Osteoporosis Prevention, Identification & Management

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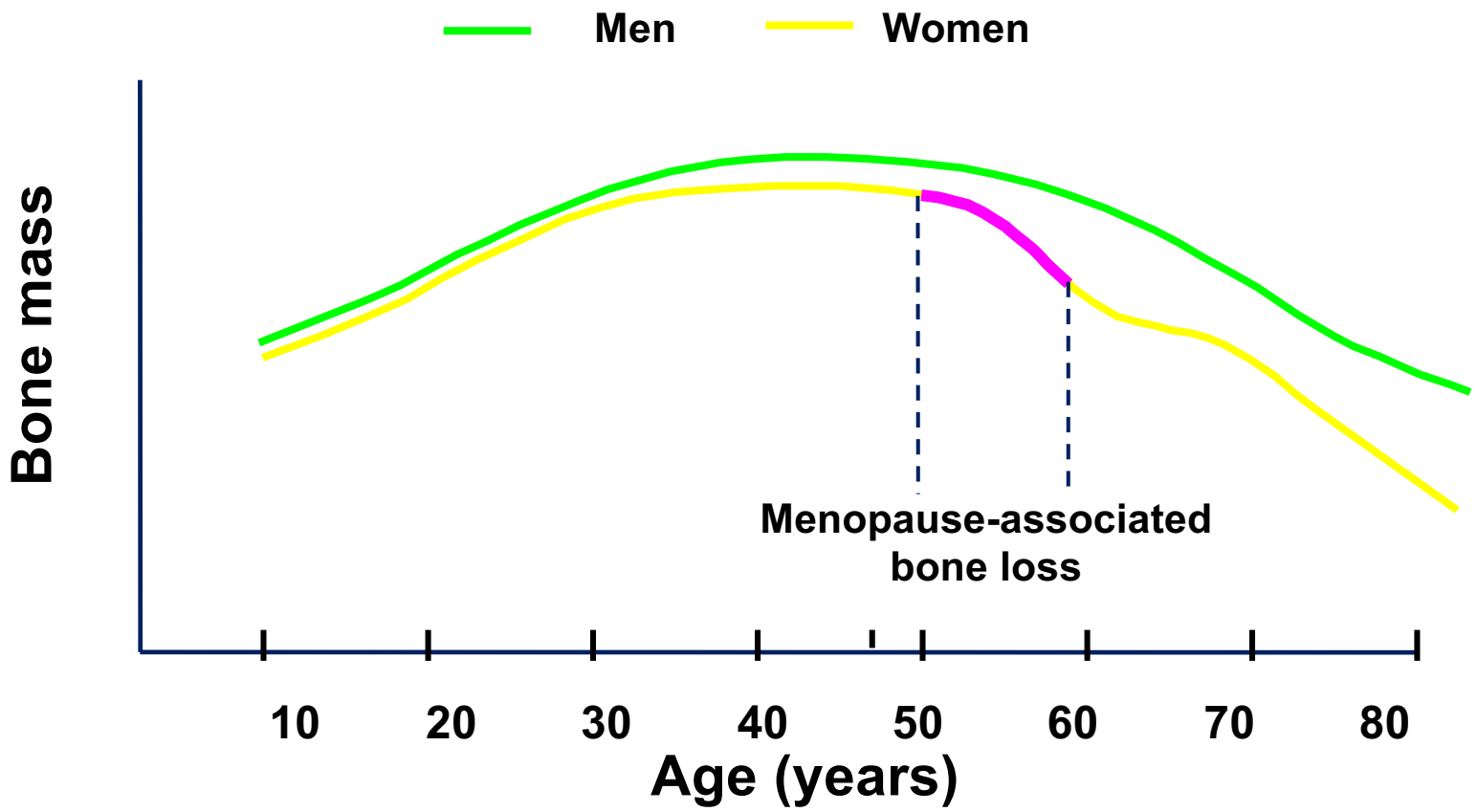
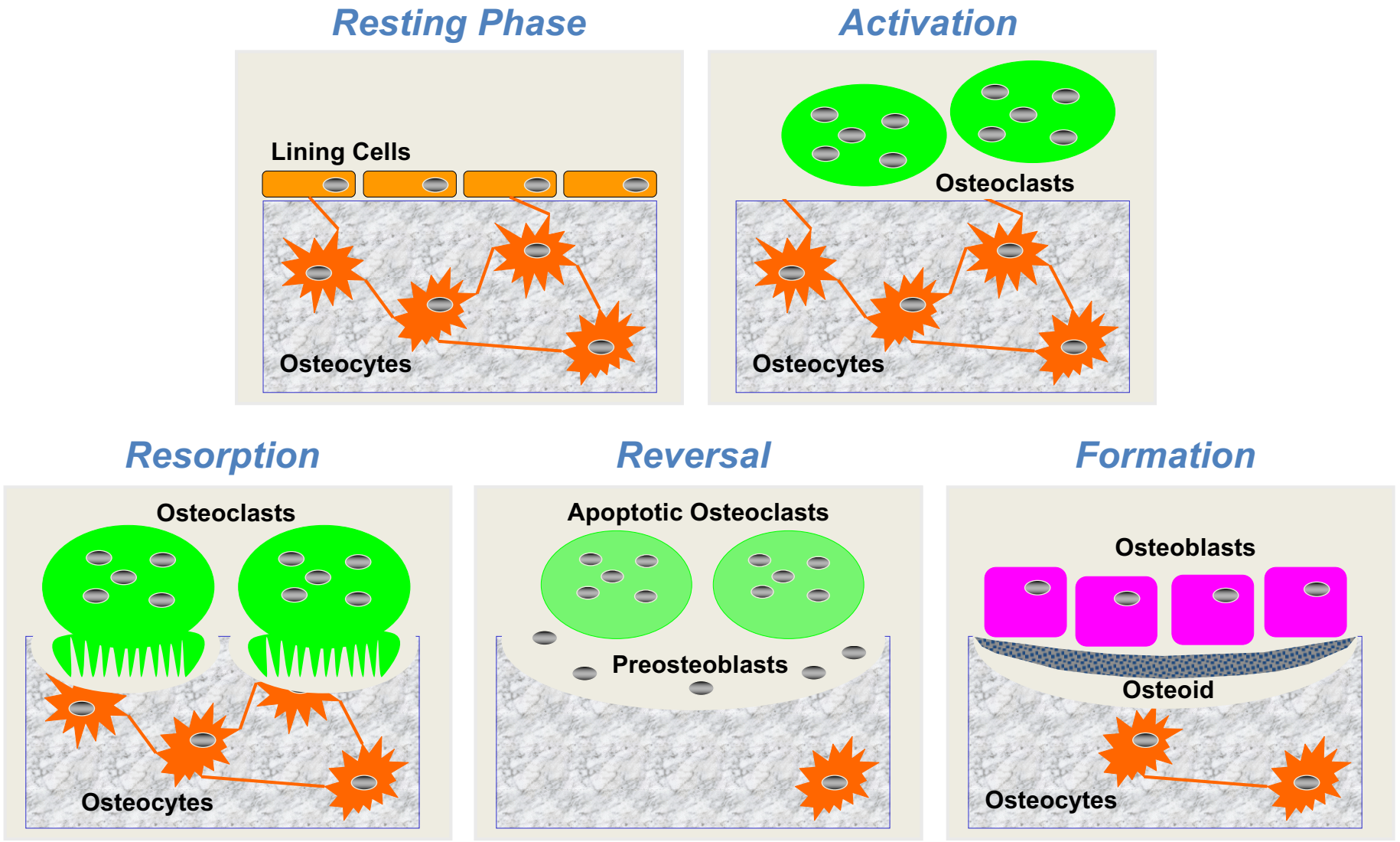
Bone Mass by Age and Sex



Adapted from Finkelstein. *Cecil Textbook of Medicine,* 21st ed. 1996;1379-1384.
Riggs et all. *N Engl J Med*. 1986;314:1676.

Bone Remodeling



Definition of Osteoporosis

"**Osteoporosis** is defined as a skeletal disorder characterized by compromised *bone strength* predisposing to an increased risk of fracture."

Bone strength = bone density + bone quality

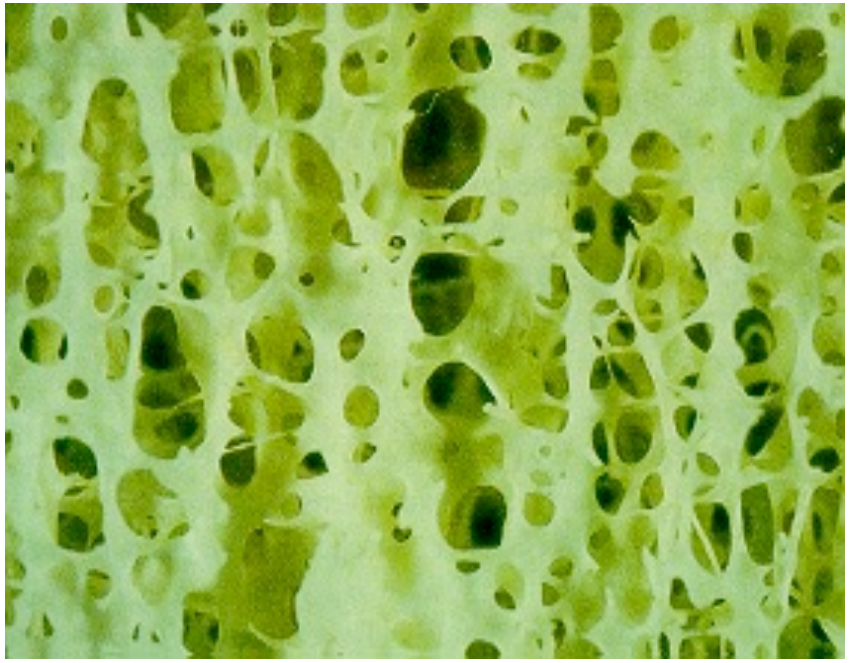
Bone density: grams of mineral/area, volume

Bone quality: architecture, turnover, damage accumulation, and mineralization

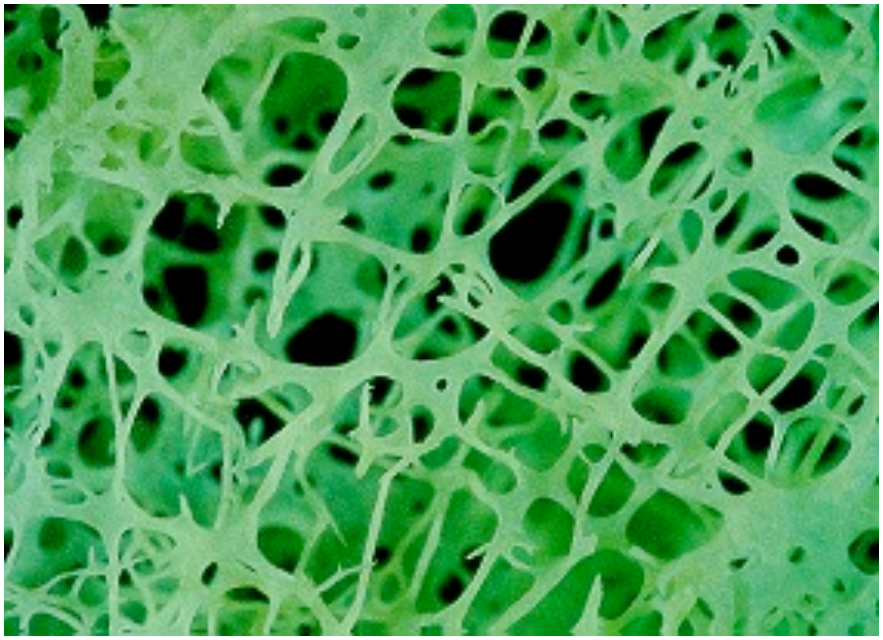
NIH Consensus Development Conference on Osteoporosis, 2000.

Morphology of Osteoporosis

Normal VETebrae



Osteoporotic VETebrae



Sources: WHO, 1996; NOF, 1999.

OP: Magnitude of the Problem

- Affects >53 million in the US
  - >10 million OP, >43 million LBM
- >2 million fractures/year
  - ~3.2 million fractures/year projected by 2040

- >300,000 hip fractures/year
  - >500,000/year projected by 2040
- Hip fx → up to 25% excess mortality in 1st year
- Hip fx → 25% require long-term nursing home
- Hip fx → 50% never regain pre-fx level of function

Camacho et al (2020). LeBoff et al (2022). NAMS (2021).

OP: Magnitude of the Problem (con't)

- 8 million ♀ & 2 million ♂ with OP in US
- Low bone mass postmenopause:
  - 10% Af Am, 16% Mexican Am, 21% White Am
- Vertebral Fx in >20% postmenopause
- 10-year Risk for subsequent fracture after low trauma fracture → 40% to 60%

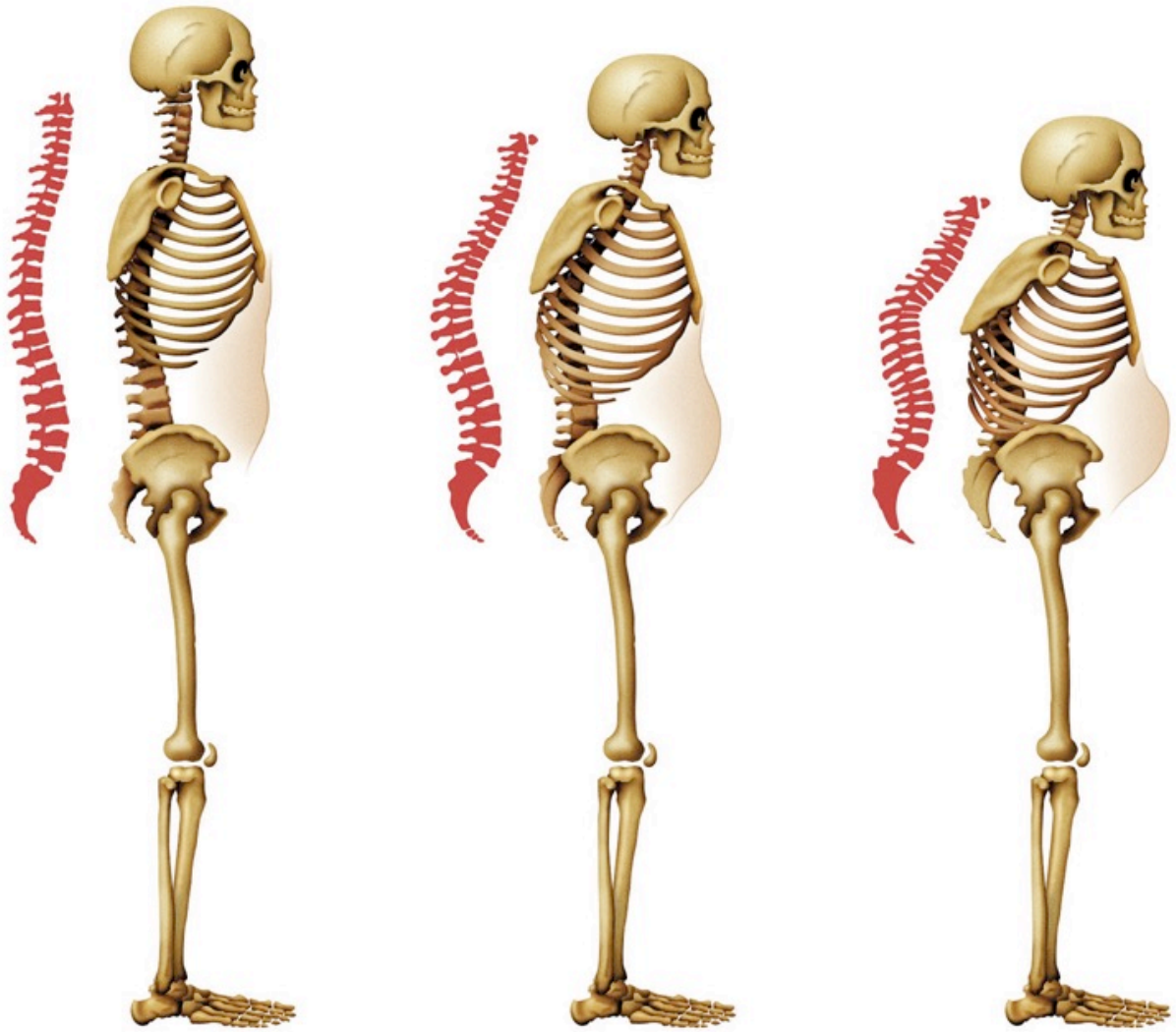
Camacho et al (2020). LeBoff et al (2022). NAMS (2021).

Lifetime risk Hip Fx @ age 50:
~6% Am Black persons
~14% Am Hispanic persons
~17% Am White persons

Fracture incidence projected to
↑ by 68% by 2040

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Vertebral Fractures → Physiologic Changes



Fractures
Back pain/Pain
Loss of Height
Deformity
Loss of mobility
Disability
Deconditioning
Depression

Bone Strength is Affected by Many Factors – Some Modifiable, Some Not

Race/Ethnicity as a Risk Factor for OP: NORA

Postmenopausal Women ≥ 50 Years Old	
Race/Ethnicity	**Odds Ratio (95% CI)**
White	1.0 (referent)
African American	0.55 (0.48–0.62)
Native American	0.97 (0.82–1.14)
Hispanic	1.31 (1.19–1.44)
Asian	1.56 (1.32–1.85)

Does not account for persons with mixed race/ethnic backgrounds

NORA: National Osteoporosis Risk Assessment; Siris et al. *JAMA*. 2001;286(22):2815.

OP Risk Factors: Difficult/Impossible to Modify

- Advanced age
- Frailty
- Family history of osteoporosis, fracture
- Prior personal fracture
- Caucasian or Asian race
- Genetics (vitamin D receptor, chromosome 11, type-I procollagen)

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

OP: Selected Predisposing Diseases

Disease Classification	Diseases
Endocrine	hyperthyroid, hyperparathyroid, estrogen or testosterone deficiency, Cushing's syndrome, hyperprolactinemia, hypercalciuria
Renal	renal failure/insufficiency, renal tubular acidosis, renal osteodystrophy
Rheumatologic	ankylosing spondylitis, rheumatoid arthritis
Gastrointestinal	gastrectomy, celiac disease, malabsorption
Hepatic	primary biliary or idiopathic cirrhosis
Infiltrative	multiple myeloma, Gaucher's disease, leukemia, mastocytosis
Connective tissue	osteogenesis imperfecta, homocystinuria, Ehlers-Danlos syndrome, Marfan's syndrome

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

OP: Selected Predisposing Medications

- Oral Glucocorticoids (long term use)
- Levothyroxine (e.g., Synthroid, Levoxyl)
- Anticonvulsants (e.g., Dilantin, Phenobarbitol, Tegretol, Depakote, Valproate)
- Methotrexate
- Heparin, Coumadin
- Lithium
- GnRHa (e.g., Lupron)
- Inhaled corticosteroids (≥1000mcg, >4yrs)
- TZDs (e.g., Actos, Avandia)
- Antacids w/ Aluminum (e.g., Amphogel, Maalox, Mylanta)
- MPA injections (e.g., Depro-provera)
- SSRIs (e.g., Paxil, Prozac)
- PPIs
- More…

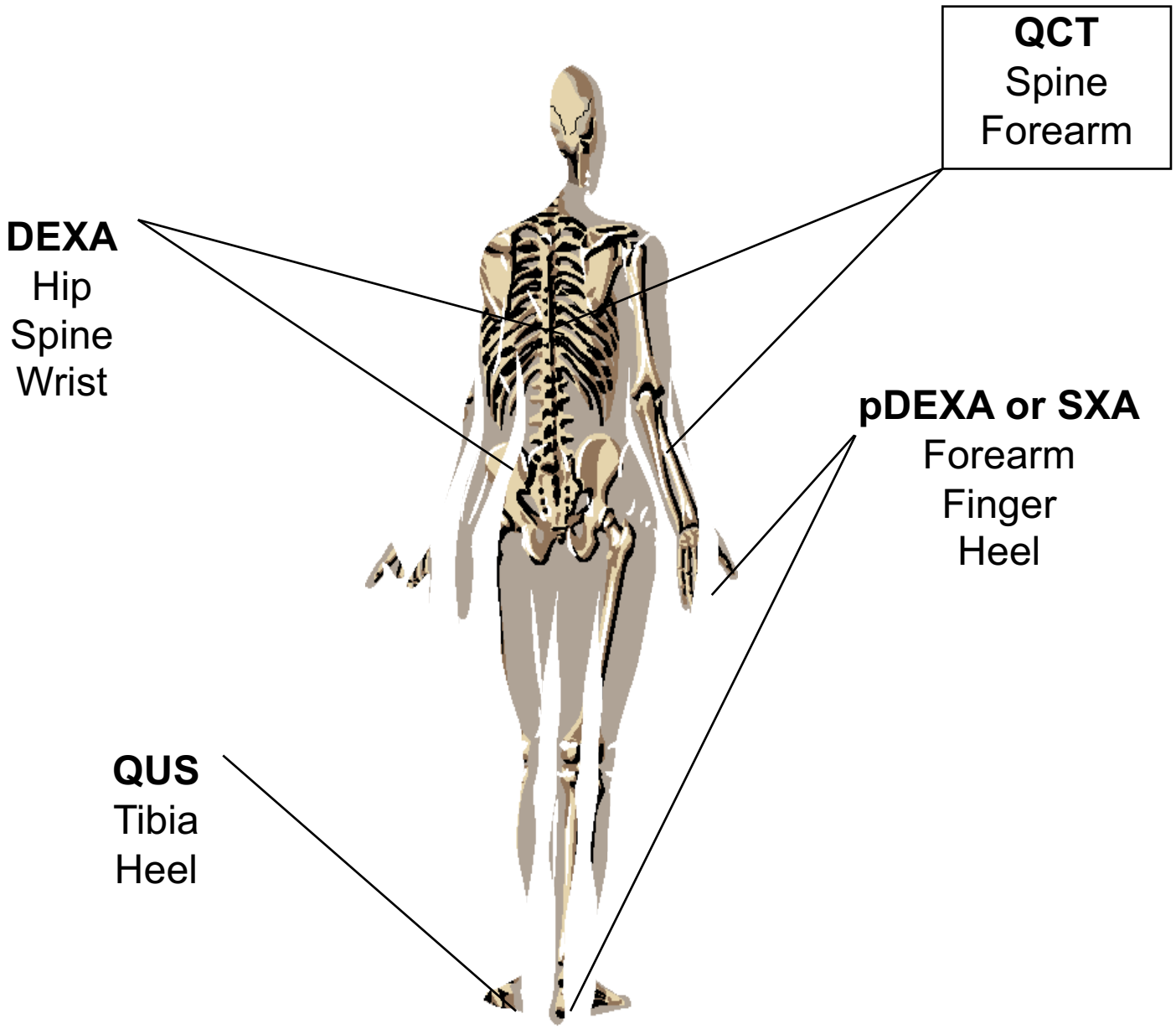
Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

OP Risk Factors: Lifestyle / Modifiable

- Low calcium/vitamin D intake
- Low body weight ($\leq$ 127 lbs; BMI $\leq$ 22)
- Limited exercise / Physical inactivity
- Excessive use of caffeine and/or alcohol
- Excessive vitamin A
- Falls
- Cigarette smoking (passive or active)

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Sites of Measurement



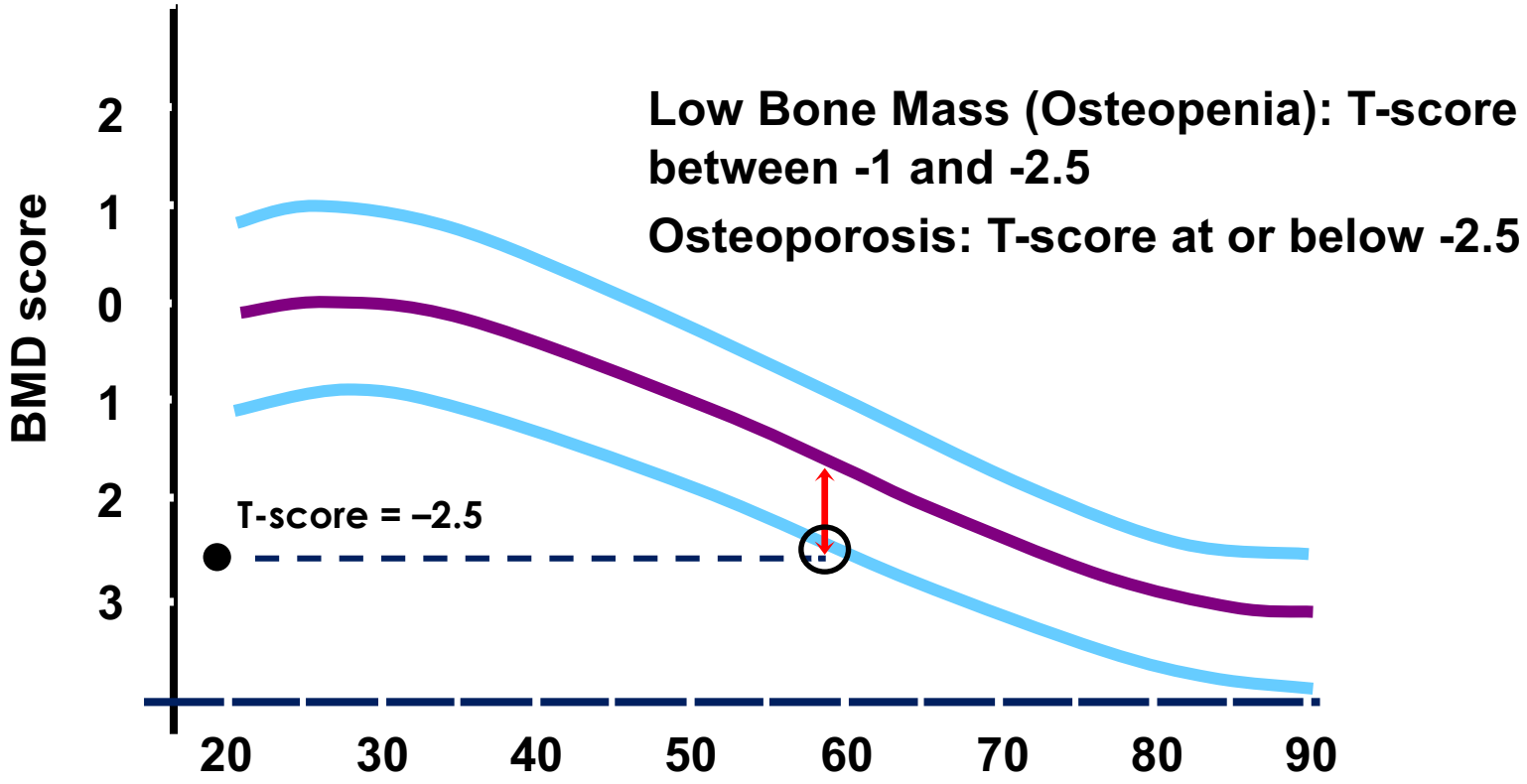
T-score

- Number of standard deviations above or below sex-matched mean reference value of young adults
- T-score = $\frac{(BMD_{patient} - BMD_{young\ normal\ reference})}{SD_{young\ normal\ reference}}$
- A comparison to peak bone mass

  Peak adult bone mass follow a normal distribution (bell-shaped curve).Low bone mass diagnosed on initial DXA does not necessarily mean prior bone loss. Person may be on the low end of the curve.
- Helps determine BMD desirable for that patient
- Used for postmenopausal women and men >50 yrs
- Each standard deviation decrease indicates a doubling of fracture risk

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

T-Scores for Low Bone Mass (Osteopenia)/Osteoporosis*



***Based on Femoral Neck DEXA**

T-score = expected BMD for "young normal" adults of same sex & ethnicity.
Z-score = expected BMD for patient's age, sex, & ethnicity.

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Z-score

- Number of standard deviations above or below age- and sex-matched mean reference value.
- Z-score = $\frac{(BMD_{patient} - BMD_{age\text{-}matched\ normal\ reference})}{SD_{age\text{-}matched\ normal\ reference}}$
- A comparison to age-adjusted bone mass

  Age-adjusted adult bone mass follow a normal distribution (bell-shaped curve). Low bone mass relative to others the same age may indicate secondary osteoporosis or that the individual is just on the low end of a normal distribution curve. Z-scores also useful in children who have not yet achieved the age of peak bone mass accrual. ay be on the low end of the curve.
- Used mostly in children and young adults

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

WHO Criteria for Interpretation of T-scores

T-score value	Classification
above or equal to -1	Normal
between -1 and -2.5	Low Bone Mass (Osteopenia)
is -2.5 or lower	Osteoporosis
is -2.5 or lower + low trauma fx(s)	Severe or established OP

*T score as measured by DXA. T score indicates the number of standard deviations below or above the average peak bone mass in sex-matched young adults.

WHO, 1994, Technical Report, http://www.who.int/en/, accessed Sept 2014

Clinical Evaluation Prior to Diagnosis, even if T-score ≤-2.5

- Medical history
  - Risk factors (Dx, medications, family hx, etc)
  - Signs and symptoms
- Physical examination
  - Height assessment (with stadiometer)
  - Clinical signs of established disease, secondary causes
- Appropriate laboratory tests
  - CBC, albumin, Ca+, RFTs, P, Mg, Liver enzymes, 25(OH) vit D, parathyroid hormone (PTH)
  - Others as appropriate if 2^{o} OP suspected

CBC=complete blood count; RFTs=renal function tests; PTH=parathyroid hormone
Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Cases

Case 1: Mrs Bones

Mrs Bones is a 72 yr old W woman who presents requesting a bone density test because her sister had a hip fracture. Denies fractures, height loss, bone pain.

PMH: dyslipidemia, hypothyroidism, lactose intolerance, h/o BCC, Barrett's esophagus

MEDS: lipitor, synthroid 150mcg daily, multivitamin & calcium (since DXA report)

SH: widowed, former librarian, smokes 1 ppd, social EtOH

FH: mother and sister with fragility fractures

Mrs Bones: PE

EXAM: BP: 128/86, P: 94, Wt: 124 #, BMI: 20

GA: Elderly, lean, fragile appearing woman

HEENT: no goiter, thyroid smooth

MSK: no kyphoscoliosis, no spinal tenderness, no bony abnormalities

Neuro: mild hyper-reflexia, no tremor

Otherwise normal exam

Mrs Bones: Diagnostics

- Will you order a DXA?
- Any other labs?

Mrs Bones: Diagnostics

- Will you order a DXA?
- Any other labs?

- DXA T-score results: Spine = -3.4,
  Fem Neck = -2.5
- Labs: Ca^{2}+ 8.7mg/dl, PO_4 2.4mg/dl, Cr 0.9, LFTs wnl, TSH 0.1, CBC normal, 25-OHD 14ng/ml

Mrs Bones: Clinical Risk Factors

Mrs Bones: Clinical Risk Factors

- Calcium intake?
  - Inadequate
- Vitamin D?
  - Vitamin D Deficiency
- Exercise?
  - Sedentary
- Personal fracture history?
  - No
- Excess alcohol intake?
  - No

Mrs Bones: Clinical Risk Factors (con't)

- Tobacco?
  - Yes
- Family Hx?
  - Yes
- Height loss?
  - No
- Secondary causes?
  - Yes, What?
  - Thyroid over-replacement, low body weight

What is needed for Mrs Bones' Management Plan?

OP Management is *multi-factorial*

- Address/reverse secondary causes
- Universal Recommendations
  - Calcium
  - Vitamin D
  - No tobacco/smoking
  - Exercise – weight bearing & resistance
  - Reduce risk for falls and fractures
- Pharmacologic treatment?

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Clinical Management – Goal is Fracture Prevention

Prevention: Lifestyle Changes for ALL Patients *Prevention & Treatment*

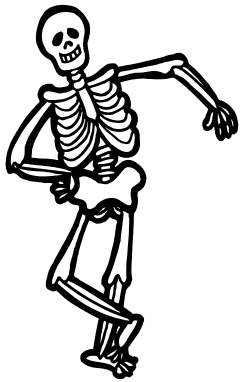
- Adequate calcium (1000-1200mg)
- Adequate vitamin D (600/800-1000IU)
- Weight bearing and muscle strengthening (resistance) exercises
- Reduce or eliminate EtOH, caffeine, tobacco
- Fall prevention

Lifestyle changes for prevention if normal BMD, ***and*** for treatment if T-score ≤-1.0

Comacho et al (2020). IOM. (2010). *Dietary Reference Intakes for Calcium and Vitamin D*. LeBoff et al (2022). NAMS (2021).

Exercise

- Routine should include weight-bearing and strengthening exercise
  - Increase bone mass
  - Improve muscle strength and balance
  - 3-4 times/week; ≥30 minutes per session



- Tailor your program to avoid injury
- **One caveat**: Excessive exercise causing missed periods increases risk of low bone mass and fracture
- Physical therapy may be helpful

Calcium and Vitamin D

- Backbone of any osteoporosis plan
- Reduces risk of hip fracture
- 1000-1200mg Ca+ (1000 19-70 yrs, 1200 > 70 yrs) from diet & supplements
- 600-1000 IU Vit D (600 1-70 yrs, 800 >70 yrs), need supplement or fortified, Cannot count on sun
  - avoid over supplementing
  - high dose vit D associated with lower BMD[1]
- Relatively safe and ↓$: 1000 mg Ca+ and 600-800 IU Vit D supplements in women already getting RDI of Ca+ from diet[2]:
  - improved hip BMD; no change fracture
  - small increase in kidney stones

[1]Burt, Billington, Rose, et al. (219). Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA 322(8)*:736-745. https://pubmed.ncbi.nlm.nih.gov/31454046/; [2]Yao, Bennett, Mafham, et al. (2019). Vitamin D and calcium for the prevention of fracture: A systematic review and meta-analysis. *JAMA Netw Open, 2*(12). e1917789. https://pubmed.ncbi.nlm.nih.gov/31860103/
Comacho et al (2020). IOM. (2010). *Dietary Reference Intakes for Calcium and Vitamin D*; LeBoff et al (2022). NAMS (2021).

Calcium Preparations

- Calcium Carbonate
  - Take with meals
  - Available in liquid, chewable, or tablet form
  - Can cause constipation or gas
  - May contain lead, arsenic if from bone meal, oyster shell, or dolomite
    - concern mainly in children, pregnant or lactating women
  - Name brands include Alka-Mints, Caltrate, OsCal, Rolaids, Titralac, Tums, Viactiv, Calburst, Naturemade, Mylanta Calcitabs
  - In general, generics work as well
- Calcium Citrate
  - Take any time
  - Available in liquid or tablet form
  - May be better tolerated than calcium carbonate, but usually more expensive
  - Name brands include Citracal
  - In general, generics work as well

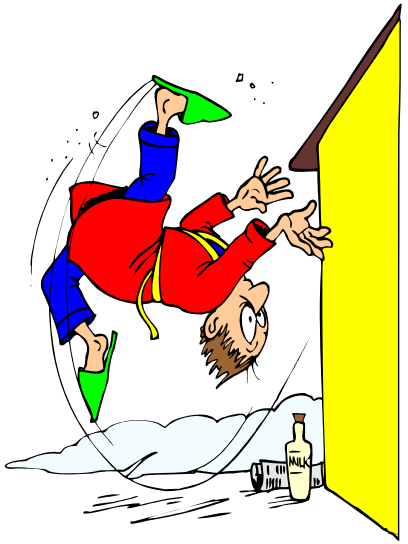
Vitamin D Supplementation

- Vitamin D_2 or D_3 for supplementation
  - avoid over supplementing
  - high dose vit D associated with lower BMD[1]
- Goal 25(OH)D >30 ng/ml
- 0-18 yrs: 2000 IU qd or 50,000 IU qwk x 6 weeks, then maintenance dose
- >18 yrs: 50,000 IU qwk or 5000-6000 IU qd x 8-12 wks then maintenance 1000 IU qd
- Obese: 6000-10,000 IU qd, maintenance of 3000-6000 IU qd
- If Renal Dz, extrarenal 1,25(OH)D production, hyperparathyroidism → serial monitoring

[1]Burt, Billington, Rose, et al. (219). Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA 322(8)*:736-745. https://pubmed.ncbi.nlm.nih.gov/31454046/;
Comacho et al (2020). Holick, Binkley, Bischoff-Ferrari, et al.(2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab. 96*(7):1911-1930; IOM. (2010). *Dietary Reference Intakes for Calcium and Vitamin D*; LeBoff et al (2022). NAMS (2021).

Fall Prevention-Lifestyle Changes

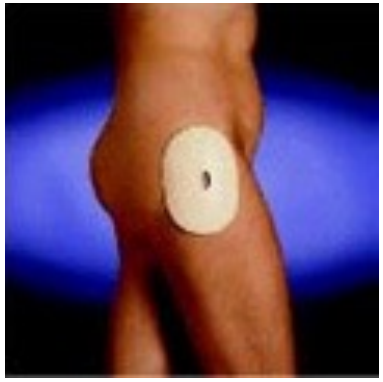
- Indoors
  - Avoid throw rugs, loose wires
  - Nightlights
- Outdoors:
  - Avoid ice, high curbs
  - Have walkway swept and clear of debris
  - Use of a cane if unsteady on feet
  - Use extra caution after dark
  - Use railings whenever possible
- Hip pads



Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Hip Pads

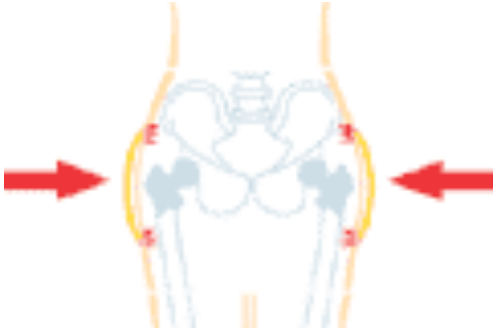
Hip Pad for Women



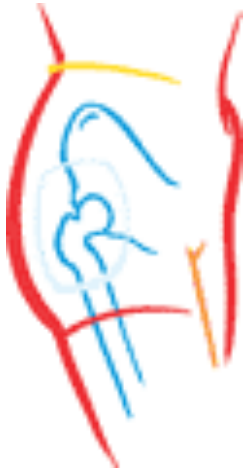
Self Sitting Hip Pad

Hip Pad for Men

Impact



Protection



Mobility

Should We Treat Mrs Bones with Pharmacotherapeutics?

Pharmacologic Treatment Guidelines

- Hip or vertebral Fx
- T score $\leq$ -2.5 at femoral neck, hip, or spine after proper evaluation to exclude secondary causes
- Low Bone Mass (Osteopenia, T score -1 to -2.5) <u>plus</u>:
  - a 10-year risk of a hip fracture ≥ 3% (FRAX score) **OR**
  - a 10-yr risk of any major osteoporotic fracture of ≥20% (FRAX score) **OR**
  - Hip, pelvis, or or distal forearm Fx
- Multiple Fx (not at hip, spine, fem neck)

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Pharmacotherapeutic Options

- ANTIRESORPTIVE/ANTIREMODELING:
  - Maintain or increase BMD by inhibiting osteoclast function to reduce resorption and allow increased osteoblast activity
  - Reduce Fx risk
  - No effects on trabecular bone
- OSTEOANABOLIC AGENTS:
  - Significant increase in BMD by increasing osteoblast activity to stimulate new bone formation
  - Improve both trabecular &/or cortical bone structure
  - Reduce Fx risk

Pharmacotherapeutic Options

- ANTIRESORPTIVE/ANTIREMODELING:
  - Bisphosphonates (alendronate*#, alendronate plus D*#, ibandronate*, risedronate*#/*, zoledronic acid*#)
  - Estrogens (ET*/HT*)
  - Calcitonin*
  - Estrogen agonist/antagonist (raloxifene*)
  - Tissue selective estrogen complex (conjugated estrogens/bazedoxifene*)
  - RANKL inhibitor (denosumab*#)
- OSTEOANABOLIC AGENTS:
  - Parathyroid hormone (PTH [1-34], teriparatide*#)
  - Analog of parathyroid hormone-related peptide (PTHrP [1-34], abaloparatide*)
  - Fully human monoclonal antibody to sclerostin (romosozumab*)

FDA approved to treat or prevent OP in *women and/or #men

Pharmacotherapeutic Selection

Fx Risk	Criteria to Consider	Recommended Medications
Very High	• Previous Fx (multiple, recent, on OP meds, on meds R/T bone loss) • Falls (previous, high risk) • T-score (↓↓, i.e., <-3.0) • Fx Prob (↑↑, i.e., FRAX >30%/>4.5%)	Osteoanabolic Human monoclonal antibody to sclerostin
High	• Fx (parent, 1 previous, not ↑↑ FRAX) • Falls (not ↑ risk) • T-score (<-2.5)	RANKL inhibitor Bisphosphonate
Moderate	• T-score (LBM + ↑FRAX or <-2.5) • No other risks	Bisphosphonate Estrogen agonist/antagonist Estrogen[P] Tissue-selective estrogen complex[P]

P=prevention

Pharmacotherapeutic Selection

- ANTIRESORPTIVE/ANTIREMODELING:
  - Bisphosphonates (alendronate*#, alendronate plus D*#, ibandronate*, risedronate*#/*, zoledronic acid*#)
  - Estrogens (ET*/HT*)
  - Calcitonin*
  - Estrogen agonist/antagonist (raloxifene*)
  - Tissue selective estrogen complex (conjugated estrogens/bazedoxifene*)
  - RANKL inhibitor (denosumab*#)
- ANABOLIC AGENTS:
  - Parathyroid hormone (PTH [1-34], teriparatide*#)
  - Analog of parathyroid hormone-related peptide (PTHrP [1-34], abaloparatide*)
  - Fully human monoclonal antibody to sclerostin (romosozumab*)

FDA approved to treat or prevent OP in *women and/or #men
Proven to ↓ Fx at both vertebral and non-vertebral sites

***What if her DXA had revealed*:**

L-Spine:	T-score -1.6
Femoral neck:	T-score -2.2
Total hip:	T-score -1.8

Would you prescribe a pharmacotherapeutic agent now?

WHO FRAX® Algorithm

Risk Factors In FRAX®

- Age*
- Sex
- Race
- BMI* (height & weight)
- Personal history of fragility fracture
- Parental history of hip fracture
- Current Smoking
- Glucocorticoid therapy
- Rheumatoid Arthritis
- Secondary Osteoporosis
- Alcohol (>3 units/day)
- Femoral Neck BMD*

*Continuous Variables
All others dichotomous

How to Calculate FRAX

- https://www.sheffield.ac.uk/FRAX/
  - Click on Calculation Tool
  - Select North America
  - Select USA
- UpToDate
  - Select: Osteoporotic Fracture Risk Assessment
  - Click on FRAX website

FRAX calculations usually reported with DXA results

FRAX® Fracture Risk Assessment Tool

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

Calculation Tool:
- Asia
- Europe
- Middle East & Africa
- North America
  - Canada
  - US
- Latin America
- Oceania

Welcome to FRA

The FRAX® tool has been d
individual patient models that
bone mineral density (BMD) at

Dr. John A Kanis
Professor Emeritus,
University of
Sheffield

The FRAX® models have been developed from studying population-based cohorts from Europe, North America, Asia and Australia. In their most sophisticated form, the FRAX® tool is computer-driven and is available on this site. Several simplified paper versions, based on the number of risk factors are also available, and can be downloaded for office use.

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture).

Clarification

The University of Sheffield launched the FRAX tool in 2008. At that time the University hosted the The World Health Organisation (WHO) Collaborating Centre for Metabolic Bone Diseases (1991-2010), and the FRAX tool is based on data generated from that centre. However, FRAX was neither developed or endorsed by WHO . Any references to the 'WHO tool' or to the WHO Collaborating Centre after it finished its work in 2010 are incorrect.

FRAX Desktop Application

Click here to view the applications available

- US (Caucasian)
- US (Black)
- US (Hispanic)
- US (Asian)

www.iofbonehealth.org

www.nof.org

www.jpof.or.jp

www.esceo.org

FRAX available as iPhone App

View in iTunes

21860308

Individuals with fracture risk assessed since 1st June 2011

https://www.sheffield.ac.uk/FRAX/

Calculation Tool

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

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

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 72 Date of Birth: Y: M: 11 D: 15
2. Sex: Male / Female
3. Weight (kg): 57.6
4. Height (cm): 167.6
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)
    T-Score -2.2

Clear Calculate

BMI: 20.5
The ten year probability of fracture (%)
with BMD

Major osteoporotic	20
Hip Fracture	7.4

If you have a TBS value, click here: Adjust with TBS

Print tool and information

Weight Conversion

Pounds → kg
124 Convert

Height Conversion

Inches → cm
66 Convert

06139936
Individuals with fracture risk assessed since 1st June 2011

For USA use only

Consider FDA-approved medical therapies in postmenopausal women and men aged 50 years and older, based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinicians judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels

https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9

Who should receive pharmacologic therapy?

To treat or not to treat?

- T-scores are diagnostic thresholds/criteria, ***not*** intervention thresholds
- Pharmacologic intervention are based on absolute fracture risk, using a combination of clinical risk factors and bone density
  - Consider the effect of age on fracture risk

Clinical uses of the FRAX® Algorithm

- Identify those who have societal-based cost-effective benefit from initiating pharmacotherapy
- Applies to patients with low bone mass (aka osteopenia, T-score between -1.0 and -2.5)
- Used for patients who have not previously received pharmacotherapy
- Possibly useful in those on drug “holiday”

Threshold for Intervention: US Perspective

Cost-effectiveness for Treatment

- 10-yr fracture probability at which osteoporosis treatment is cost-effective
  - Defined as <$60,000 per QALY Gained for US

- 3% for Hip
- 20% (approximately) for major osteoporosis-related fracture

Tosteson ANA, et al. 2008 Osteoporos Int; Dawson-Hughes, et al, 2008 Osteoporos Int.

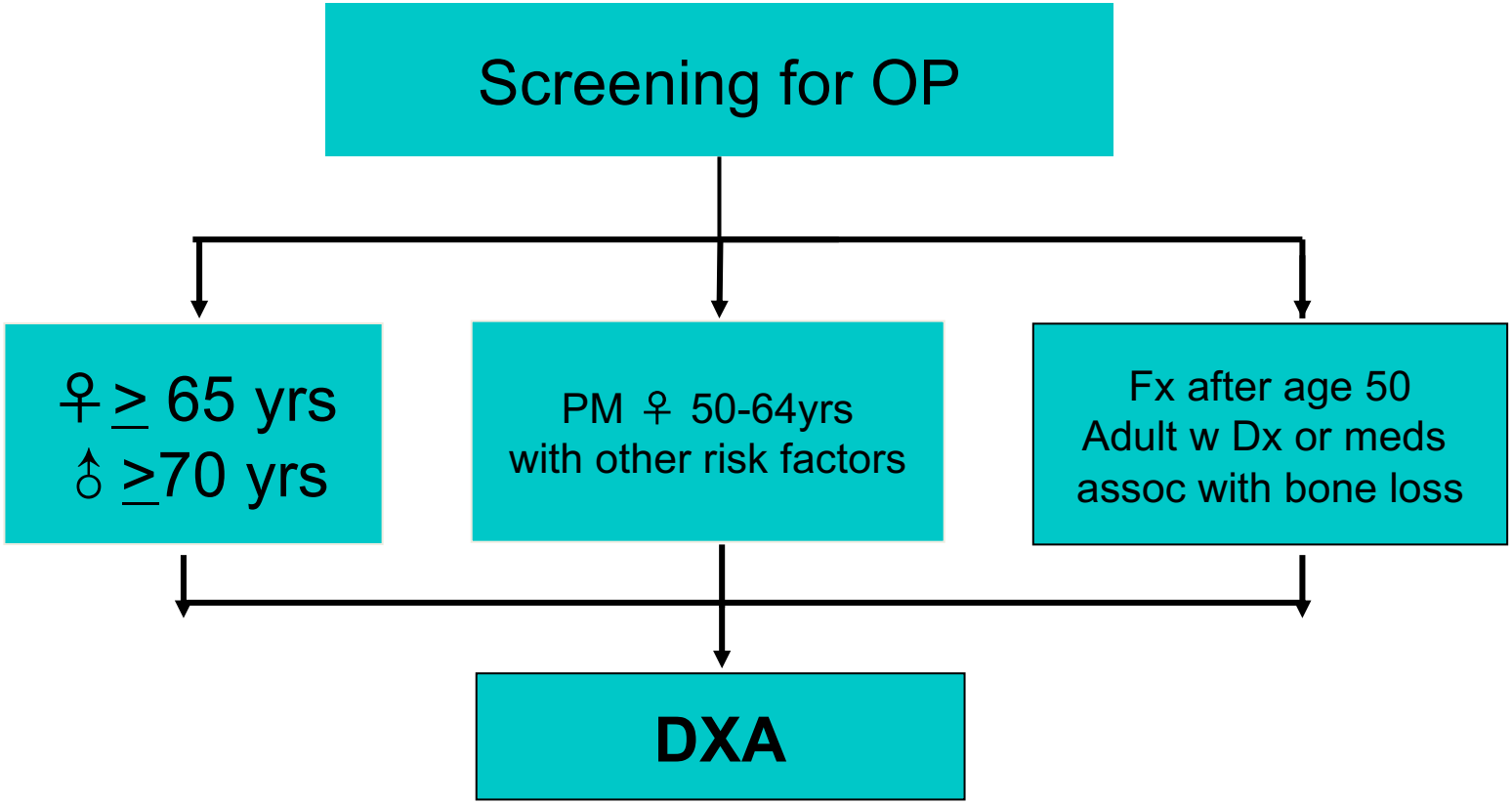
Case 2: Ms Graves

56 yr old woman with Graves hyperthyroidism, history of tobacco use and +family history for hip fracture

Will you order a DXA?

Why or why not?

Who to Screen for OP?



PM = Postmenopausal

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

USPSTF Clarification

- The recommendation to screen persons with clinical risk is somewhat subjective

- USPSTF clarifies by recommending BMD screening for all who have increased OP risk identified by using a clinical OP risk assessment tool (e.g., FRAX® calculated risk w/o BMD of ≥9.3%, the calculated risk for any major OP fx in a white woman of 65 years w/o other risks)

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).
USPSTF. 2018. OP to prevent fractures: screening.
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/osteoporosis-screening

Ms Graves: Diagnostic Results

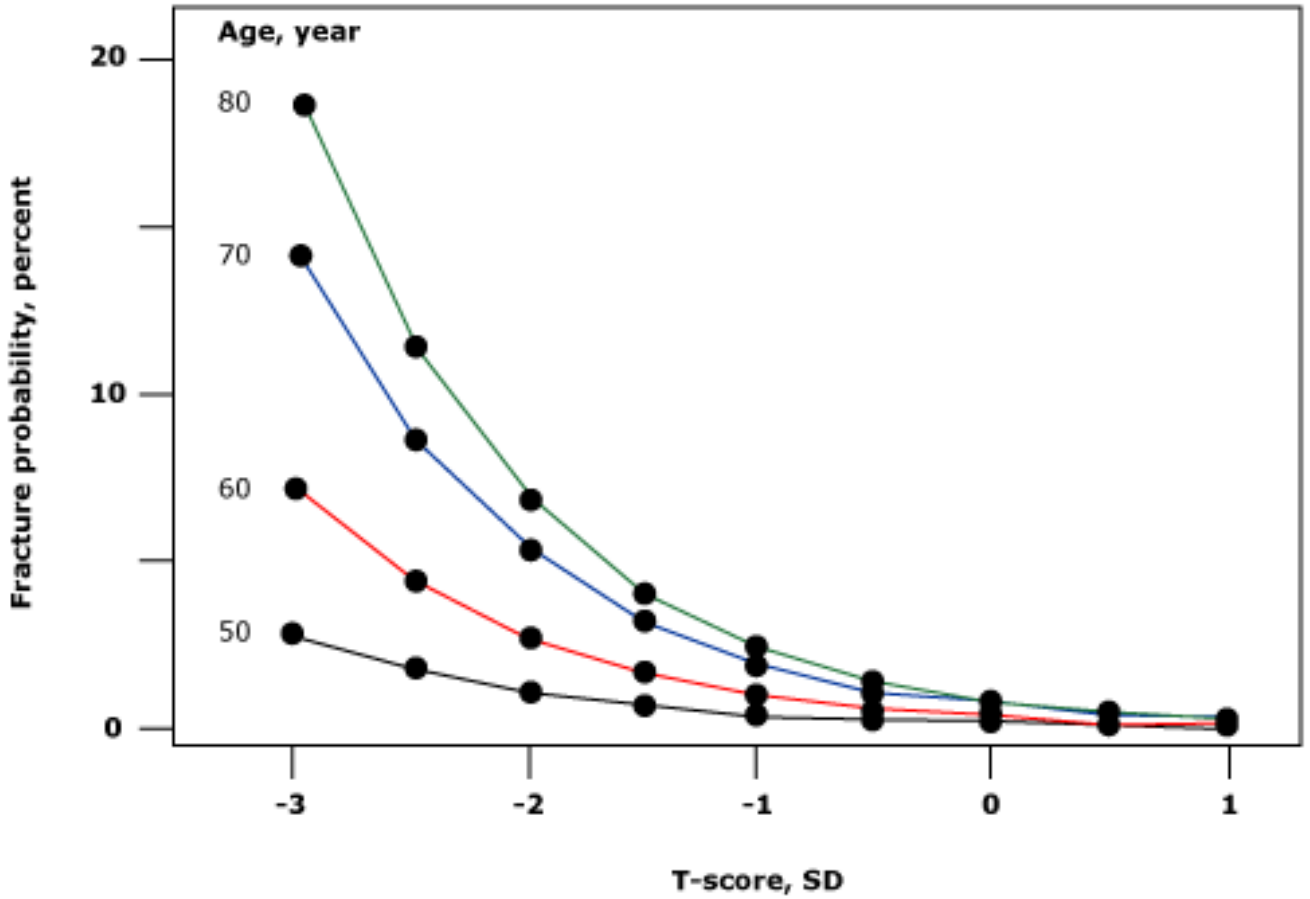
DXA:

- Spine T-score = -2.3
- Femoral neck T = -2.2
- Total hip T-score = -1.8

FRAX:

- 10yr risk for any fracture: 16%
- 10yr risk for hip fracture: 1.3%

Fracture Risk by Age and T-score



Kanis JA. Osteo Inter 2001, 12: 989.

Should We Treat Ms Graves with Pharmacotherapeutics?

Pharmacologic Treatment Guidelines

- Hip or vertebral Fx
- T score $\leq$ -2.5 at femoral neck, hip, or spine after proper evaluation to exclude secondary causes
- Low Bone Mass (Osteopenia, T score -1 to -2.5) <u>plus</u>:
  - a 10-year risk of a hip fracture ≥ 3% (FRAX score) **OR**
  - a 10-yr risk of any major osteoporotic fracture of ≥20% (FRAX score) **OR**
  - Hip, pelvis, or or distal forearm Fx
- Multiple Fx (not at hip, spine, fem neck)

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Pharmacotherapeutic Options

- ANTIRESORPTIVE/ANTIREMODELING:
  - Maintain or increase BMD by inhibiting osteoclast function to reduce resorption and allow increased osteoblast activity
  - Reduce Fx risk
  - No effects on trabecular bone
- OSTEOANABOLIC AGENTS:
  - Significant increase in BMD by increasing osteoblast activity to stimulate new bone formation
  - Improve both trabecular &/or cortical bone structure
  - Reduce Fx risk

Pharmacotherapeutic Options

- ANTIRESORPTIVE/ANTIREMODELING:
  - Bisphosphonates (alendronate*#, alendronate plus D*#, ibandronate*, risedronate*#/*, zoledronic acid*#)
  - Estrogens (ET*/HT*)
  - Calcitonin*
  - Estrogen agonist/antagonist (raloxifene*)
  - Tissue selective estrogen complex (conjugated estrogens/bazedoxifene*)
  - RANKL inhibitor (denosumab*#)
- OSTEOANABOLIC AGENTS:
  - Parathyroid hormone (PTH [1-34], teriparatide*#)
  - Analog of parathyroid hormone-related peptide (PTHrP [1-34], abaloparatide*)
  - Fully human monoclonal antibody to sclerostin (romosozumab*)

FDA approved to treat or prevent OP in *women and/or #men

Pharmacotherapeutic Selection

Fx Risk	Criteria to Consider	Recommended Medications
Very High	• Previous Fx (multiple, recent, on OP meds, on meds R/T bone loss) • Falls (previous, high risk) • T-score (↓↓, i.e., <-3.0) • Fx Prob (↑↑, i.e., FRAX >30%/>4.5%)	Osteoanabolic Human monoclonal antibody to sclerostin
High	• Fx (parent, 1 previous, not ↑↑ FRAX) • Falls (not ↑ risk) • T-score (<-2.5)	RANKL inhibitor Bisphosphonate
Moderate	• T-score (LBM + ↑FRAX or <-2.5) • No other risks	Bisphosphonate Estrogen agonist/antagonist Estrogen[P] Tissue-selective estrogen complex[P]

P=prevention

Pharmacotherapeutic Selection

- ANTIRESORPTIVE/ANTIREMODELING:
  - Bisphosphonates (alendronate*#, alendronate plus D*#, ibandronate*, risedronate*#/*, zoledronic acid*#)
  - Estrogens (ET*/HT*)
  - Calcitonin*
  - Estrogen agonist/antagonist (raloxifene*)
  - Tissue selective estrogen complex (conjugated estrogens/bazedoxifene*)
  - RANKL inhibitor (denosumab*#)
- ANABOLIC AGENTS:
  - Parathyroid hormone (PTH [1-34], teriparatide*#)
  - Analog of parathyroid hormone-related peptide (PTHrP [1-34], abaloparatide*)
  - Fully human monoclonal antibody to sclerostin (romosozumab*)

FDA approved to treat or prevent OP in *women and/or #men
Proven to ↓ Fx at both vertebral and non-vertebral sites

Medication-Related Osteonecrosis of the Jaw (MRONJ)

- What is it?
  - Current or prior treatment with bisphosphonates, denosumab, romosozumab
  - Exposed bone/bone probed via fistula for >8 weeks
  - No hx radiation to jaw/mouth
- Staging
  - At risk, 0, 1, 2, 3
- Who gets it?
  - Bisphosphonates: 0.2% to 0.05% (vs placebo 0% to 0.02%)
  - Denosumab: 0.04% to 0.3%
  - Romosozumab: 0.03% to 0.05% (vs placebo 0%)
- Rare event (higher risk if cancer)

Ruggerio SL, Dodson TB, Agbaloo, T et al (2022). American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaw – 2022 update. American Association of Oral and Maxillofacial Surgeons 2022. https://doi.org/10.1016/j.joms.2022.02.008. Available at: https://www.joms.org/article/S0278-2391(22)00148-3/fulltext

MRONJ (con't)

- Recommendations:
  - Optimize oral health
  - Thorough oral exam prior to initiating
  - Continue regular dental care while on BP tx
  - Risk may be ↑ if on medication for > years
  - Controversy about drug holiday prior to extractions, invasive procedures

Ruggerio SL, Dodson TB, Agbaloo, T et al (2022). American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaw – 2022 update. American Association of Oral and Maxillofacial Surgeons 2022. https://doi.org/10.1016/j.joms.2022.02.008. Available at: https://www.joms.org/article/S0278-2391(22)00148-3/fulltext

Atypical Femur Fracture (AFF)

- Extremely rare event that has been associated with OP medication use
- May be preceded by pain in groin/thigh area
- Obtain X-rays or single-energy X-ray absorptiometry
- Risk for AFF is far less than the risks associated with hip fracture

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Esophageal Inflammation and Bisphosphonates

- Risk with oral meds
- Rationale for method of taking meds: swallow on empty stomach with plain water, remain upright and no food/drink for 30-60 minutes after

- Avoid oral bisphosphonates in patients with Barrett's esophagus, GERD

Case 3: Ms Albright

Ms Albright has been treated with weekly alendronate 70mg for the past 5 yrs for osteoporosis identified via DXA
(spine T-score = -2.9)

She has tolerated therapy well and has not had any fractures.

Monitoring & Follow-up

- For patients with OP or advanced bone loss (T-score <-2.0) → repeat DXA every 1-2 yrs
- Note least significant change (LSC) and direction of BMD (↑ vs ↓)
- When BMD stabilized, repeat DXA every 2-3 yrs
- Important for patient to continue with:
  - Exercise: weight bearing, resistance
  - Diet: calcium, vit D and
  - Medications: Take exactly as Rx'd

Camacho, Petak, et al. (2016). AACE & ACE Clin Px Guidelines for Dx & Tx PMO. *Endocrine Px, 22*(S 4), 1-42. National Osteoporosis Foundation. *Clinician's Guide to Prevention and Treatment of Osteoporosis. 2014* Gourlay ML, Fine JP, Preisser JS, et al. N Engl J Med 2012;366:225-33.

Monitoring & Follow-up

- Patients not taking OP Meds → repeat BMD when clinically appropriate
- Patients taking OP Meds → repeat labs and BMD in 1-2 years, sooner if clinically indicated
  - ➢ Consider least significant change
- Vertebral imaging if height loss, back pain, posture change, or suspicion d/t X-ray findings
- When BMD stabilized, repeat DXA every 2-3 yrs
- Reinforce plan of care at every visit
  - – exercise, Ca+, vit D, no tobacco, fall safety, meds exactly as Rx'd

Comacho et al (2020). LeBoff et al (2022). NAMS (2021).

Ms Albright: DXA Today

DXA now shows:

- Spine T-score: -2.3
- Femoral neck T: -2.0
- Total hip T-score: -1.8

How long should therapy continue? What about a "drug holiday?"

Fracture Intervention Trial–Long Term Extension (FLEX)

- Evaluated drug 'holiday' vs continuing therapy with alendronate after 5 years
- Decline in BMD after stopping alendronate relatively small; slower than with estrogen, raloxifene, & teriparatide
- Fracture results:
  - Non-vertebral fractures: No increase in fracture rates
  - Clinical vertebral fractures: More among placebo group, however incidence low in both groups
    - placebo 5.3% vs alendronate 2.4%

Black, D. M. et al. JAMA 2006;296:2927-2938.

BMD Change in FLEX Participants

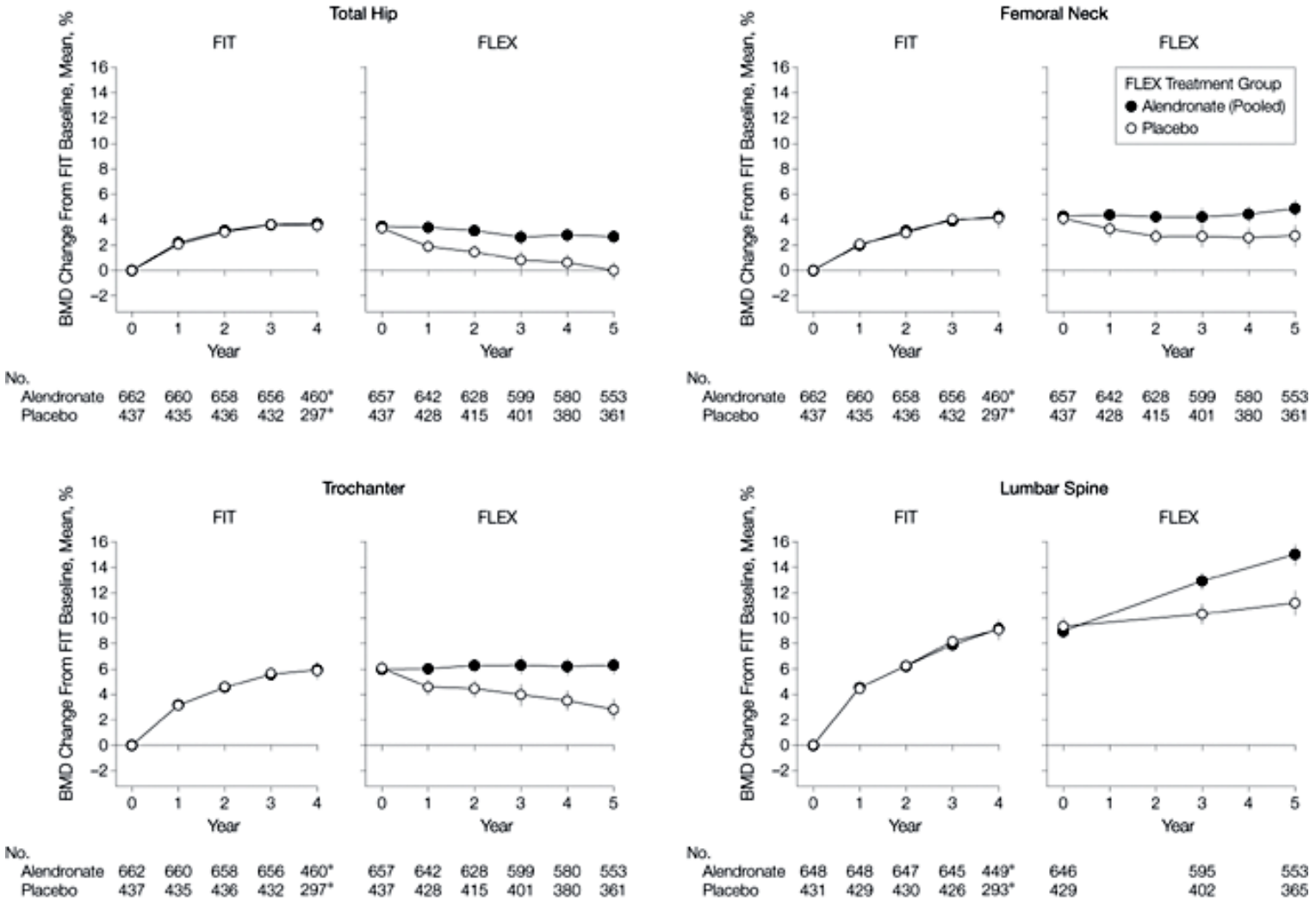


Figure 2. BMD Change in FLEX Participants. BMD indicates bone mineral density; FIT, Fracture Intervention Trial; FLEX, Fracture Intervention Trial Long-term Extension. Error bars indicate 95% confidence intervals. Data are shown for the period spanning the beginning of FIT through the completion of FLEX, a total of 10 years.
***Measured in clinical fracture arm only.**

Black, D. M. et al. JAMA 2006;296:2927-2938.

FLEX Trial

- Data suggest that for many women discontinuing alendronate for up to 5 years is not associated with significantly increased fracture risk
- Potential candidates: stable BMD, no prior vertebral fractures, and low risk
- However, women at higher risk for vertebral fractures may benefit from continued treatment beyond 5 years

Black, D. M. et al. JAMA 2006;296:2927-2938.

FREEDOM Trial Extension

- **F**racture **R**eduction **E**valuation of **D**enosumab in **O**steoporosis
  - Progressive ↓ risk for vert fx w long-term Rx
  - No increase in adverse events with long-term use
  - BMD falls quickly after cessation of use
    - Case reports of fx in 2-10 ms after D/C reported

McClung M, Harris ST, Miller PD, et al. Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday. *Am J Med* 2013;126:13-20. Hanley DA, McClung MR, Davison KS, et al; Writing Group for the Western Osteoporosis Alliance. Western Osteoporosis Alliance Clinical Practice Series: evaluating the balance of benefits and risks of long-term osteoporosis therapies. *Am J Med* 2017;130:862.e1-862.e7. Anastasilakis AD, Polyzos SA, Makras P, Aubrey-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res* 2017;32:1291-1296.

Who can take a “drug holiday?”

HOW TO MANAGE WOMEN AFTER 3-5 YEARS ON OP MEDICATIONS?

Re-assess Overall Fracture Risk

Consider:

- Fracture(s)?
- Co-morbidities/Medications?
- Fall Risk?
- High Risk =
  - +Spine, hip, or multiple OP Fx before/during Rx
  - +High Fx risk (hi FRAX @ baseline, Meds, Dz)
  - Persistent low BMD (Fem Neck T-score <-2.5 or <-2.0 if elderly/frequent falls)

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.; Birkhauser, M (2018). Duration and management of osteoporosis drug treatment after discontinuation. IMS Menopause Live, Jan 14. Camacho, Petak, et al. (2016). AACE & ACE Clin Px Guidelines for Dx & Tx PMO. *Endocrine Px, 22*(S 4), 1-42.

Consider the Medication: MHT

- Bone metabolism effects stop after D/C
- Effects on trabecular bone & BMD last ≥2 yr after D/C
- WHI showed no ↑ Fx up to 5 yr after D/C
- Overall ↓ Fx risk can last up to 16 yrs after D/C

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.; Birkhauser, M (2018). Duration and management of osteoporosis drug treatment after discontinuation. IMS Menopause Live, Jan 14.

Consider the Medication: EAA

- If at high risk for Fx and on EAA for 3-5 years, consider change to:
  - Bisphosphonate
  - Denosumab

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.; Birkhauser, M (2018). Duration and management of osteoporosis drug treatment after discontinuation. IMS Menopause Live, Jan 14.

Consider the Medication: Bisphosphonate

- After 3 (IV) or 5 (oral) years treatment, consider:
  - D/C if tx >5yrs & normal risk
  - Drug holiday if low or moderate risk
  - Change to denosumab if high risk
  - Change to teriparatide (24ms x 2 lifetime), abaloparatide (24ms cumulative), if incident VTE, or continue bisphosphonate (oral x 10 yrs; IV x 6 yrs)

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.; Birkhauser, M (2018). Duration and management of osteoporosis drug treatment after discontinuation. IMS Menopause Live, Jan 14.

Consider the Medication: Denosumab

- After 3-5 yrs tx:
  - Reassess risk
  - If high risk continue up to 10 yr (esp if on aromatase inhibitor)
  - If D/Cing use bisphosphonate or EAA to maintain BMD effects

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.; Birkhauser, M (2018). Duration and management of osteoporosis drug treatment after discontinuation. IMS Menopause Live, Jan 14.

Consider the Medication: PTH

- Effects stop after D/C
- Sequential therapy with bisphosphonate or denosumab

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.; Birkhauser, M (2018). Duration and management of osteoporosis drug treatment after discontinuation. IMS Menopause Live, Jan 14.

When to Stop Bisphosphonate "Drug Holiday"

- Monitor patients after discontinuation
- Drug holiday can last variable time periods. Not clear when to restart therapy
- Different providers use different clinical variables:
  - Duration
  - % decline in BMD
  - Increase in bone markers > premenopausal range
  - ?FRAX
- Uncertain whether the findings in FLEX apply to other bisphosphonates

For Women at Higher Risk

- Consider transfer to denosumab – data lacking; however, data demonstrate that longer term use of denosumab is safe and effective

McClung M (2018). Drug holidays in women treated for postmenopausal osteoporosis. NAMS Practice Pearl, Ap 19.

Case 4: Mr Spur

75yr old male with HTN, COPD and prostate cancer currently managed with androgen deprivation therapy. Fell on ice and sustained L hip fracture, s/p ORIF, did well in STR. Comes in for a post-discharge clinic visit.

MEDS: goserelin (Zoladex), albuterol (Ventolin) inhl, mometasone (Asmanex) inhl, vitamin D 800units daily.

Mr Spur: PE

- EXAM: BP 138/84, HR 78, Afebrile. Ambulating with walker, appears comfortable. Mild pain with rotation L hip. Otherwise unremarkable.

Mr Spur: Diagnostics

- Will you order a DXA?
- Any other labs?

Labs: CBC, lytes, LFTs, calcium wnl. Cr 1.3, eGFR 45. PSA 0.1, 25-hydroxyvitamin D 29ng/dl

DXA:

- spine T-score: -2.2
- Femoral neck T: -2.4 (non-fractured hip)
- Total hip T-score: -2.3

What is your next step?

Resources

- NIH - National Heart, Lung, and Blood Institute
  - http://www.nhlbi.nih.gov/
- The Hormone Foundation
  - http://www.hormone.org/
- Nat'l Center for Complimentary and Alt Medicine
  - http://nccam.nih.gov/
- National Osteoporosis Foundation
  - http://www.nof.org/
- Herbal Product Information
  - http://consumerlabs.com
- North American Menopause Society
  - http://www.menopause.com

References

Camacho, P. M., Petak, S. M., Binkley, N., et al. (2020). American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis – 2020 update. *Endocrine Practice, 26*(Suppl 1), 1-46. DOI: 10.4158/GL-2020-0524SUPPL. Available online: https://www.sciencedirect.com/science/article/pii/S1530891X20428277

LeBoff, M. S., Greenspan, S. L., Insogna, K. L., Lewiecki, E., M., Saag, K. G., Singer, A. J., & Siris. (2022). The clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis Internationa.* https://doi.org/10.1007/s00198-021-05900-y. Available online: https://link.springer.com/content/pdf/10.1007/s00198-021-05900-y.pdf

North American Menopause Society. (2021). NAMS position statement Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause 28*(9), 973-997. DOI: 10.1097/GME.0000000000001831. Available online: https://www.menopause.org/docs/default-source/professional/2021-osteoporosis-position-statement.pdf