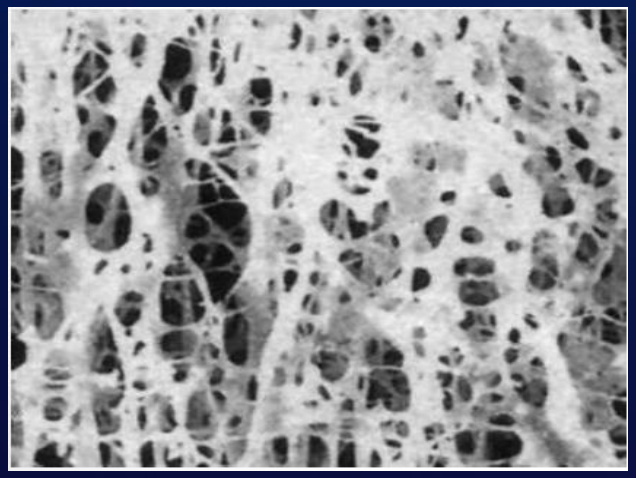
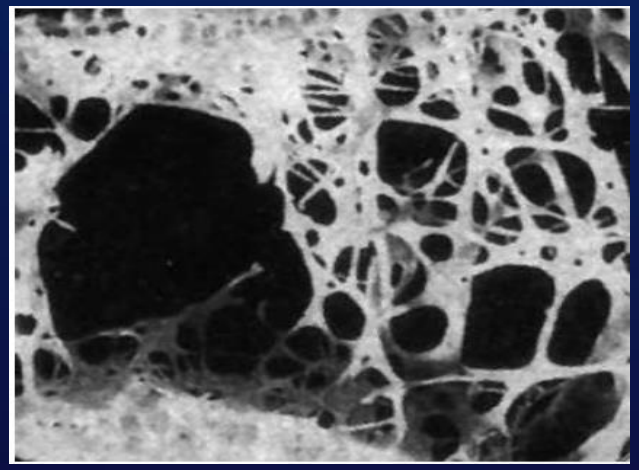
April 30, 2019

Osteoporosis

- Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture particularly at the spine, hip, wrist, humerus, and pelvis.
- Osteoporotic fractures (fragility fractures, low-trauma fractures) are those occurring from a fall from a standing height or less, without major trauma such as a motor vehicle accident.



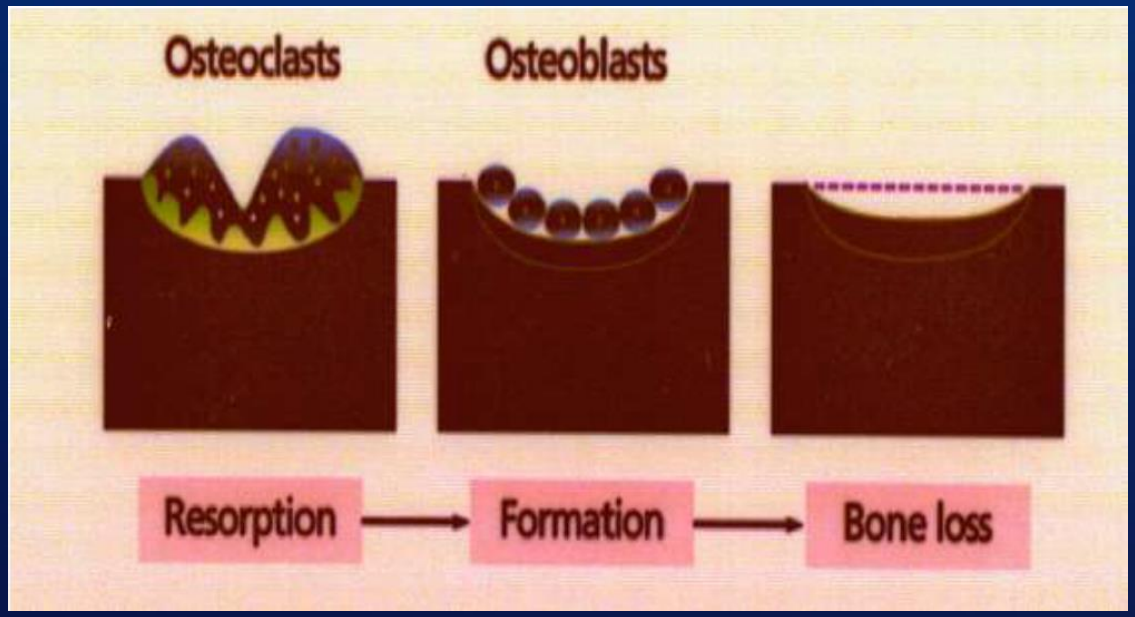
Normal bone



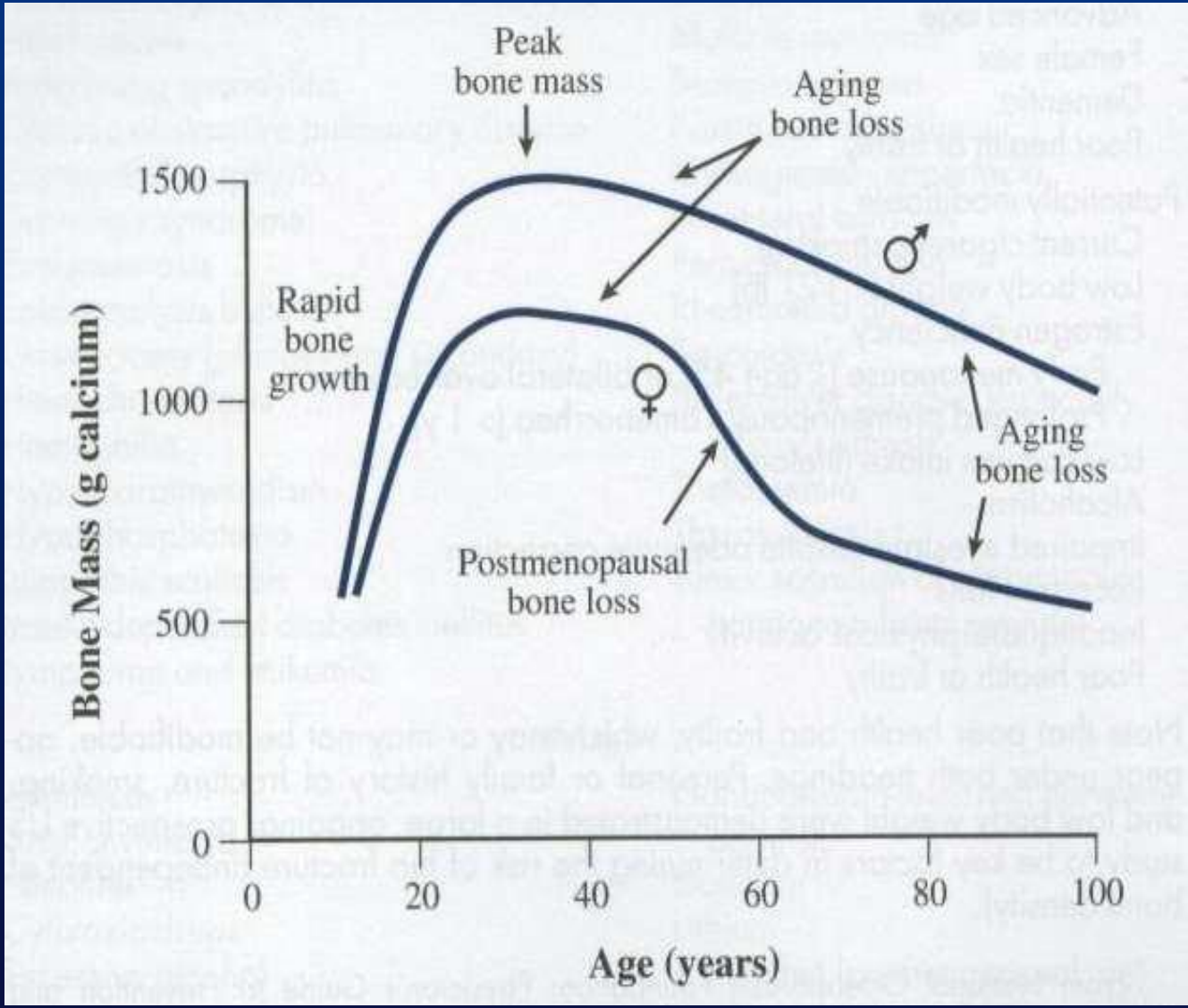
Osteoporotic bone

Osteoporosis Pathophysiology

Bone mass density loss reflects *imbalance* between resorption and formation
– – bone resorption accelerated



- The biggest culprit for osteoporosis is the accelerated bone loss during menopause



Kassem, Melton, Riggs. Involutional osteoporosis. In Feldman, Kelsay (eds) 1996. Osteoporosis. New York, Academic Press, pp 691-702

DXA (Dual Energy X Ray Absorptiometry)

- DXA measures bone mineral content (BMC, in grams) and bone area (BA, in square centimeters), then calculates "areal" BMD in g/cm^2 by dividing BMC by BA

WHO Definition of Osteoporosis

WHO Definition of Osteoporosis Based on BMD		
Classification	**BMD**	**T-score**
Normal	Within 1 SD of the mean level for a young-adult reference population	T-score at -1.0 and above
Low Bone Mass (Osteopenia)	Between 1.0 and 2.5 SD below that of the mean level for a young-adult reference population	T-score between -1.0 and -2.5
Osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population	T-score at or below -2.5
Severe or Established Osteoporosis	2.5 SD or more below that of the mean level for a young-adult reference population	T-score at or below -2.5 with one or more fractures

The T-score compares an individual's BMD with the mean value for young adults and expresses the difference as a standard deviation score.

T Scores Vs Z Scores

- T-score: Number of SDs from the mean BMD of white females age 20 to 29 years in the NHANES III database

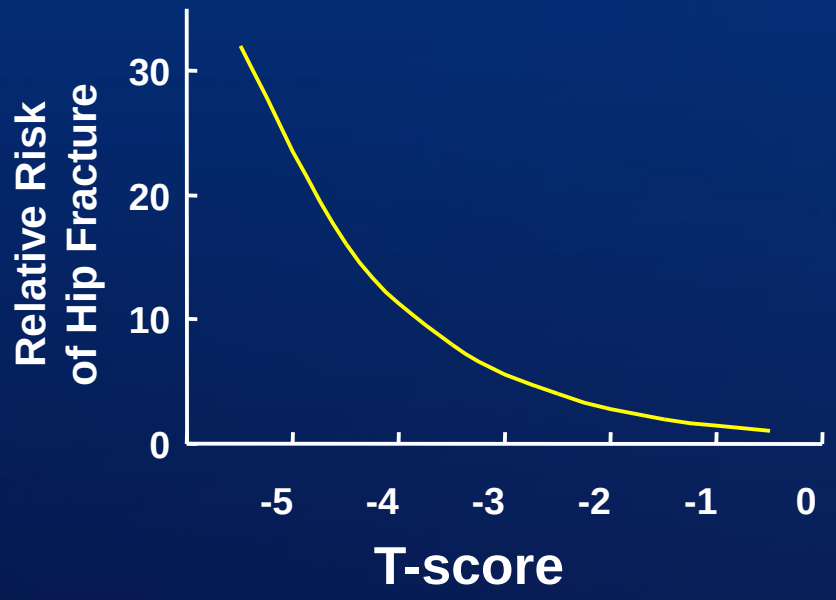
  -Applied to postmenopausal women and men > 50 years.

- Z-score: based on difference between the individual's BMD and mean of a reference population of same gender, age, ethnicity

  - Used for premenopausal women and men under age 50

  - Low BMD : Z score ≤ 2.0

Strong Relationship Between Bone Density and Bone Strength



- Bone density accounts for 60% to 80% of bone strength
- Best early predictor of fracture risk[2]

1. Kushida K. *Clin Calcium.* 2004;14:11-17.
2. Fogelman J, Blake GM. *J Nucl Med*. 2000;41:2015-2025.

The Clinical Challenge

- Often asymptomatic

  -Until fracture occurs

  -Even after some fractures (eg, 2/3 of vertebral fractures are asymptomatic)

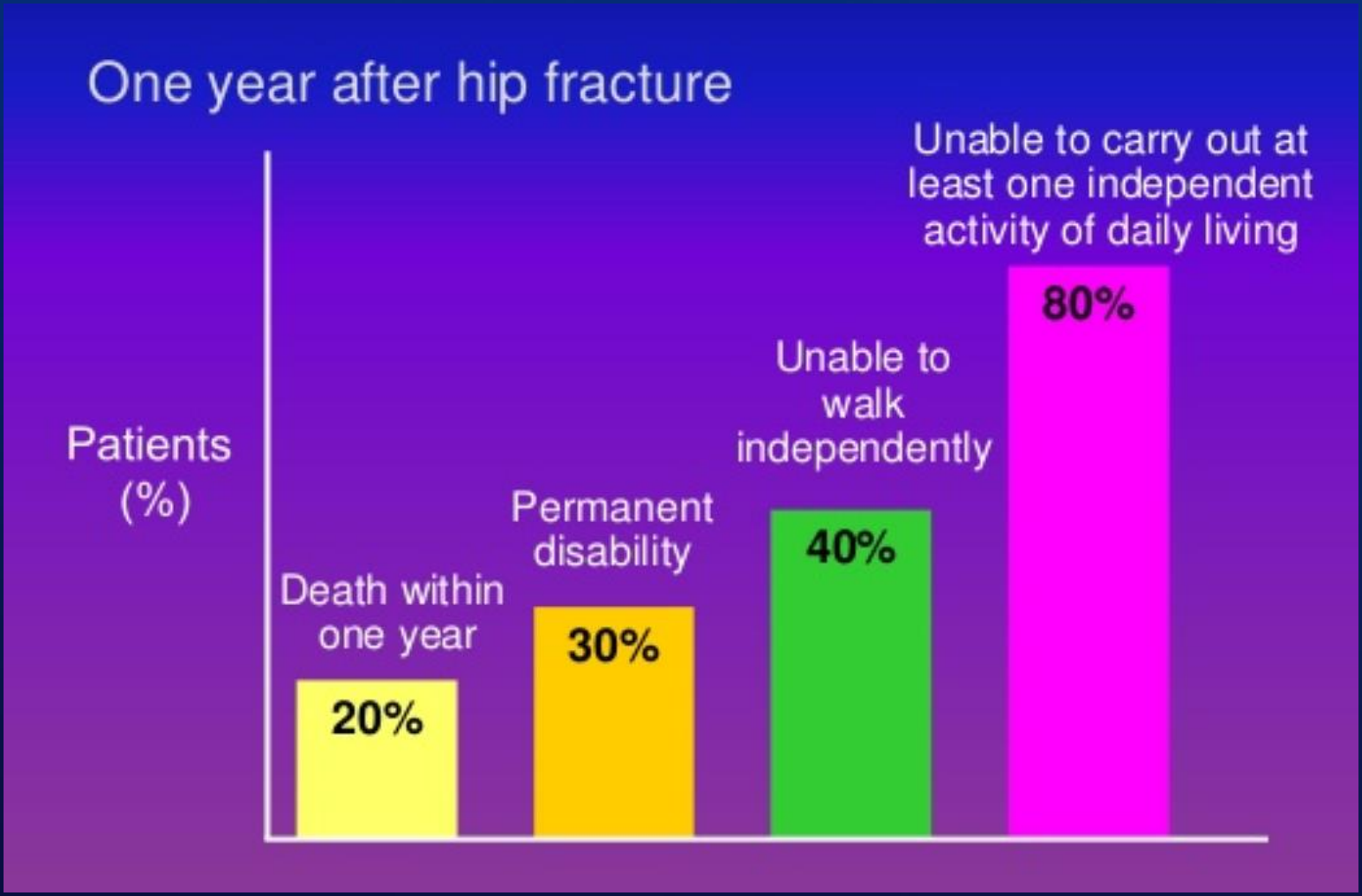
1. South-Paul JE. *Am Fam Physician*. 2001;63:1121-1128.
2. Lenchnik L, et al. *AJR.* 2004;183:949-958.

Serious Public Health Problem

- Affects 10 million Americans (80% women)
- 2 million fractures yearly
- Half of all postmenopausal women and a quarter of men over 50 years old will have an osteoporosis related fracture

US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004. Available at: http://www.surgeongeneral.gov/library/reports/bonehealth/full_report.pdf. Accessed September 13, 2013.

Consequences of hip fracture



Cooper. Am J Med 1997; 103 (2A): 12s-19s

HEDIS Measure	% Compliance*
Beta-blocker persistence after a heart attack	81.3%
Breast cancer screening	70.5%
Colorectal cancer screening	62.4%
Osteoporosis management after a fracture	**22.8%**

NCQA State of Healthcare 2012 -HMO Statistics (Commercial or Medicare data from 2011).
http://www.ncqa.org/Portals/0/State%20of%20Health%20Care/2012/SOHC%20Report%20Web.pdf.

Guidelines for Bone Density Testing

- Screening
  - All women age 65 and older[1,2]
  - All men age 70 and older[1]
- Test postmenopausal women and men >50 if[1]:
  - Fracture after age 50
  - Clinical risk factors for osteoporosis
  - Conditions/medications associated with bone loss
    - RA, hyperparathyroidism, celiac disease, IBD
    - Oral glucocorticoids, anticonvulsants, proton pump inhibitors, SSRIs, aromatase inhibitors

1. Adapted from National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis.* Washington, DC: National Osteoporosis Foundation; 2013. Available at: http://www.nof.org/hcp/clinicians-guide. Accessed September 13, 2013.
2. US Preventive Services Task Force. *Ann Intern Med.* 2002;137:526-528.

Be on the Lookout for Silent Fractures

- 2/3 vertebral fractures unrecognized by patients/clinicians
- Indicate very high risk for future spine and hip fractures
- The presence of a vertebral compression fracture makes the clinical diagnosis of osteoporosis, regardless of T-score on dual-energy x-ray absorptiometry (DEXA) scan, and treatment is recommended
- Consider Vertebral Fracture Assessment (VFA) if vertebral fracture is suspected clinically. Can be done at the time of BMD testing- less cost, lower radiation than X rays

Xu WW, et al. *Bone.* 2011;2:307-311. National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis.* Washington, DC: National Osteoporosis Foundation; 2013. Available at: http://www.nof.org/hcp/clinicians-guide . Accessed September 13, 2013.

Vertebral Imaging

Consider vertebral imaging tests for the following individuals:***
• All women age 70 and older and all men age 80 and older if BMD T-score at the spine, total hip or femoral neck is ≤ -1.0.
• Women age 65 to 69 and men age 70 to 79 if BMD T-score at the spine, total hip or femoral neck is ≤ -1.5
• Postmenopausal women and men age 50 and older with specific risk factors: ▪ Low trauma fracture during adulthood (age 50) ▪ Historical height loss of 1.5 inches or more (4 cm)* ▪ Prospective height loss of 0.8 inches or more (2 cm)** ▪ Recent or ongoing long term glucocorticoid treatment

* Current height compared to peak height during young adulthood

** Cumulative height loss measured during interval medical assessment

*** If bone density testing is not available, vertebral imaging may be considered based on age alone

National Osteoporosis Foundation

- 68 y.o. white obese (185 lb) female with rheumatoid arthritis, seizures, HTN, and hypothyroidism comes in to your office to establish care. She is on methotrexate, dilantin, losartan, metoprolol, and levothyroxine. She is also a smoker with 40 pack history. She drinks 2-3 glasses wine a day.
- Bone density - T score for her right hip is -2.4.
- Her Ten year probability of fracture
- Major osteoporotic fracture is 21%
- Hip fracture is 9.5%
- Would you start pharmacologic therapy?

- Fracture risk highest in patients with osteoporosis; more fractures occur in patients with osteopenia.
- Osteopenia patients outnumber those with osteoporosis 3:1

FRAX

- Goal –identify patients with osteopenia at high fracture risk.
- Calculates estimate of 10 year hip fracture risk and total major osteoporotic fracture risk.
- Considers BMD and other risk factors.
- Applies to patients before treatment.
- Do not use in men <50 or premenopausal women.

FRAX Risk Factors

Clinical Risk Factors Included in the FRAX Tool	
Current age	Rheumatoid arthritis
Gender	Secondary causes of osteoporosis: Type1 (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition or malabsorption and chronic liver disease
A prior osteoporotic fracture (including clinical and asymptomatic vertebral fractures)	Parental history of hip fracture
Femoral neck BMD	Current smoking
Low body mass index (BMI, kg/m^2)	Alcohol intake (3 or more drinks/d)
Oral glucocorticoids $\geq$5 mg/d of prednisone for >3 months (ever)	

National Osteoporosis Foundation

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

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
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

Weight Conversion

Pounds → kg

Convert

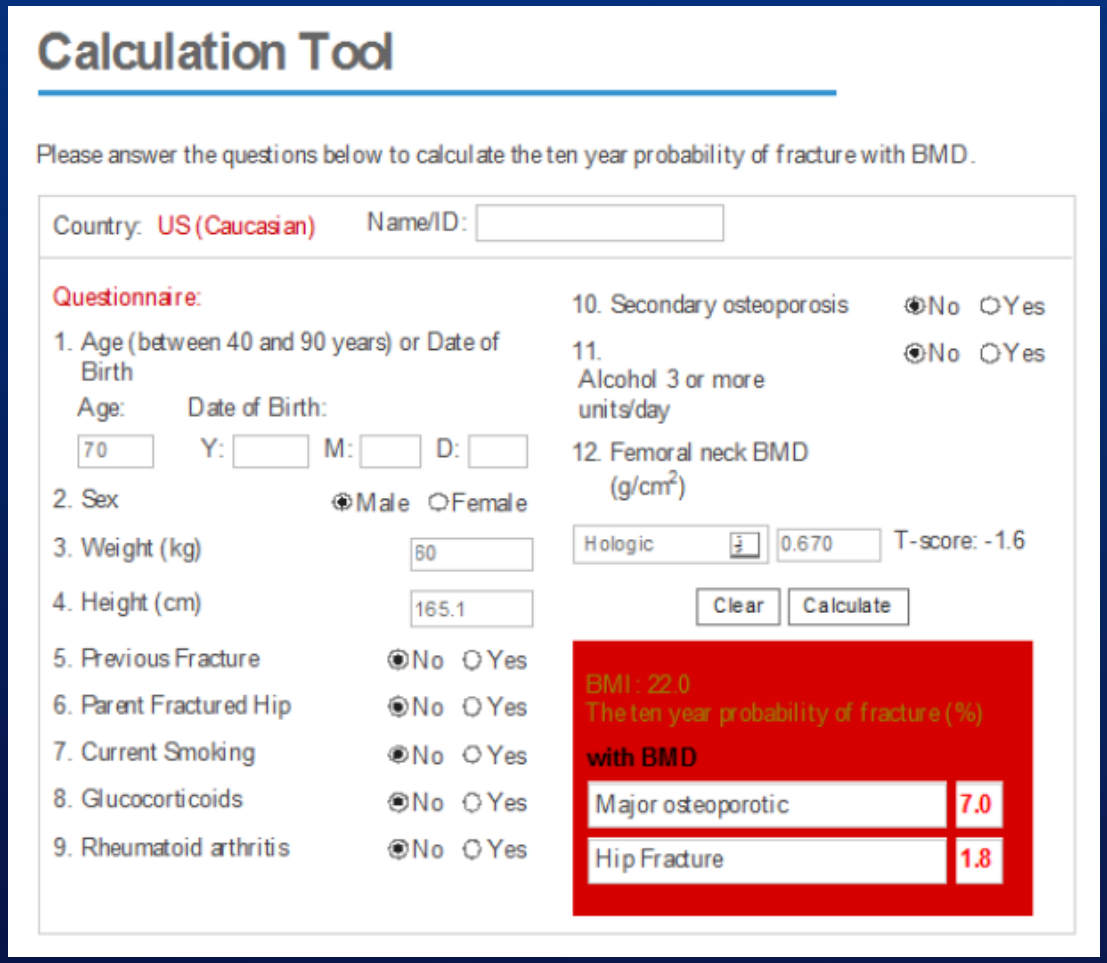
Height Conversion

Inches → cm

Convert

02051495

FRAX Score



Calculation Tool

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

Country: US (Caucasian) Name/ID:

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 70 Date of Birth: Y: M: D:
2. Sex ◉Male ○Female
3. Weight (kg) 60
4. Height (cm) 165.1
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) Hologic 0.670 T-score: -1.6

Clear Calculate

BMI: 22.0
The ten year probability of fracture (%)
with BMD

Major osteoporotic	7.0
Hip Fracture	1.8

- Threshold for treatment :

➢ 3% Hip Fracture, 20% Major osteoporotic Fracture in the next 10 years

- 68 y.o. white obese (185 lb) female with rheumatoid arthritis, seizures, HTN, and hypothyroidism comes in to your office to establish care. She is on methotrexate, dilantin, losartan, metoprolol, and levothyroxine. She is also a smoker with 40 pack history. She drinks 2-3 glasses wine a day.
- You order a Dexa scan and the T score for her right hip is -2.4.
- Her Ten year probability of fracture
- Major osteoporotic fracture is 21%
- Hip fracture is 9.5%
- Would you start pharmacologic therapy?

Causes of Osteoporosis

- Tobacco
- Excess alcohol
- Medications
  - Anticonvulsants - (Dilantin)
  - Steroids >5mg/d for >6 months
  - Depo-provera
  - Heparin/warfarin
  - Immunosuppressants
  - GnRH agonist
- Hypogonadism
- Vitamin D deficiency
- Diseases
  - Rheumatoid or other inflammatory arthritis
  - Multiple myeloma, lymphoma
  - Hyperthyroidism
  - Hyperparathyroidism
  - Cushing's syndrome
  - Marfans and Ehlers – Danlos
  - Renal disease
  - Osteogenesis imperfecta
  - Liver disease

Laboratory Evaluation

- CMP – calcium, renal function, liver function including alkaline phosphatase, phosphorus
- CBC
- 25-OH vitamin D
- Thyroid function
- 24 hour urine calcium excretion
- PTH
- Tissue transglutaminase antibody (celiac sprue)
- Serum protein electrophoresis
- Urine cortisol (if suspicion for cortisol excess)
- Testosterone (in men with osteoporosis)

Management of Osteoporosis

Lifestyle Measures

- Adequate nutrition, particularly calcium and vitamin D
  - Calcium: 1000 – 1200 mg daily (diet plus supplements if needed)
  - Vitamin D: Aim for level > 30 (~1000 units daily)

Foods and drinks with calcium

Food	Calcium, milligrams
Milk (skim, 2 percent, or whole, 8 oz [240 mL])	300
Yogurt (6 oz [168 g])	250
Orange juice (with calcium, 8 oz [240 mL])	300
Tofu with calcium (1/2 cup [113 g])	435
Cheese (1 oz [28 g])	195 to 335 (hard cheese = higher calcium)
Cottage cheese (1/2 cup [113 g])	130
Ice cream or frozen yogurt (1/2 cup [113 g])	100
Soy milk (8 oz [240 mL])	300
Beans (1/2 cup cooked [113 g])	60 to 80
Dark, leafy green vegetables (1/2 cup cooked [113 g])	50 to 135
Almonds (24 whole)	70
Orange (1 medium)	60

- Weight bearing exercise
- Discourage smoking
- Discourage alcohol abuse
- Reduction of risks for falling: consider OT evaluation for home hazards, minimize sedating medications.

Pharmacologic Therapy for Osteoporosis

After exclusion of secondary causes, treat postmenopausal women and men age 50 and older who have…

Osteoporosis

Clinical diagnosis:
Hip or spine fracture

DXA diagnosis:
T-score -2.5 or below in the spine or hip

T-scores between -1.0 and -2.5 and

10-year risk of fractures:

≥3% for hip fracture
or
≥20% for a major osteoporotic fracture

National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis.* Washington, DC: National Osteoporosis Foundation; 2013. Available at: http://www.nof.org/hcp/clinicians-guide. Accessed September 13, 2013.

Pharmacologic Therapy for Osteoporosis

Antiresorptives

- Bisphosphonates
- Denosumab
- SERM (Raloxifene)
- Estrogen

Anabolic Agents

- Teriparatide (PTH 1-34)
- Abaloparatide (PTHrP 1-34)

Bisphosphonates

- Alendronate (Fosamax) – 70 mg weekly
- Risedronate (Actonel) – 35 mg weekly, 150 mg monthly
- Zoledronic acid (Reclast) – 5 mg IV yearly
- Ibandronate (Boniva) – 150 mg monthly, 3 mg IV every 3months

➢ Not recommended for creatinine clearance below 35 (alendronate and Zoledronic acid) or < 30 (risedronate, ibandronate)

Bisphosphonates: Effects

- Increased bone density in the spine by 5% to 8% and at the hip by 3% to 6% after 3 years
- Reduced incidence of vertebral fractures by 40% to 70%
- Alendronate, risedronate and zoledronic acid reduced non-vertebral fractures (25% to 40%), including hip fractures (40% to 60%), in women with osteoporosis
- Ibandronate: Overall, no effect observed on non-vertebral or hip fractures. (Ibandronate is not recommended to reduce nonvertebral or hip fracture risk)

Oral bisphosphonates

- Should not be used in patients with active GI disease.
- Should be taken on an empty stomach after overnight fast with 8 oz of plain water while in an upright position
- Patient should not have food, drink, supplements for at least 30 min (alendronate, risedronate) or 60 min (ibandronate) to enhance absorption.
- Patients should remain upright (sitting or standing) for at least 30 minutes to minimize reflux
- Calcium and vitamin D supplements should be separated at least 1 hour from bisphosphonate

Side Effects

- Oral bisphosphonates:

-Upper GI side effects (reflux, esophagitis).

-Avoid in patients with achalasia, esophageal stricture, Barrett's esophagus, esophageal varices, Roux en Y gastric bypass

- IV bisphosphonates:

- Acute phase reaction of low grade fever, myalgias, arthralgias within 24- 72 hours
- The frequency and severity can be reduced by pretreatment with acetaminophen or ibuprofen

Risks Shared by Oral and IV Bisphosphonates

- Hypocalcemia:
- More with IV bisphosphonates
- Check calcium, vit D. Ensure adequate calcium and vitamin D intake.
- Rare musculoskeletal pain
- Jaw Osteonecrosis
- Atypical femur fractures

“Osteonecrosis” of the Jaw (ONJ)

- An area of exposed alveolar or palatal bone that typically shows poor healing over several months

- Risk of ONJ : 1:10,000 to 1:100,000 patient years

- 95% of cases have been reported with high-dose, chronic IV bisphosphonate treatment of myeloma and cancer metastatic to bone

- Known risk factors: invasive dental procedures, oral trauma, periodontitis, poor oral hygiene, radiotherapy to the jaw, chemotherapy, corticosteroids, infection

- If invasive dental procedure (dental implant or extraction) is planned, delay bisphosphonate therapy till healing is complete.

1. Woo SB, et al. *Ann Intern Med.* 2006;144:753-761. 2. Sutton EE, Riche DM. *Ann Pharmacother*. 2012;46:1000-1009.
3. Khosla S, et al. *J Bone Miner Res.* 2007;22:1479-1491.

Atypical Fractures of Femur in Patients Taking Anti-Resorptive Agents Long Term

- Association with long term bisphosphonate use
- May begin with stress reaction or stress fracture of lateral femoral cortex (A)
- Transverse fractures of femoral diaphysis or in subtrochanteric region (B)
- Often bilateral
- Prodromal pain in thigh or groin in 70%
- Extremely rare- Treating 10,000 osteoporotic women for 3 years, would prevent 1000 fractures (110 hip fractures) while causing 0.08 AFF.

Park-Wyllie LY, et al. *JAMA*. 2011;305:783-789. Shane E, et al. *J Bone Miner Res*. 2013 May 28. [Epub ahead of print]. Watts NB, Diab DL. *J Clin Endocrinol Metab.* 2010;95:1555-1565. Meier RP. *Arch Intern Med*. 2012;172:930-936.

Monitoring Response to Therapy

- Repeat DXA one to two years after initiating therapy and less frequently thereafter if BMD is stable.
- The same instrument should be used for serial DXA studies
- Comparison should be done using BMD in g/cm^2, not T-score.
- BMD that is stable or improving is evidence for a treatment response
- Significant BMD decrease

- Adherence, secondary causes, inadequate absorption, inadequate intake of calcium and vitamin D.

- A calculated change of about 4% likely represents a statistically significant change

- A 72-year-old woman see for osteoporosis fu. History of a hip fracture 5 years ago sustained after a mild fall. DXA scan then showed left hip T-score of −2.8 and vertebral T-score of −2.7. She has been maintained on alendronate therapy since that time. Medical history is also significant for hypertension. Medications are alendronate, hydrochlorothiazide, calcium, and vitamin D. Family history is significant for osteoporosis in her mother, sister, and maternal aunt. She has a 35-pack-year tobacco use history and continues to smoke.
- Exam – unremarkable
- calcium - 8.6 mg/dL, 25-hydroxyvitamin D - 44 ng/mL, kidney function normal
- Repeat DEXA shows a stable bone mineral density.

Which of the following is the most appropriate treatment of this patient's osteoporosis?

A Change to denosumab

B Change to teriparatide

C Continue alendronate therapy

D Initiate a drug holiday

Duration of Therapy

- Low fracture risk, stable BMD, T score better than -2.5, no previous fractures

-Alendronate and risedronate: Discontinue drug after 5 years

-Zoledronic acid: Discontinue drug after 3 years

-There appears to be residual BMD and fracture benefit.

- High fracture risk (history of osteoporotic fracture before or during therapy, T score < -3.5 in absence of fractures)

- Alendronate, risedronate: Continue for 10 years
- Zoledronic acid : Continue for 6 years

Bisphosphonate Holidays

- Follow BMD and bone turnover markers during a drug holiday (every 2- 4 years) and reinitiate therapy if bone density declines or markers increase
- BMD gains remain but are slowly lost during 3 to 5 years

Watts NB et al; AACE Osteoporosis Task Force. *Endocr Pract.* 2010;16(Suppl 3):1-37.
Whitaker M, et al. *N Engl J Med*. 2012;366(22):2048-2051.

Which of the following is the most appropriate treatment of this patient's osteoporosis?

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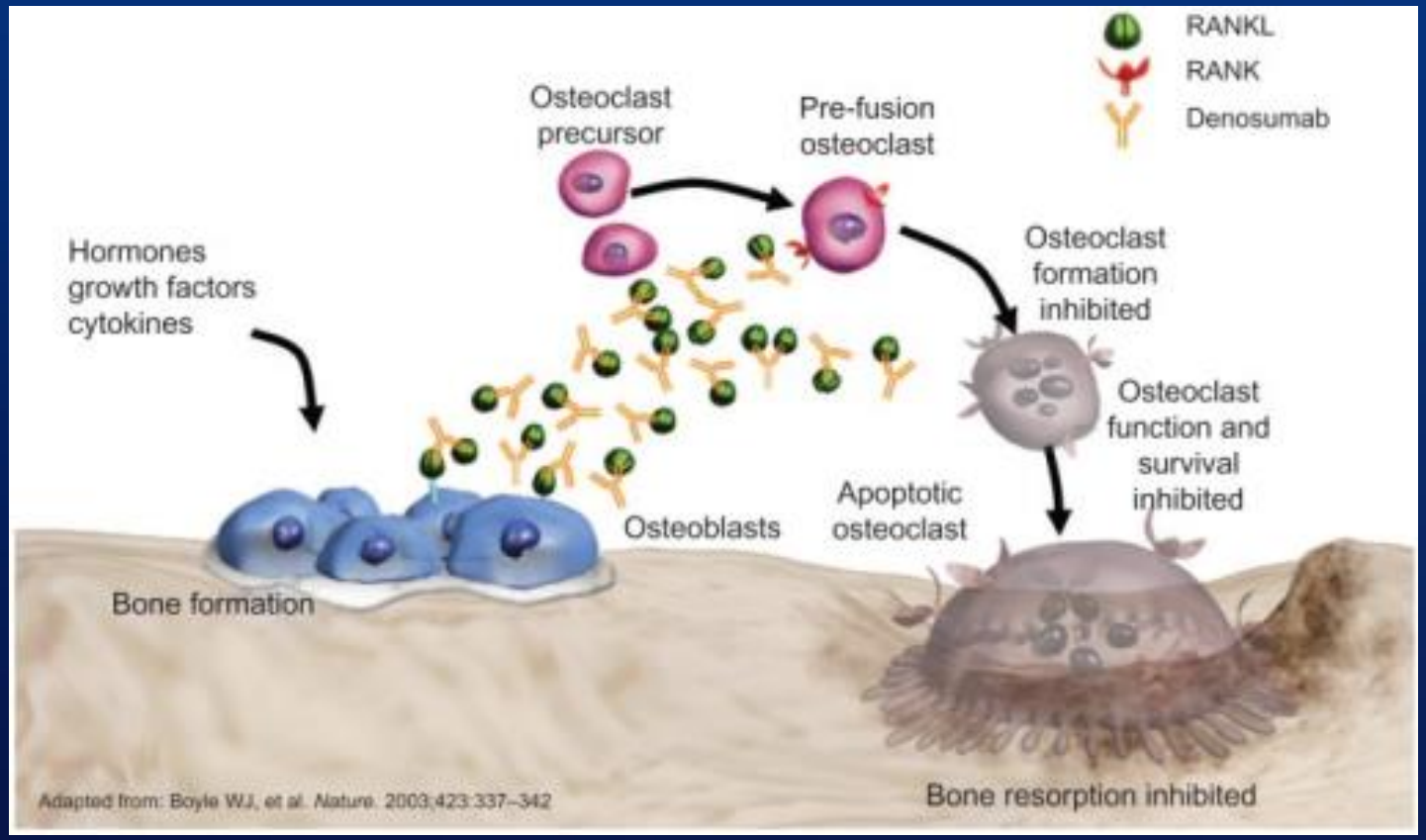
Denosumab (Prolia)



- Humanized monoclonal antibody to RANK Ligand
- Prevents formation of active osteoclasts
- Inhibits bone resorption

Lipton A, Smith MR, Ellis GK, Goessl C - Clin Med Insights Oncol (2012)

Denosumab

- 60 mg subcutaneously every 6 months
- Can be used in patients at high risk for fracture

  -impaired renal function

  -intolerant of or unresponsive to bisphosphonates

  -have difficulty with the dosing requirements of oral bisphosphonates.
- Increased risk for hypocalcemia with severe renal impairment (CrCl < 30 ml/ min). Check calcium in 10- 14 days after giving denosumab.

J Clin Endocrinol Metab, May 2019, 104(5):1595–1622

- Effects are reversible with discontinuation of therapy which results in bone loss and increased bone turnover.
- Increased risk of multiple vertebral fractures, after stopping denosumab.
- Should be given timely (every six months)
- Fracture reduction data up to ten years
- Administer antiresorptive therapy (bisphosphonate, HT or SERM) when denosumab is stopped.

J Clin Endocrinol Metab, May 2019, 104(5):1595–1622

Anabolic Therapies

- Stimulate bone formation rather than inhibiting bone resorption

  -Teriparatide (recombinant human PTH [1-34])

  20 mcg SC daily

  - Abaloparatide (PTHrP 1-34)

  80 mcg SC daily

Candidates for anabolic therapies

- Severe osteoporosis and high risk for fracture –

- T-score of -3.5 or below even in the absence of fractures

- T-score of -2.5 or below plus a fragility fracture

- Multiple vertebral fractures

- Fail other osteoporosis therapies
  (fracture and/or loss of BMD in spite of compliance with therapy)

- Treatment duration limited to 2 years
- Antiresorptive (preferably bisphosphonate) is given to preserve the gains in BMD.


Thank
You