THE UNIVERSITY OF ARIZONA | COLLEGE OF MEDICINE PHOENIX

# Osteoporosis

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# Disclosures

- Dexcom, Inc.: consultant and speaker

None of these companies make or market products for osteoporosis or bone health. None of them was involved in creating this presentation.

**Off-label use:** This talk discusses some uses that are not FDA-approved, including romosozumab in men and combination osteoporosis therapy.

# Objectives

- Identify who should be screened for osteoporosis and how to assess fracture risk (DXA, FRAX)
- Interpret DXA results and diagnose osteoporosis, including diagnosis by fragility fracture
- Evaluate for secondary causes and distinguish osteoporosis from osteomalacia
- Counsel on nonpharmacologic measures and fall prevention
- Select treatment and recognize major adverse effects (GI, hypocalcemia, ONJ, AFF)
- Monitor therapy, plan drug holidays, and coordinate follow-up

## Which one of these people should be treated for osteoporosis?



A. 65 y/o F who had screening DEXA which showed T-score -2.8 in right femoral neck
B. 79 y/o F with screening DEXA with lowest T-score -0.9 in lumbar spine with recent left hip fracture
C. 57 y/o F with multiple fractures and severe Vitamin D deficiency, low phosphate, and DEXA with lowest T-score -3.0
D. 72 y/o M with history of prostate cancer on androgen deprivation therapy with screening DEXA with normal T-scores in hip and spine, but distal 1/3 radius -3.2
E. 52 y/o F with chronic back pain, x-ray showed compression fracture at L1, no trauma
F. 71 y/o M who slipped on ice and developed left humerus fracture
G. 60 y/o F with DEXA which showed lowest T-score -2.1 in left femoral neck with FRAX score for major osteoporotic fracture 16% and hip fracture 4%

# Approach to Osteoporosis

- Diagnose those at highest risk
  - Screening by DXA
  - Assessment of risk by FRAX score
- Exclude secondary causes of low BMD
- Select appropriate treatment
  - Nonpharmacologic
  - Pharmacologic
    - Antiresorptive Agents
      - Bisphosphonates
      - Estrogen, SERMs
      - RANKL Inhibition
    - Anabolic Agents
      - PTH/PTHrP analogs
      - Sclerostin inhibitor.
- Monitoring of therapy









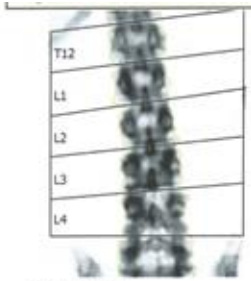


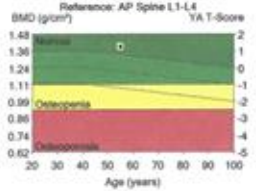

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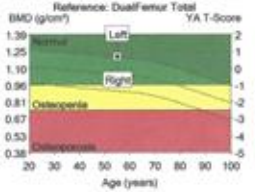
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Reference: AP Spine L1-L4




Reference: DualFemur Total




| Region | BMD [1] (g/cm²) | Young-Adult [2,7] T-Score | Age-Matched [3] Z-Score | WHO Classification [11] |
|---|---|---|---|---|
| AP Spine L1-L4 | 1.392 | 1.3 | 1.5 | Normal |
| DualFemur Total | | | | |
| Left | 1.199 | 0.7 | 1.0 | Normal |
| Right | 1.195 | 0.6 | 1.0 | Normal |
| Mean | 1.197 | 0.7 | 1.0 | Normal |
| Difference | 0.004 | 0.0 | 0.0 | - |

1 - Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for AP Spine L1-L4); (± 0.010 g/cm² for DualFemur Total Mean)
2 - NHANES (ages 20-30) / USA (ages 20-40) AP Spine Reference Population (v107); NHANES (ages 20-30) / USA (ages 20-40) Femur Reference Population (v107)
3 - AP Spine Matched for Age, Weight (males 25-100 kg), Ethnic; DualFemur Matched for Age, Weight (males 25-100 kg), Ethnic
7 - DualFemur Total Mean T-Score difference is 0.0. Asymmetry is None.
11 - World Health Organization - Definition of Osteoporosis and Osteopenia for Caucasian Women: Normal = T-Score at or above -1.0 SD; Osteopenia = T-Score between -1.0 and -2.5 SD; Osteoporosis = T-Score at or below -2.5 SD; (WHO definitions only apply when a young healthy Caucasian Women reference database is used to determine T-Scores.)

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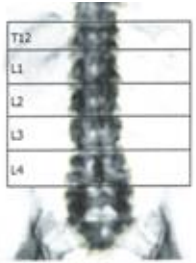



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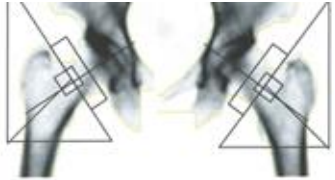
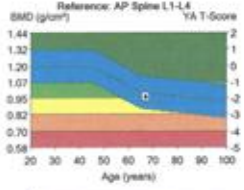


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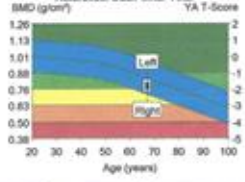
Hip Axis Length Comparison (mm)




Reference: AP Spine L1-L4




Reference: DualFemur Total




| Region | BMD [1] (g/cm²) | Young-Adult [2,7] T-Score | Age-Matched [3] Z-Score | WHO Classification [11] |
|---|---|---|---|---|
| AP Spine L1-L4 | 0.952 | -2.0 | -0.3 | - |
| DualFemur Total | | | | |
| Left | 0.793 | -1.7 | -0.4 | - |
| Right | 0.766 | -1.9 | -0.6 | - |
| Mean | 0.779 | -1.8 | -0.5 | - |
| Difference | 0.027 | 0.2 | 0.2 | - |

1 - Statistically 68% of repeat scans fall within 1SD (± 0.010 g/cm² for AP Spine L1-L4); (± 0.010 g/cm² for DualFemur Total Mean)
2 - NHANES (ages 20-30) / USA (ages 20-40) AP Spine Reference Population (v107); NHANES (ages 20-30) / USA (ages 20-40) Femur Reference Population (v107)
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**Table 4**
**World Health Organization Criteria for Classification of Osteopenia and Osteoporosis**

| Category | T-score |
|---|---|
| Normal | –1.0 or above |
| Low bone mass (osteopenia)[a] | Between –1.0 and –2.5 |
| Osteoporosis | –2.5 or below |

[a] Fracture rates within this category vary widely. The category of "osteopenia" is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.

- T-scores apply to postmenopausal women and men ≥50.
- In premenopausal women and men <50, use Z-scores; ≤ –2.0 means "below expected range for age," not osteoporosis.

**Table 6**
**2020 AACE Diagnosis of Osteoporosis in Postmenopausal Women**

1. T-score –2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2. Low-trauma spine or hip fracture (*regardless of bone mineral density*)
3. T-score between –1.0 and –2.5 **and** a fragility fracture of proximal humerus, pelvis, or distal forearm
4. T-score between –1.0 and –2.5 **and** high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds

Abbreviations: AACE = American Association of Clinical Endocrinologists; FRAX® = fracture risk assessment tool; TBS = trabecular bone score.

# Who should be screened for osteoporosis?



A. 63 y/o F who slipped in bathtub and had tibial fracture
B. 55 y/o F on long-term intraarticular corticosteroid injections for chronic knee pain
C. 42 y/o M with primary hyperparathyroidism
D. 51 y/o F who weighs 50kg
E. 38 y/o F who had total hysterectomy (including oophorectomy) at age 30 for fibroids
F. 71 y/o M with no significant PMH, active cyclist, no personal or family history of fractures
G. 60 y/o M with chest x-ray done for SOB, which had small comment of “osteopenia” in radiology report

**Table 7**
**Assessment for Fracture Risk and Osteoporosis in Postmenopausal Women**

- Medical history and physical examination to identify:
  - Prior fracture without major trauma (other than fingers, toes, skull) after age 50 years
  - Clinical risk factors for osteoporosis
    - Age ≥65 years
    - Low body weight (<57.6 kg [127 lb])
    - Smoking
    - Early menopause
    - Excessive alcohol intake (more than 3 drinks daily)
  - Secondary osteoporosis
  - Height loss of kyphosis
  - Risk factors for falling (see Table 9)
  - Patient's reliability, understanding, and willingness to accept interventions
- Lateral spine imaging with standard radiography or vertebral fracture assessment in patients with unexplained height loss, self-reported but undocumented prior spine fractures, or glucocorticoid therapy equivalent to ≥5 mg of prednisone per day for 3 months or more
- Bone mineral density measurements in those at increased risk for osteoporosis and fractures and willing to consider pharmacologic treatment if low bone mass is documented:
  - All women 65 years of age or older
  - Younger postmenopausal women
    - With a history of fracture(s) without major trauma
    - Starting or taking long-term systemic glucocorticoid therapy **Prednisone ≥2.5 mg for >3 months**, per ACR 2022
    - With radiographic osteopenia
    - With clinical risk factors for osteoporosis (low body weight, cigarette smoking, family history of spine or hip fractures, early menopause, or secondary osteoporosis)
- In women who are candidates for pharmacologic therapy, laboratory evaluation to identify coexisting conditions that may contribute to bone loss or interfere with therapy (or both).

**Table 9**
**Factors that Increase Risk of Falling and Fracture**

Neurologic disorders
- Parkinson disease
- Seizure disorder
- Peripheral neuropathy
- Prior stroke
- Dementia
- Impaired gait or balance (or both)
- Autonomic dysfunction with orthostatic hypotension

Impaired vision
Impaired hearing
Frailty and deconditioning

Proximal myopathy
Sarcopenia

Hypoglycemia (including iatrogenic)

Medications
- Sedatives and hypnotics
- Antihypertensive agents
- Narcotic analgesics

Environmental factors
- Poor lighting
- Stairs
- Slippery floors
- Wet, icy, or uneven pavement
- Uneven roadways
- Electric or telephone cords
- Walking large dogs, being tripped up by small dogs
- Throw rugs
- Positioning in a wet or dry bathtub







AACE 2020

## Table 10
## Indications for Bone Mineral Density Testing

All women 65 years of age or older

All postmenopausal women

- With a history of fracture(s) without major trauma
- With osteopenia identified radiographically
- Starting or taking long-term systemic glucocorticoid therapy (≥3 months)

Other perimenopausal or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions

- Low body weight (<127 lb or body mass index <20 kg/m$^2$)
- Long-term systemic glucocorticoid therapy (≥3 months)
- Family history of osteoporotic fracture
- Early menopause
- Current smoking
- Excessive consumption of alcohol

Secondary osteoporosis

**Prednisone ≥2.5 mg for >3 months**, per ACR 2022

Endo Society/BHOF 2022

# Endocrine Society Guidelines

- Screening men at “increased risk for osteoporosis” by measurement of BMD
- Age > 70 (considered risk factor)
- Age 50-69 with additional risk factor
  - History of fracture after age 50
  - Delayed puberty
  - Hypogonadism
  - Hyperparathyroidism
  - Hyperthyroidism
  - COPD
  - Drugs such as glucocorticoids or GnRH agonists
  - Alcohol abuse
  - Smoking
  - Other causes of secondary osteoporosis

USPTF 2025

# USPTF Guidelines: Osteoporosis Screening

- Women ≥65: DXA, with or without a risk assessment (Grade B)
- Postmenopausal women <65: use a risk tool first (FRAX, OST, ORAI), then DXA if risk is increased (Grade B)
- Men: insufficient evidence (I); Endocrine Society and BHOF screen men ≥70, or 50–69 with risk factors
- Note: risk tools are less accurate in Black, Asian, and Hispanic patients

# Approach to Osteoporosis

- Diagnose those at highest risk
  - Screening by DXA
  - **Assessment of risk by FRAX score**
- Exclude secondary causes of low BMD
- Select appropriate treatment
  - Nonpharmacologic
  - Pharmacologic
    - Antiresorptive Agents
      - Bisphosphonates
      - Estrogen, SERMs
      - RANKL Inhibition
    - Anabolic Agents
      - PTH/PTHrP analogs
      - Sclerostin inhibitor.
- Monitoring of therapy



**Table 8**
**Risk Factors Included in FRAX®**

Country of residence
Ethnicity (U.S. models only—white, black, Hispanic, and Asian)
Age (accepts ages between 40 and 90 years)
Sex
Weight (kg) and height (cm) used to calculate body mass index; a converter from English to metric units is provided within the FRAX® tool
Family history (either parent with a hip fracture)
Personal history of fragility fracture, including radiographic vertebral fracture
Glucocorticoid use (prednisolone 5 mg daily or more for 3 months or longer, current or past)
Rheumatoid arthritis (confirmed diagnosis)
Smoking (current)
Alcohol use (2 or more units daily)
Secondary osteoporosis[a] (specifically mentioned are type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease)
BMD. Femoral neck BMD should be entered. The model also works without BMD.

AND Type 2 Diabetes

Abbreviations: BMD = bone mineral density; FRAX® = fracture risk assessment tool.
[a]Because the effects of causes of secondary osteoporosis on fracture risk are assumed to be mediated through changes in BMD, a "yes" answer to this question does not change fracture risk if BMD is entered into the risk tool.
Reproduced with permission from Watts NB, et al. *J Bone Miner Res*. 2009;24:975-979 (274).



FRAX® Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References

# 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

**Table 7**
**Risk Factors Included in FRAX®**

| |
|---|
| Country of residence |
| Ethnicity (US models only—white, black, Hispanic, and Asian) |
| Age (accepts ages between 40 and 90 y) |
| Sex |
| Weight (kg) and height (cm) used to calculate body mass index; a converter from English to metric units is provided within the FRAX® tool |
| Family history (either parent with a hip fracture) |
| Personal history of fragility fracture, including radiographic vertebral fracture |
| Glucocorticoid use (prednisolone ≥5 mg daily for 3 mo or longer, current or past) |
| Rheumatoid arthritis (confirmed diagnosis) |
| Smoking (current) |
| Alcohol use (>3 units daily) |
| Secondary osteoporosis[a] (specifically mentioned are type 1 diabetes, osteogenesis imperfect in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption and chronic liver disease) |
| BMD[b]. Either T-score or femoral neck BMD can be entered. The model also works without BMD. |

Abbreviations: BMD = bone mineral density; FRAX® = Fracture Risk Assessment Tool.

[a] Because the effects of causes of secondary osteoporosis on fracture risk are assumed to be mediated through changes in BMD, a "yes" answer to this question does not change fracture risk if BMD is entered into the risk tool.

[b] If the T-score is used, prior correction with the "FRAX® patch" is required. If BMD is used, data are entered as $g/cm^2$ after identification of the densitometer manufacturer.

Reproduced with permission from Watts et al. *J Bone Miner Res*. 2009;24:975-979 (1 [EL 4; CPG NE]).

# Advantages and Limitations of FRAX

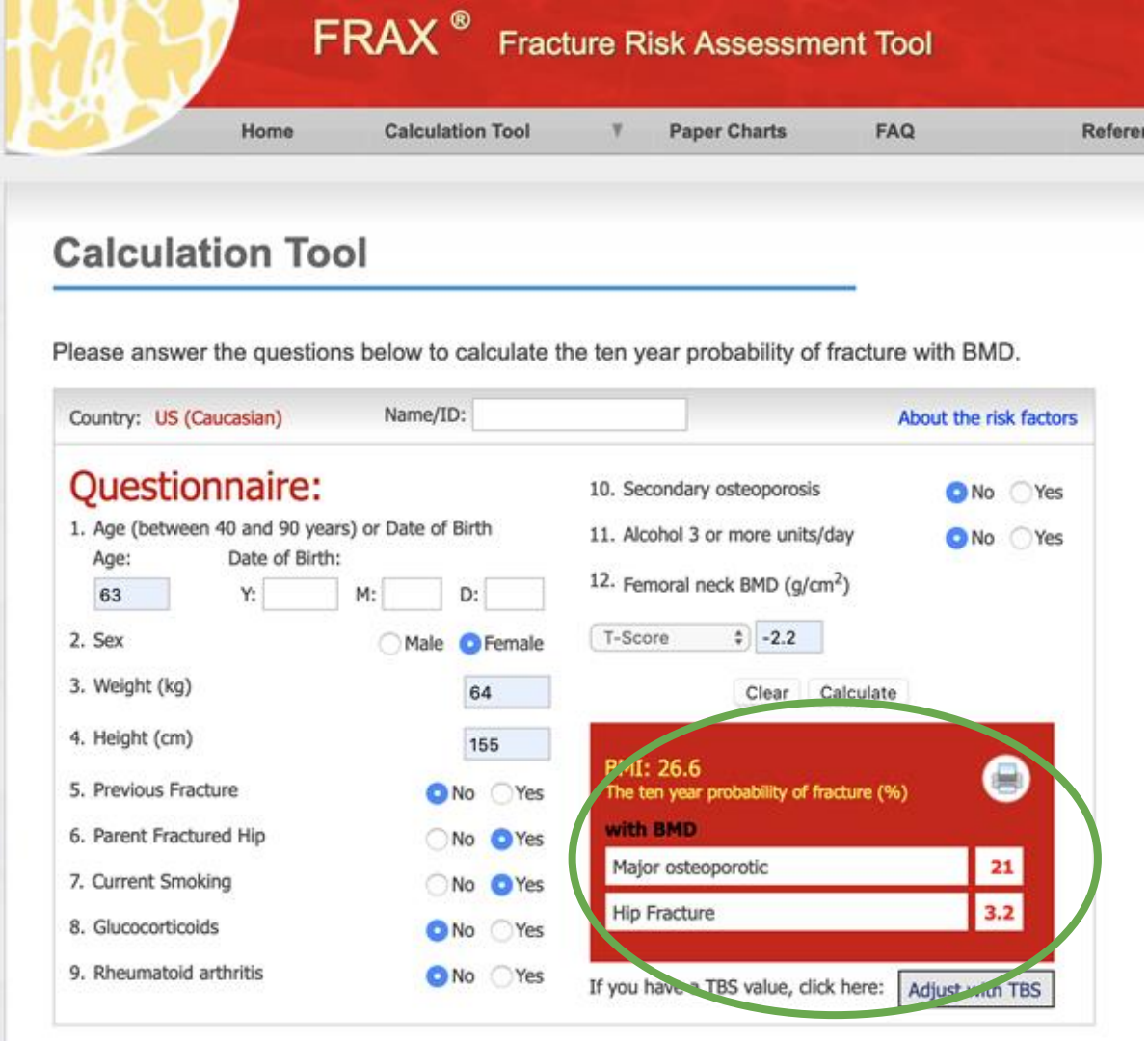
- Advantages
  - Identifies patients to treat where we have limited evidence of treatment efficacy (non-osteoporotic)
- Limitations
  - Only incorporates femoral neck BMD
  - Does not include fall-related risk factors for fracture (not a true fracture risk predictor)
    - *FRAXplus can adjust for lumbar spine BMD, TBS, falls, glucocorticoid dose, recent fracture, and type 2 diabetes duration.*
  - Does not apply to young adults (age <40)
  - Was not designed for patients on treatment for osteoporosis (FRAX validated for untreated patients)
  - Not needed or not very helpful if:
    - Patient already has an osteoporosis diagnosis
    - Osteoporotic fracture history
    - When rapid bone loss is anticipated (early menopause, stopping HRT, hormone deprivation therapy, beginning glucocorticoid therapy)
    - Secondary osteoporosis
- Remember to distinguish between diagnostic thresholds (BMD) and intervention thresholds (risk based-- FRAX)

# Case 1

63 y/o F, current smoker, and parent with hip fracture presents with DEXA which showed lowest T-score -2.2 in left femoral neck.

What is the diagnosis?

What is the next step?


FRAX ® Fracture Risk Assessment Tool
Home
Calculation Tool
Paper Charts
FAQ
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:
63
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
64
4. Height (cm)
155
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/cm2)
T-Score
-2.2
Clear
Calculate
BMI: 26.6
The ten year probability of fracture (%)
with BMD
Major osteoporotic
21
Hip Fracture
3.2
If you have a TBS value, click here:
Adjust with TBS

# Case 1

63 y/o F, current smoker, and parent with hip fracture presents with DEXA which showed lowest T-score -2.2 in left femoral neck with FRAX score for major osteoporotic fracture 21% and hip fracture 3.2%.

What is the diagnosis?

What is the next step?

# Meets Treatment Threshold for Osteoporosis. What's next?



1. Evaluate for secondary causes of osteoporosis
2. Evaluate for prevalent vertebral fractures
3. Consider using bone turnover markers (BTMs) in initial evaluation and follow up of osteoporosis patients
    a. Elevated levels can predict more rapid rates of bone loss and higher fracture risk
    b. Recommend referring to a specialist who knows how to utilize these correctly otherwise it can lead to unnecessary testing
4. Counsel on calcium, vitamin D, exercise, and fall prevention
5. Start pharmacologic therapy.

# Approach to Osteoporosis

- Diagnose those at highest risk
  - Screening by DXA
  - Assessment of risk by FRAX score
- **Exclude secondary causes of low BMD**
- Select appropriate treatment
  - Nonpharmacologic
  - Pharmacologic
    - Antiresorptive Agents
      - Bisphosphonates
      - Estrogen, SERMs
      - RANKL Inhibition
    - Anabolic Agents
      - PTH/PTHrP analogs
      - Sclerostin inhibitor.
- Monitoring of therapy



0013-7227/02/$15.00/0
*Printed in U.S.A.*

The Journal of Clinical Endocrinology & Metabolism 87(10):4431–4437
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doi: 10.1210/jc.2002-020275

# Yield of Laboratory Testing to Identify Secondary Contributors to Osteoporosis in Otherwise Healthy Women

CARA TANNENBAUM, JULIE CLARK, KEVIN SCHWARTZMAN, SYLVAN WALLENSTEIN, ROBERT LAPINSKI, DIANE MEIER, AND MARJORIE LUCKEY

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# Osteoporotic Females with Secondary Cause

- 173 females (ages 46-87) without known secondary osteoporosis or prior lab abnormalities underwent lab evaluation
  - CBC
  - CMP
  - 24-hour urine calcium
  - PTH
  - Vitamin D
  - TSH
  - SPEP
- **44% were found to have a secondary cause**

# Osteoporotic Females with New Diagnoses

- Vitamin D Deficiency (Vit D < 20): 20%
- Hypercalciuria: 10%
- Malabsorption: 7%
  - Celiac Disease: 3
- Hyperparathyroidism: 3%
  - Primary: 1
  - Secondary: 5
- Over-replacement with levothyroxine: 2%
- Cushing Disease: < 1%
- Other: 1%

**Table 11**
**Causes of Secondary Osteoporosis in Adults**

| Endocrine or metabolic causes | Nutritional/GI conditions | Drugs | Disorders of collagen metabolism | Other |
|---|---|---|---|---|
| Acromegaly | Alcoholism | Antiepileptic drugs[a] | Ehlers-Danlos syndrome | AIDS/HIV[a] |
| Diabetes mellitus<br>Type 1<br>Type 2 | Anorexia nervosa | Aromatase inhibitors | Homocystinuria due to cystathionine deficiency | Ankylosing spondylitis |
| Growth hormone deficiency | Calcium deficiency | Chemotherapy/ immunosuppressants | Marfan syndrome | Chronic obstructive pulmonary disease |
| Hypercortisolism | Chronic liver disease | Depo-Provera | Osteogenesis imperfect | Gaucher disease |
| Hyperparathyroidism | Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass) | Glucocorticoids | | Hemophilia |
| Hyperthyroidism | | Gonadotropin-releasing hormone agents | | Hypercalciuria |
| Hypogonadism | | Heparin | | Immobilization |
| Hypophosphatasia | | Lithium | | Major depression |
| Porphyria | | Proton pump inhibitors | | Myeloma and some cancers |
| Pregnancy | | Selective serotonin reuptake inhibitors | | Organ transplantation |
| | Total parenteral nutrition | Thiazolidinediones | | Renal insufficiency/ failure |
| | Vitamin D deficiency | Thyroid hormone (in supraphysiologic doses) | | Renal tubular acidosis |
| | | | | Rheumatoid arthritis |
| | | | | Systemic mastocytosis |
| | | | | Thalassemia |

Abbreviations: AIDS = acquired immunodeficiency syndrome; GI = gastrointestinal; HIV = human immunodeficiency virus; GI = gastrointestinal.

[a] Phenobarbital, phenytoin, primidone, valproate, and carbamazepine have been associated with low bone mass.

**Table 12**
**Laboratory Tests to Consider in Detecting Secondary Osteoporosis**

Complete blood cell count

Serum chemistry, including calcium, phosphate, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes

24-h collection for calcium, sodium, and creatinine excretion (to identify calcium malabsorption or hypercalciuria)

Serum 25-hydroxyvitamin D

Additional tests if clinically indicated might include (but not limited to):

Serum intact parathyroid hormone concentration for possible primary or secondary hyperparathyroidism

Serum thyrotropin

Tissue transglutaminase antibodies for suspected celiac disease

Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma

Urinary free cortisol or other tests for suspected adrenal hypersecretion

Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis

Bone marrow aspiration and biopsy to look for marrow-based diseases

Undecalcified iliac crest bone biopsy with double tetracycline labeling

- Recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management
- May be helpful in the assessment of patients with the following:
  - Suspected osteomalacia or mastocytosis when laboratory test results are inconclusive
  - Fracture without major trauma despite normal or high bone density
  - Vitamin D-resistant osteomalacia and similar disorders to assess response to treatment

Genetic testing for unusual features that suggest rare metabolic bone diseases

# Labs to Consider for Secondary Osteoporosis

1. **CBC**
2. **CMP**
3. **PTH panel (with Ca2+)**
4. **25-hydroxy-Vitamin D**
5. **24-Hour Urine Calcium**
    a. **After patient is vitamin D replete and getting calcium 1200mg/day x 2 weeks**
6. **TSH**
7. **TTG antibodies (if signs of malabsorption)**
8. **SPEP/UPEP (if suspicion)**
9. **Testosterone (if male)**

# Case 2: "Severe Osteoporosis"?

- **58 y/o F referred for "severe osteoporosis"**
  - 2 years of diffuse bone pain and proximal muscle weakness, attributed to fibromyalgia
  - Difficulty rising from a chair; waddling gait
  - Roux-en-Y gastric bypass 12 years ago; lost to follow up, stopped supplements years ago
- DXA: lumbar spine T-score -3.4, femoral neck T-score -3.1
- Started on alendronate 8 months ago by her PCP
- Now with worsening pain and a new rib "fracture" on chest x-ray
- **What is missing from this picture?**

# Case 2: The Labs

- Calcium 8.5 mg/dL (lower end of normal), albumin 3.8 g/dL
- **Phosphorus 2.1 mg/dL (LOW)**
- **Alkaline phosphatase 120 U/L (HIGH)**
- **25-OH vitamin D 8 ng/mL (very low)**
- **PTH high end of normal**
- **24-hour urine calcium 22 mg (LOW)**
- Creatinine and eGFR normal

**What is happening in this patient?**

# Why Did the DXA Mislead Us?

- **Osteomalacia is a defect of MINERALIZATION, not of bone mass**
- Undermineralized osteoid attenuates x-rays poorly, so DXA reports it as low BMD
- A T-score measures mineral content; it cannot distinguish bone quantity from bone quality
- The same trap applies to:
  - Renal osteodystrophy
  - Hypophosphatasia
  - Any severe, prolonged vitamin D deficiency

# Causes of Osteomalacia

- **Vitamin D deficiency**
  - Nutritional / inadequate sun exposure
  - Malabsorption: bariatric surgery, celiac disease, pancreatic insufficiency, IBD
- **Chronic kidney disease / renal osteodystrophy**
- **Renal phosphate wasting**
  - Tumor-induced osteomalacia (check FGF23)
  - X-linked hypophosphatemia, Fanconi syndrome
- **Drugs**
  - Long-term anticonvulsants (phenytoin, phenobarbital)
  - Tenofovir, adefovir
  - IV ferric carboxymaltose (FGF23-mediated hypophosphatemia)
  - Chronic phosphate binders and antacids
- **Hypophosphatasia: the mirror-image trap**
  - LOW alkaline phosphatase; bisphosphonates are contraindicated

# Distinguishing Metabolic Bone Diseases

| Condition | Ca | Phos | Alk Phos | PTH | 25-OH D | Urine Ca |
|---|---|---|---|---|---|---|
| **Osteoporosis** | Normal | Normal | Normal | Normal | Variable | Nl / High |
| **Osteomalacia (vit D def)** | Low-nl | LOW | HIGH | High | LOW | LOW |
| **Primary hyperparathyroidism** | HIGH | Low | Nl / High | High | Variable | High |
| **Renal osteodystrophy** | Low / nl | HIGH | High | High | Low | Low |
| **Paget disease of bone** | Normal | Normal | VERY HIGH | Normal | Normal | Normal |
| **Hypophosphatasia** | Nl / high | Nl / high | LOW | Nl / low | Normal | High |

# Beware of Silent Vertebral Fractures

- **Most common fracture type**
- **⅔ are unrecognized by physician and patients**
- Consider spine imaging or Vertebral Fracture Assessment if T-score < -1 and:
  - Kyphosis
  - Historical height loss of 1.5” or more
  - Conditions associated with high risk for vertebral fracture (glucocorticoids, COPD, women > 70, men > 80)
  - Self-reported history of vertebral fracture
  - Glucocorticoid therapy (>/= 5mg prednisone or equivalent for > 3 months)

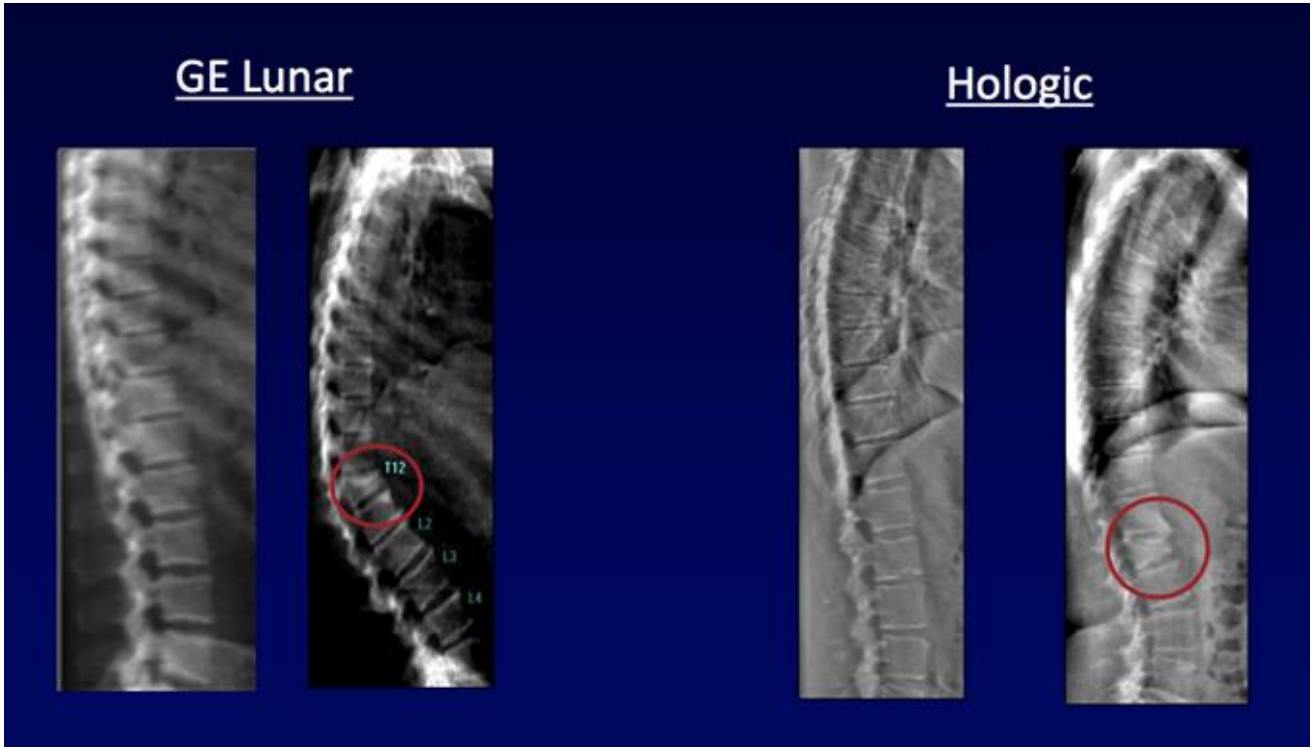
**Table 6**
**Assessment for Fracture Risk and Osteoporosis in Postmenopausal Women**

- Medical history and physical examination to identify:
  - Prior fracture without major trauma (other than fingers, toes, skull) after age 50
  - Clinical risk factors for osteoporosis
    - Age ≥65
    - Low body weight (<57.6 kg [127 lb])
    - Family history of osteoporosis or fractures
    - Smoking
    - Early menopause
    - Excessive alcohol intake (≥3 drinks daily)
  - Secondary osteoporosis
  - Height loss or kyphosis
  - Risk factors for falling
  - Patient's reliability, understanding, and willingness to accept interventions
- Lateral spine imaging with standard radiography or vertebral fracture assessment in patients with unexplained height loss, self-reported but undocumented prior spine fractures, or glucocorticoid therapy equivalent to ≥5 mg prednisone daily for 3 months or more

# Vertebral Fracture Assessment

- “New” technology using central DXA which permits imaging of thoracic and lumbar spine to evaluate for the presence of vertebral fractures
- Up to 2/3 of patients who have vertebral fractures are asymptomatic
- Benefits:
  - Lower cost than plain x-rays
  - Lower radiation exposure than plain x-rays
  - Can be done at the same time as BMD measurement
  - Predicts future fracture risk
    - Better predictor of future fracture than a low BMD alone
  - These patients demonstrate a greater response to medical therapy than patients without prior fracture

# Vertebral Fracture Assessment (VFA)



# How do we assess bone turnover?

- **Bone is constantly being remodeled**
  - **First, bone is broken (bone resorption)**
  - **Then, bone is being rebuilt (bone formation)**
- **The resorption and reformation of bone is important for repair of microfractures and to allow modification of structure in response to stress and other biochemical forces**
- **Both formation and resorption are tightly coupled so bone mass does not change**
- **Bone diseases occur when these two are uncoupled**

# What are Bone Turnover Markers?

- BTM's are a measurement of collagen breakdown products and other molecules released from osteoclasts and osteoblasts during the process of bone resorption and formation
- **Markers specific to bone formation:**
  - Bone-specific alkaline phosphatase (BSAP)
  - Osteocalcin
  - **N-terminal propeptide of type 1 procollagen (P1NP)**
- **Markers specific to bone resorption:**
  - N-terminal Telopeptide of type 1 collagen (NTX)
  - **C-terminal Telopeptide of type 1 collagen (CTX)**
  - Pyridinoline cross-links

# How can we use Bone Turnover Markers?

- BTMs provide dynamic assessment of skeletal activity
- **Can’t be used to diagnose osteoporosis**
- Elevated levels of BTMs can predict more rapid rates of bone loss and are associated with increased fracture risk (independent of BMD)
- These markers respond quickly to therapy
- **Use in clinical practice is limited by high in vivo and assay variability, poor predictive ability in individual patients, and lack of evidence-based thresholds for clinical decision making**

# Bone Turnover Markers (BTMs)

- **Significant reductions in BTMs have been associated with fracture reduction**
- Antiresorptive therapy can likely be deemed effective if BTMs during therapy are at or below the median value for premenopausal women
- In 2010, IOF proposed serum C-telopeptide (S-CTX) and serum carboxy-terminal propeptide of type 1 collagen (PINP) can be used as reference analytes for BTMs in clinical and observational studies
  - **S-CTX is preferred resorption marker**
  - **PINP is preferred formation marker**

# Bone Turnover Markers (BTMs)

- Fasting morning CTX may be helpful in evaluating nonresponders with bone loss or fracture on therapy or to ID patients with high bone turnover
    - Elevated CTX is associated with high bone turnover and could represent **malabsorption** or **poor compliance** and the **need for evaluation for causes of secondary osteoporosis**
- Of note, recent fractures will transiently increase BTMs
- **Summary: BTMs may be useful in certain situations for fx risk assessment or determining medication compliance, drug absorption, or therapeutic efficacy**

**Please do not order! Consult endocrinology!**

# Approach to Osteoporosis

- Diagnose those at highest risk
  - Screening by DXA
  - Assessment of risk by FRAX score
- Exclude secondary causes of low BMD
- **Select appropriate treatment**
  - Nonpharmacologic
  - Pharmacologic
    - Antiresorptive Agents
      - Bisphosphonates
      - Estrogen, SERMs
      - RANKL Inhibition
    - Anabolic Agents
      - PTH/PTHrP analogs
      - Sclerostin inhibitor.
- Monitoring of therapy



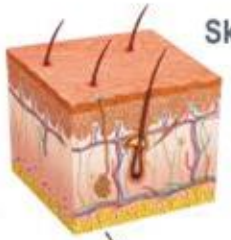
# Nonpharmacologic Management



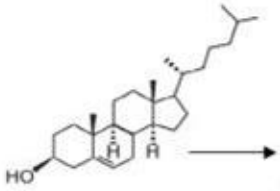
- Vitamin D
  - Measure serum 25-OH-Vit D in patients who are at risk for Vit D deficiency
  - Maintain serum 25-OH-Vit D >/= 30 in patients with osteoporosis (preferable range 30-50)
  - Supplement with Vit D3 if needed (1000-2000 IU of daily maintenance therapy to maintain optimal serum Vit D level)
  - Higher doses may be necessary in presence of certain factors
    - Obesity, malabsorption, transplant patients, certain ethnicities, older individuals
- Counsel patients to maintain adequate dietary intake of calcium (total intake of 1200mg/day)



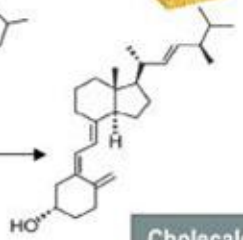
UV light



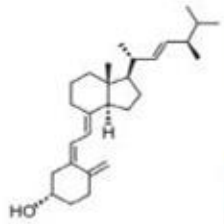
Skin



7-dehydrocholesterol



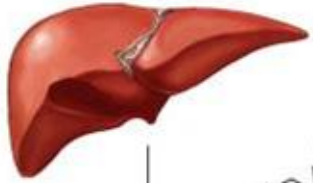
Cholecalciferol (Vit. D3)



Ergocalciferol (Vit. D2)

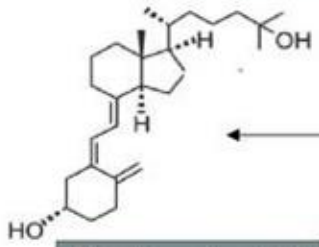
Vitamin D food sources



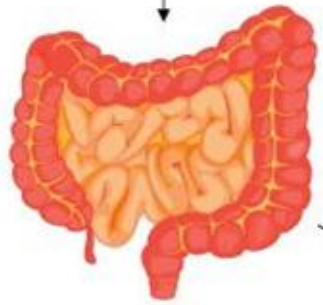


Liver

1,25-hydroxyvitamin D



25-hydroxyvitamin D3

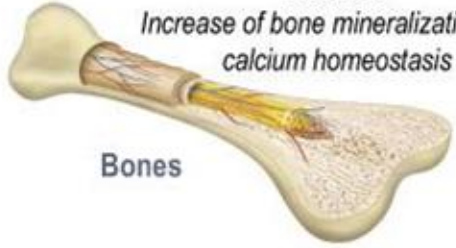


GI track

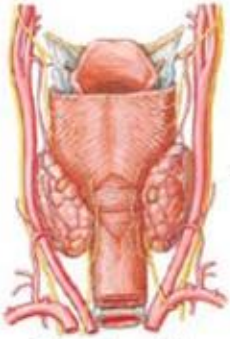


**Results:**

*Increase of bone mineralization and calcium homeostasis*



Bones

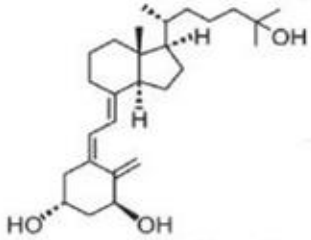


Parathyroid

*Hypocalcaemia stimulates PTH secretion*



Kidneys



*Increase calcium absorption*

# Nonpharmacologic Management: Counseling







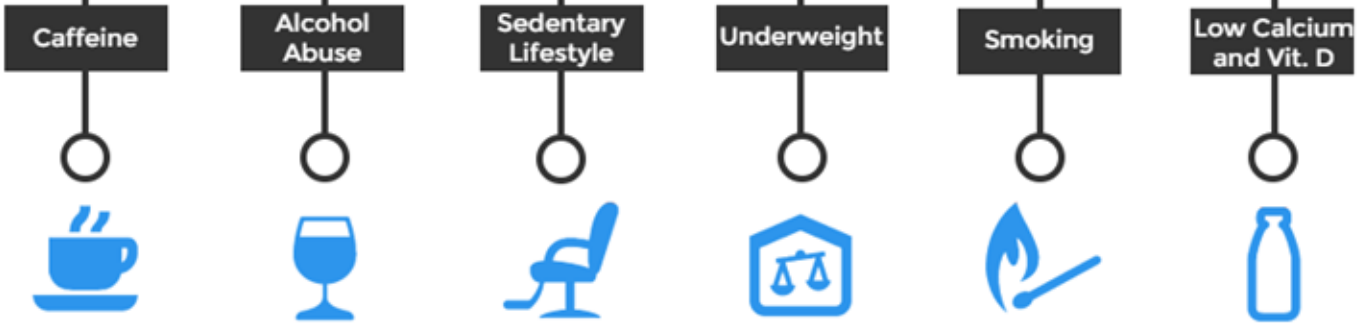

- Limit alcohol intake to no more than 2 units per day
- Avoid or stop smoking
- Maintain active lifestyle
  - Weight bearing, balance, and resistance exercises
- Reduce risk of falls, particularly among the elderly
- Hip protectors in individuals with high risk of falling
- Referral for physical therapy, which may reduce discomfort, prevent falls, and improve quality of life





# Osteoporosis

## Controllable Risk Factors




In addition, some medications (such as corticosteroids), estrogen deficiency, and long-term use of contraceptives can increase risk of osteoporosis.

Non-controllable risk factors include old age, female sex and White or Asian ethnicity.

National Osteoporosis Foundation

# BONING UP ON OSTEOPOROSIS

## Fracture Prevention for Daily Activities

Performing daily activities correctly is just as important as choosing the right exercises if you have low bone density. Try the postures below or view the video tutorials to see if you are performing your everyday activities correctly!

### Fracture Prevention Tips:

- **Spine Protection**
  Avoid rounding forward and excessive twisting
- **Hip + Wrist Protection**
  Practice balance and standing on one leg regularly to prevent falls

### If you have low bone density, you may be at risk for fracture:

- Strengthening the muscles of your mid-back and legs has been shown to be most effective for building bone and fracture prevention.
- **Posture and Balance Exercises**
  Posture correction and dynamic balance challenges have been shown to be effective in fall and fracture prevention.

## EVERYDAY ACTIVITIES

**Keep your back straight.**
**Avoid rounding your spine & shoulders.**

### General Lifting:



Stand with your feet a little wider than your hips, keep knees in line with middle toes as you squat to lift an object. Hinge at the hips, keep the

### Unpacking Groceries:



Keep spine lengthened and straight, chest lifted and knees bent. Rest knees against bumper to brace your body. Hinge at the hips instead of rounding the back to reach

### Lifting a Pet:



Stand with your feet a little wider than your hips, keep knees in line with middle toes as you squat to lift a pet or child. Hinge at the hips, keep the










# Fall Prevention Guide

from Right at Home

*with the expert advice of Dr. Rein**




**Rein Tideiksaar, Ph.D., PA-C, (or Dr. Rein, as he is more commonly known) is a gerontologist and a geriatric physician's assistant. He is President of FallPrevent, LLC, in Blackwood, N.J., a consulting company providing educational, legal and marketing services related to fall prevention for the elderly. Dr. Rein's professional profile is located on LinkedIn.*

## Fall Prevention Around the House

**1/3** of aged adults fall each year, and among older adults, falls are the leading cause of both FATAL and nonfatal injuries*

# What do you tell patients to help them avoid falls?



# Fall Prevention Counseling















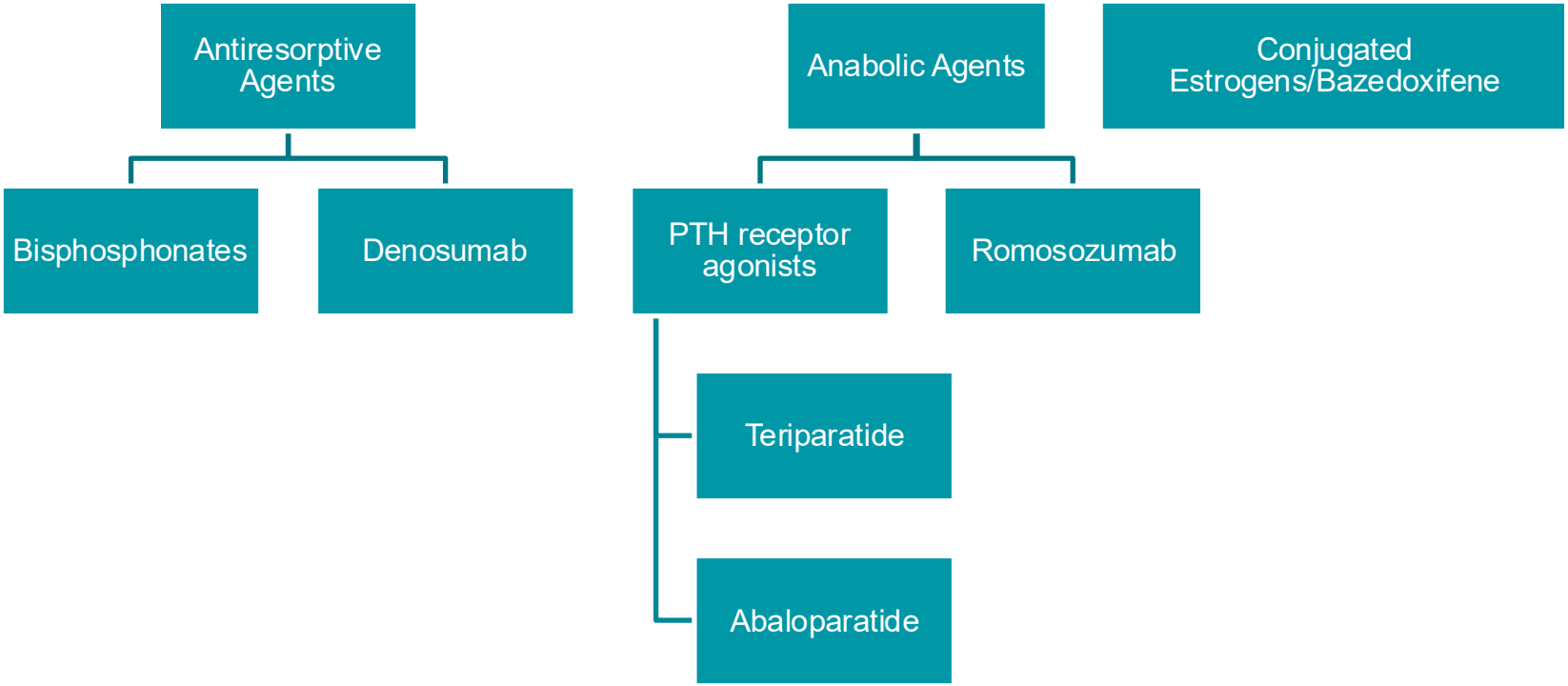




# Who needs pharmacologic therapy?

- Hip or vertebral fragility fracture, regardless of BMD
- T-score ≤ –2.5 at the spine, femoral neck, total hip, or 33% radius
- T-score –1.0 to –2.5 with FRAX ≥20% (major osteoporotic) or ≥3% (hip)
- Osteopenia plus a fragility fracture of the proximal humerus, pelvis, or distal forearm *(AACE)*

# Approach to Pharmacologic Management



# OSTEOCLAST



"The Demo Crew"

- Breaks down old bone
- Resorbs bone tissue
- Makes way for new, healthy bone

I clear out the old so we can build something stronger!

# OSTEOBLAST



"The Build Crew"

- Builds new bone matrix
- Helps mineralize and strengthen bone
- Creates strong, healthy bone

I build it back stronger and healthier!

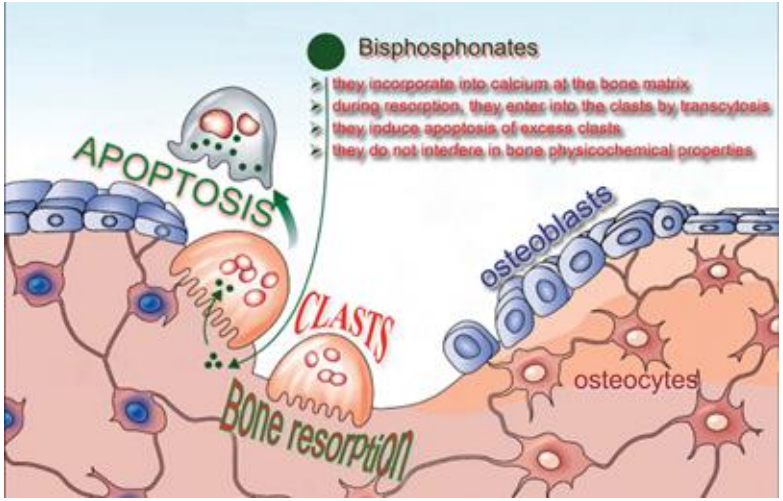
## BONE REMODELING: A TEAM EFFORT

Osteoclasts demo the old. Osteoblasts build the new.
Together, they keep your bones strong! ♥



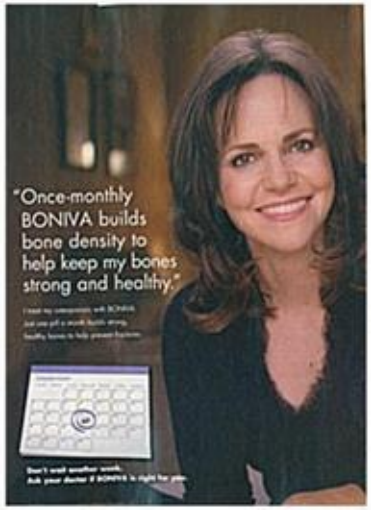
# Bisphosphonates

- Bind avidly to hydroxyapatite crystals in bone at sites of remodeling
- Enter osteoclasts by endocytosis
- Inhibits osteoclast function
- Induces apoptosis of excess osteoclasts
- Unbound drug rapidly excreted by kidney
    - Avoided below CrCl 30-35



# Bisphosphonates

- 4 Bisphosphonates are approved in US for prevention and treatment of osteoporosis:
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronic acid















| Bisphosphonate | Postmenopausal Osteoporosis | Osteoporosis in Men | Glucocorticoid Induced Osteoporosis |
|---|---|---|---|
| Alendronate | x | x | x |
| Ibandronate | x | - | - |
| Risedronate | x | x | x |
| Zoledronic Acid | x | x | x |

| Bisphosphonate | Vertebral Fracture | Non-Vertebral Fracture | Hip Fracture |
|---|---|---|---|
| Alendronate | + | + | + |
| Ibandronate | + | - | - |
| Risedronate | + | + | + |
| Zoledronic Acid | + | + | + |

# Bisphosphonate: Benefits

- Effective protection from fractures
  - Vertebral fractures by 60-70%
  - Multiple vertebral fractures by 75-96%
  - Hip fracture by 40-50% (not ibandronate)
  - Non-vertebral fractures by 20-35% (not ibandronate)
- Fracture risk reduction observed **within 6-12 months** of beginning therapy
- Multiple dosing options (IV, oral, weekly, monthly)
- Generally well tolerated
- Very safe in clinical trials



# Bisphosphonates: Challenges

- Upper GI Intolerance
  - **No evidence in clinical trials (***LO's list Upper GI Irritation)**
  - Strong perception of UGI intolerance limits acceptance and persistence of therapy
  - **How to take it:** fasting, a full glass of water, and staying upright 30–60 minutes.
  - **Contraindications:** esophageal stricture or achalasia, inability to stay upright, and hypocalcemia.
  - **Alternative**: Intravenous administration
    - 30% patients may have acute phase reaction (flu-like syndrome)
- Renal Thresholds
  - Zoledronic acid and alendronate contraindicated when CrCl < 35
  - Risedronate and ibandronate contraindicated when CrCl < 30
- Osteonecrosis of Jaw
- Atypical Femoral Fractures

# Osteonecrosis of the Jaw



- Defined as the presence of exposed bone in the maxillofacial region that did not heal within 8 weeks.
- Incidence unknown
  - Estimated 1/10,000 - 1/250,000 patient years
- Pathogenesis uncertain
- **Recognized association; risk very low at osteoporosis doses.**
- Most reported cases involve **oncology-dose** antiresorptives
- AAOMS 2022: evidence to support or refute a pre-procedure drug holiday remains INCONCLUSIVE



# Bisphosphonates and ONJ



- Risk factors:
  - Most often in patients receiving high dose bisphosphonates for cancer-related bone disease
  - After invasive dental procedures
  - Poor oral hygiene

- **AAOMS 2022 / ADA: for most osteoporosis patients, NO alteration of the dental operative plan is needed. Optimize dental health at the time antiresorptive therapy is started, not by interrupting it later.**

Journal of Bone and Mineral Research
JBMR
ASBMR
The American Society for Bone and Mineral Research

Editorial | Free Access

# Bisphosphonate-Associated Osteonecrosis of the Jaw: Report of a Task Force of the American Society for Bone and Mineral Research**

Sundeep Khosla, David Burr, Jane Cauley, David W Dempster, Peter R Ebeling, Dieter Felsenberg, Robert F Gagel, Vincente Gilsanz, Theresa Guise, ... See all authors

First published: 04 December 2009 | https://doi.org/10.1359/jbmr.0707onj | Cited by: 852

* Drs Koka, McGowan, Mohla, Ruggiero, and Shum state that they have no conflicts of interest. The conflicts for Drs Khosla, Shane, Burr, Cauley, Dempster, Ebeling, Felsenberg, Gagel, Guise, McCauley, McKee, Pendrys, Raisz, Shafer, Silverman, Van Poznak, Watts, and Woo are detailed within the manuscript.

* Published online on July 19, 2007

# Bisphosphonates Atypical Femoral Fractures

- Several small series of cases experiencing unusual lower extremity fractures
  - Younger than average osteoporosis patients
  - Often on other drugs (steroids)
  - Average duration on therapy > 7 years
  - Duration-dependent risk
    - 2/100,000 after 2 years
    - 20/100,000 after 5 years
    - 113/100,000 after 9-10 years
  - Other risk factors: Asian ancestry and femoral bowing
- Atypical femoral fractures
  - Occur after minimal trauma
  - Transverse, non-comminuted fracture
  - Thickened cortices
  - Slow or absent healing
  - **Prodromal thigh or groin pain → image both femurs**



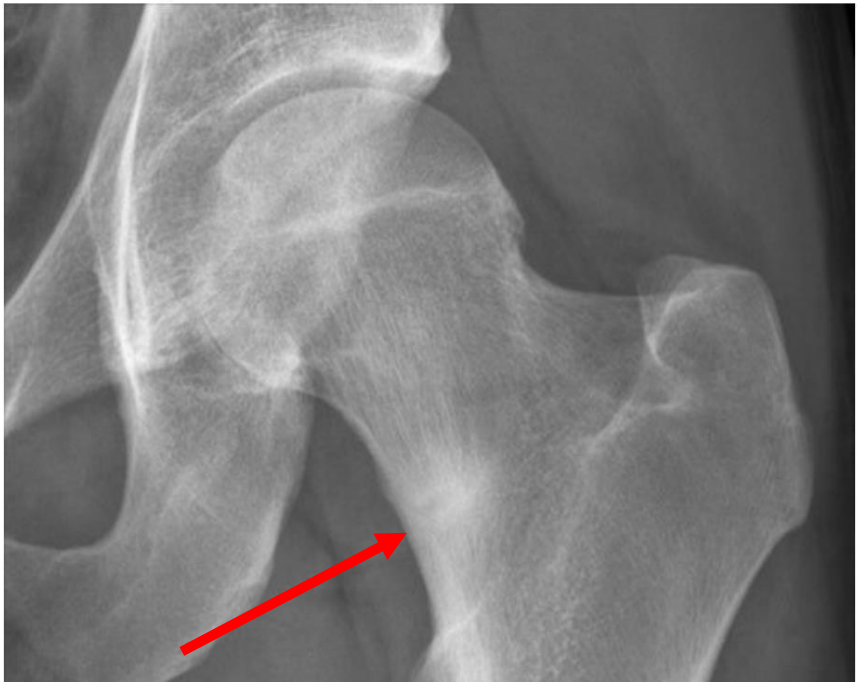
# Looser Zones vs Atypical Femoral Fracture

Looser Zones (Pseudofractures) - Osteomalacia

- Transverse lucencies perpendicular to the cortex with sclerotic margins
- Classic sites: medial femoral neck, pubic rami, ribs, scapula, ulna
- Frequently bilateral and symmetric

Do NOT confuse with atypical femoral fracture (AFF):

- AFF: Lateral femoral cortex, transverse, beaked, focal periosteal thickening



# Looser Zones vs Atypical Femoral Fracture

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Original Article | Free Access

# Incidence of atypical nontraumatic diaphyseal fractures of the femur

Richard M Dell, Annette L Adams, Denise F Greene, Tadashi T Funahashi, Stuart L Silverman, Eric O Eisemon, Hui Zhou, Raoul J Burchette, Susan M Ott

First published: 26 July 2012 | https://doi.org/10.1002/jbmr.1719 | Cited by: 156

# Incidence of Atypical Femoral Fractures

- All femur fractures from 2007-2011 in 1,835,116 patients older than 45
- 142 patients had atypical fractures; of these, 128 had bisphosphonate exposure.
- No significant correlation between duration of use (5.5 ± 3.4 years) and age (69.3 ± 8.6 years) or bone density (*T*-score −2.1 ± 1.0).
- 188,814 patients who had used bisphosphonates.
- Age-adjusted incidence rates for an atypical fracture were 1.78/100,000/year with exposure from 0.1 to 1.9 years, and increased to 113.1/100,000/year with exposure from 8 to 9.9 years.
- Conclusions:
  - Incidence increases with longer duration of bisphosphonate use
  - The rate is much lower than the expected rate of hip fractures in elderly osteoporotic patients.
  - **Patients at risk for osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years.**

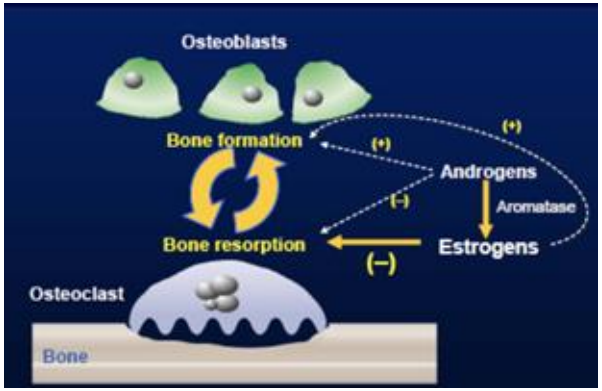
# Bisphosphonate Holiday

- Consider it (not a rule, but an opportunity)
  - After 5 years of oral bisphosphonates
  - After 3 years of intravenous bisphosphonates
- Justification: risk of atypical fracture may decrease, fracture protection wanes slowly
- If drug holiday is instituted, repeat DEXA in 1-2 years
  - If bone density is stable, repeat DEXA in 1-2 years
  - If bone density declines during drug holiday, restart treatment
  - If bone density increases, check DEXA report (osteosclerosis, etc.)
- Keep secondary causes of osteoporosis at forefront of your mind if bone density declines significantly

# Why do bisphosphonates worsen osteomalacia?

- Osteomalacia ≠ osteoporosis.
- Osteomalacia is a mineralization defect
  - Osteoid (bone matrix) is laid down but cannot calcite properly.
  - Bisphosphonates treat osteoporosis (reduced bone quantity with normal mineralization), so usi ng them in osteomalacia targets the wrong problem entirely.
- Bisphosphonates are pyrophosphate analogues that directly inhibit mineralization (which is the problem).
- Bisphosphonates suppress bone turnover, preventing repair of unmineralized osteoid (frozen bone state)
- By suppressing osteoclast activity, bisphosphonates reduce calcium release from bone→ hypocalcemia→ Reduces mineralization.
- **Takeaway: Make sure you have the correct diagnosis before treatment!**

# Impact of Estrogen Deficiency




- Increased cytokine production (IL-1, IL-6, TNFa)
- Increased RANKL production and RANKL expressing cells
  - → Increased recruitment, activation, and life-span of osteoclasts
  - → Increased number and depth of bone resorption cavities
  - → Accelerated bone turnover
- Decreased bone formation (increased osteoblast apoptosis, increased sclerostin)
- Decreased renal tubular calcium reabsorption→ Increased urine calcium loss
- Increased ultrafilterable calcium→ Increased urine calcium loss
- **Remodeling imbalance + High Turnover + Urine calcium loss → Accelerated bone loss**

# HOW ESTROGEN SUPPORTS STRONG BONES

Estrogen helps keep bone remodeling in balance by working with both osteoclasts (the bone breakers) and osteoblasts (the bone builders).

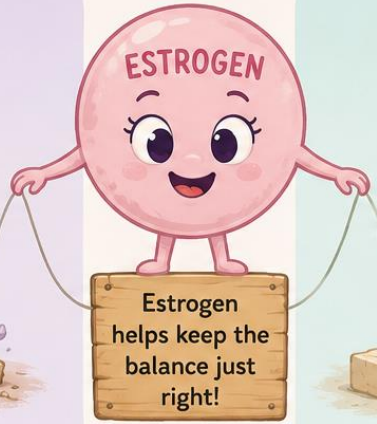
## ESTROGEN & OSTEOCLASTS

(The Bone Breakers)

**Estrogen keeps osteoclasts in check.** It slows down their overactivity so they don't break down too much bone.




Result: Less bone breakdown, less risk of bone loss.




## ESTROGEN & OSTEOBLASTS

(The Bone Builders)

**Estrogen supports osteoblasts.** It helps them build new bone and keeps bones strong and dense.



Result: More bone building, stronger, healthier bones.

### THE BIG PICTURE:

Estrogen keeps bone remodeling in balance—less breakdown, more building.



Balanced remodeling = strong bones for life.

### WHY IT MATTERS:

When estrogen drops (like in menopause), breakdown can speed up and building can slow down—leading to weaker bones and higher fracture risk.

**BOTTOM LINE:** Estrogen is a key protector of your bones by calming the bone breakers and cheering on the bone builders. Keeping your estrogen in a healthy range helps keep your bones strong now and in the future.

# Estrogen for Bone Health

- Indicated in treatment of menopausal symptoms
- Effectively prevents bone loss in postmenopausal women, but not first line therapy for bone health
- Skeletal effects wane quickly upon stopping treatment
  - No long-term skeletal benefits of short-term therapy
- Estrogen reduced risk of fractures in Women's Health Initiative
  - However, effect in women with osteoporosis was not adequately evaluated
- Don't forget about males on aromatase inhibitors (body builders, men who go to testosterone clinics, etc.)-- Men need estrogen for bone health too!

# Selective Estrogen Receptor Modulators

- Molecules that act as estrogens on some tissues, but antiestrogens on others
- Raloxifene
- Bazedoxifene + Estrogen
    - FDA approved for prevention (not treatment) of osteoporosis in combination with estrogen

# Raloxifene

- Only SERM approved by US FDA for osteoporosis treatment
- Estrogen agonist at bone and liver, promoting conservation of BMD
  - Neutral effect at the endometrium and is a potent anti-estrogen at the breast, decreasing breast cancer risk among high risk women
- Skeletal Effects:
  - Decreases vertebral fracture incidence in older osteoporotic women
  - Decreases biochemical markers ~30%
  - 3-year BMD increases of 2-3% at hip and spine
  - *No reduction in hip or nonvertebral fractures*
- Dose: Raloxifene 60mg daily
- Adverse effects: VTE (similar to estrogen), hot flashes, leg cramps

# Bazedoxifene + Estrogen

- New vertebral fracture risk reduction: 42%
- Non-vertebral fracture risk reduction of 52% in high risk subgroup
- Increase in VTE events at all doses, but not statistically significant
- FDA approved combination of conjugated estrogens 0.45mg/Bazedoxifene 20mg (DUAVEE) for vasomotor symptoms and prevention of postmenopausal osteoporosis
- Approved alone in Europe for treatment of osteoporosis

# ACP Guidelines for Osteoporosis (2023)

- Recommends against ERT or HRT for osteoporosis treatment alone
  - ERT/HRT appropriate for VMS and osteoporosis, not for osteoporosis alone
  - Alternative in early postmenopausal women
- Bisphosphonates are first line for women (strong recommendation) and men (conditional).
- Denosumab is second line.
- Anabolic therapy (teriparatide, abaloparatide, romosozumab), followed by a bisphosphonate, for very high-risk women.
- Individualize treatment for women over 65 with osteopenia.

# Denosumab (Prolia)

- Human monoclonal IgG2 antibody that binds to RANKL with very high affinity and specificity
- Administered subcutaneously (60mg) every 6 months






# Denosumab: Benefits

- Skeletal effects: (FREEDOM Study)
  - Reduces spine fractures by 68%
  - Reduces hip fractures by 40%
  - Reduces nonvertebral fractures by 20%
  - Rapid, marked, sustained, reversible reduction in bone turnover
  - FREEDOM Extension Study:
    - BMD in lumbar spine and total hip regions continue to increase out to 6 years
    - Fracture rates remain low or lower than in years 1-3
    - Rates of adverse events and fractures were similar in years 4-6 to that in years 1-3
- **No renal dose adjustment, BUT see 2024 boxed warning (next slide)**
- **Severe hypocalcemia risk much higher in CKD, especially dialysis**

# Denosumab: Adverse events

- Skin Lesions
  - Not related to injection site or timing
  - Increased incidence of eczema and skin rash
  - Increased incidence of serious events related to cellulitis
- **BOXED WARNING (2024): severe hypocalcemia in advanced CKD**
  - **Highest risk on dialysis or with CKD-MBD; see dedicated slide**
  - **Make sure normal vitamin D and calcium before starting (and on supplementation)**
- Very rare cases of ONJ and atypical femur fractures
  - ONJ occurred in patients receiving denosumab 120mg q month in **oncology patients**
  - Very rare cases of atypical femur fractures seen in studies and in clinical practice
    - Of those in clinical practice, most had received bisphosphonates

# Denosumab: FDA Boxed Warning (January 2024)

- **Severe hypocalcemia in patients with advanced CKD**
  - Highest risk: patients on dialysis and those with CKD-mineral and bone disorder (CKD-MBD)
- **In dialysis-dependent women 65+, severe hypocalcemia within 12 weeks occurred in 41% on denosumab vs 2% on oral bisphosphonate**
- Onset typically 2-10 weeks after each injection
- May be asymptomatic, or present with seizures, arrhythmia, tetany, paresthesias, or confusion
- **Before and during therapy:**
  - Assess renal function; correct hypocalcemia and vitamin D deficiency FIRST
  - Ensure adequate calcium and vitamin D (activated vitamin D if CKD-MBD)
  - Check calcium within 2-4 weeks after each dose in CKD, and more often in advanced CKD
- Use in advanced CKD should involve a clinician with CKD-MBD expertise

# Effects of Discontinuing Denosumab

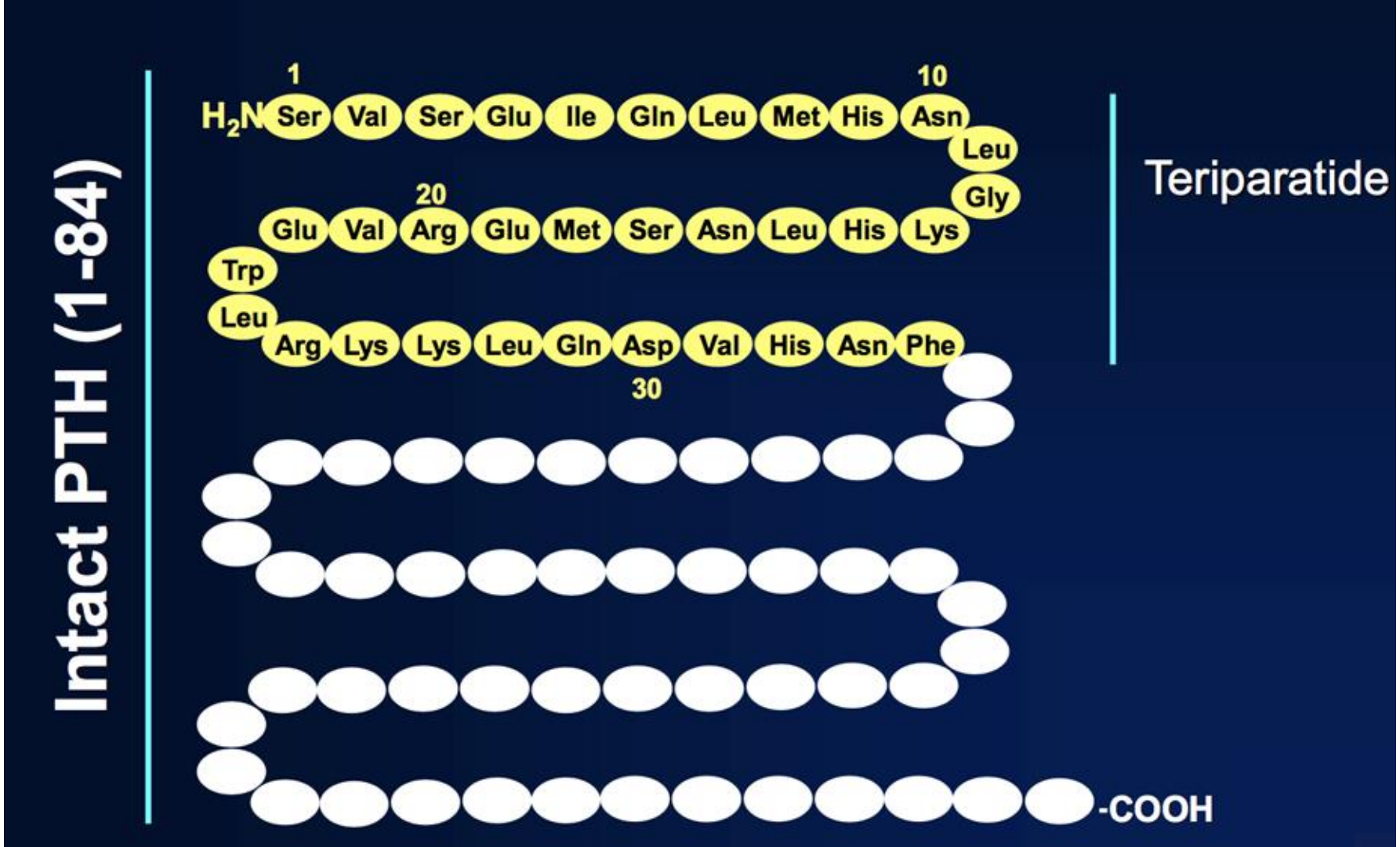
- Postmenopausal women treated with denosumab for 2 years, then treatment stopped:
  - BMD returned to near baseline after 1 year
  - BTMs increased quickly, returning to baseline 2 years after stopping treatment
  - Vertebral fracture risk returns within months of stopping therapy→ Rebound multiple vertebral fractures
- Therefore, no drug holiday recommended unless switching to bisphosphonate and then discontinuing
  - Transition Plan: Start a bisphosphonate (zoledronate) ~6 months after the last dose.

# When to use Denosumab?

- Option for patients:
  - Who are intolerant of other therapies
  - Concerns about GI absorption
  - Advanced CKD (CrCl <30) (once CKD-MBD is excluded)
    - **Correct calcium and vitamin D first, check calcium 2–4 weeks after each dose (boxed warning)
  - Who appear to respond poorly to other therapies

# Parathyroid Hormone

- Osteoporosis is well known to be associated with severe primary hyperparathyroidism
- **Seems counterintuitive that PTH improves BMD and decreases risk of fractures in patients with osteoporosis**
  - Based on constant vs intermittent exposure to PTH
  - Primary Hyperparathyroidism: PTH concentrations are high and vary little throughout the day
  - Administration of low dose PTH as daily pulse injections has been shown to increase BMD
- rh-PTH (1-34)


Intact PTH (1-84)
Teriparatide
1
10
20
30
H2N
Ser Val Ser Glu Ile Gln Leu Met His Asn Leu Gly
Glu Val Arg Glu Met Ser Asn Leu His Lys
Trp Leu
Arg Lys Lys Leu Gln Asp Val His Asn Phe
-COOH

# Abaloparatide/Teriparatide: Benefits

- Skeletal Benefits:
  - Reduction in vertebral fractures (65% for teri, 86% for abalo)
  - Reduction in nonvertebral fractures (53% for teri, 43% for abalo)
  - Effective in women with mild or severe previous fragility fractures
  - Effective in glucocorticoid-induced osteoporosis (teriparatide)
  - Effective in male osteoporosis

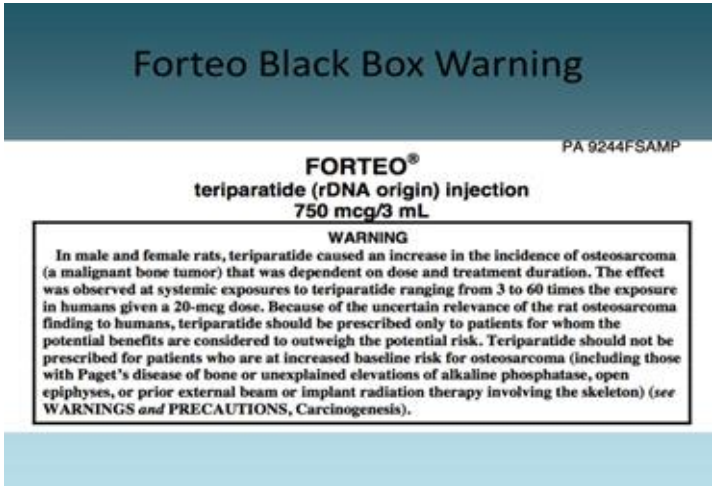


# Abaloparatide/Teriparatide: Limitations

- **2-yr lifetime cap removed from teriparatide label (Nov 2020)**
- Insurance: Generally only approved for individuals who can not use other osteoporosis treatments
- Adverse effects:
  - Hypercalcemia
  - Hypercalciuria
  - Bone pain
  - Orthostatic Hypotension with initial doses
- **Contraindications:**
  - **Patients with conditions with increased risk for osteosarcoma**
    - **Paget disease of bone**
    - **Increased alkaline phosphatase**
    - **Open epiphyses**
    - **Patients who have received radiation therapy involving skeleton**
    - **History of bony mets**
- **Avoid these drugs in hypercalcemia or hyperparathyroidism.**

# Abaloparatide/Teriparatide and Risk of Osteosarcoma?

- Boxed warning REMOVED from the teriparatide label in November 2020
- No oncogenic signals after 15 years of human use worldwide (over 2 million patient exposures)
- Osteosarcoma retained as a warning/precaution, not a boxed warning; abaloparatide followed the same path



# Effects of Discontinuing Abaloparatide/Teriparatide

- Bone loss resumes
- And most, if not all, bone gained may be lost
- **Therefore, recommended that PTH therapy be followed by antiresorptive agent** (maintaining the gain in BMD achieved with PTH administration)

# Romosozumab

- Monoclonal antibody that binds sclerostin (regulatory factor in bone metabolism)
- Sclerostin inhibition increases bone formation (stimulates osteoblasts), and to lesser extent, decreases bone resorption
- Postmenopausal women
- 210mg SC monthly x 12 months (2 injections)
  - Anabolic effect wanes after 12 months
  - Follow with antiresorptive treatment if needed




- No renal dosing adjustment (risk of hypocalcemia)
- Most common AEs: Arthralgias, headaches, hypersensitivity, injection site reactions
- ONJ, AFF

# Romosozumab

**Black Box Warnings**

May increase the risk of MI, stroke, and CV death

Do not initiate in patients who have had an MI or stroke within the preceding year

Consider whether the benefits outweigh the risks in patients with other CV risk factors

If a patient experiences an MI or stroke during therapy, discontinue drug immediately

# Approach to Pharmacologic Management

## Treatment Sequencing: A Key Paradigm Shift

- A major evolution in osteoporosis management is the emphasis on **"anabolic-first" sequencing for very high-risk patients**
- Key principles:
  - Anabolic agents (teriparatide, abaloparatide, romosozumab) must be followed by antiresorptive therapy (bisphosphonate or denosumab) to maintain BMD gains
  - Starting with an anabolic agent before an antiresorptive produces greater BMD gains (especially at the hip) than the reverse sequence
  - Transitioning from denosumab to teriparatide/abaloparatide should be avoided due to transient bone loss; switching from denosumab to romosozumab may prevent this
  - The ASBMR/BHOF 2024 position statement endorses goal-directed (treat-to-target) therapy, using total hip BMD as the most useful treatment target to guide decisions about treatment intensification

# Approach to Osteoporosis

- Diagnose those at highest risk
  - Screening by DXA
  - Assessment of risk by FRAX score
- Exclude secondary causes of low BMD
- Select appropriate treatment
  - Nonpharmacologic
  - Pharmacologic
    - Antiresorptive Agents
      - Bisphosphonates
      - Estrogen, SERMs
      - RANKL Inhibition
    - Anabolic Agents
      - PTH/PTHrP analogs
      - Sclerostin inhibitor.
- **Monitoring of therapy**



# How is treatment monitored?

- Baseline axial (spine and hip) DXA and repeat every 1-2 years until stable
  - Then continue with follow up DXA at a less frequent interval, depending on clinical circumstances
- Monitor serial changes in lumbar spine, total hip, or femoral neck BMD
  - If spine, hip, or both are not evaluable, consider monitoring using 33% radius

# How is treatment monitored?

- Follow up of patients should ideally be conducted in the **same facility with the same machine**
  - Compare BMD (g/cm²), not T-scores
  - A change is real only if it exceeds the facility's **least significant change (LSC),** typically about 3–5%
  - Smaller changes are measurement noise and are not treatment failure
- Consider using bone turnover markers for assessing patient compliance and therapy efficacy (have a specialist help you with this)

# What is successful treatment of osteoporosis?

- Successful treatment of osteoporosis is defined as stable or increasing BMD with no evidence of new fractures or fracture progression
- For patients taking antiresorptive agents, target for treatment success is BTMs at or below the median value for premenopausal women (specialist referral)
- Consider alternative therapy or reassessment for causes of secondary osteoporosis in patients who have recurrent fractures or significant bone loss while on therapy
- A single fracture on therapy is not necessarily evidence of treatment failure, but suggests fracture risk is high

# How long should patients be treated?

- **Teriparatide: 2-yr lifetime cap removed (2020)**
- **Abaloparatide: 2 years**
- **Romosozumab: 12 months**
- **Bisphosphonates**:
  - Oral:
    - Consider “bisphosphonate holiday” after **5 years of stability in moderate-risk patients**
    - Consider “bisphosphonate holiday” after **6-10 years of stability in higher risk patients**
  - IV (Zoledronate):
    - Consider drug holiday after **3 annual doses in mod-risk patients and after 6 annual doses in higher risk patients**
- **Denosumab**: A drug holiday is not recommended
- The ending of the holiday should be based on individual patient circumstances (fracture risk or change in BMD or bone turnover markers)
  - Other therapeutic agents should be continued for as long as clinically appropriate
- **ACP’s Simpler Rule**: Consider stopping after 5 years unless there’s a strong indication to continue.

# Is combination therapy better than treatment with a single agent?

- Until the effect of combination therapy on fracture risk is demonstrated, **AACE does not recommend concomitant use of these osteoporosis agents for prevention or treatment of postmenopausal osteoporosis**
- If estrogen is given for tx of menopausal symptoms or raloxifene is administered to reduce risk of breast cancer, an additional agent such as bisphosphonate, denosumab, or teriparatide may be considered in higher risk patients
- **Combined denosumab and teriparatide achieves a better BMD response vs either agent alone, but no fracture data are available**

# Should sequential use of therapeutic agents be considered?

- **Treatment with abaloparatide/teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy**

# Should vertebral augmentation be considered for compression fractures?

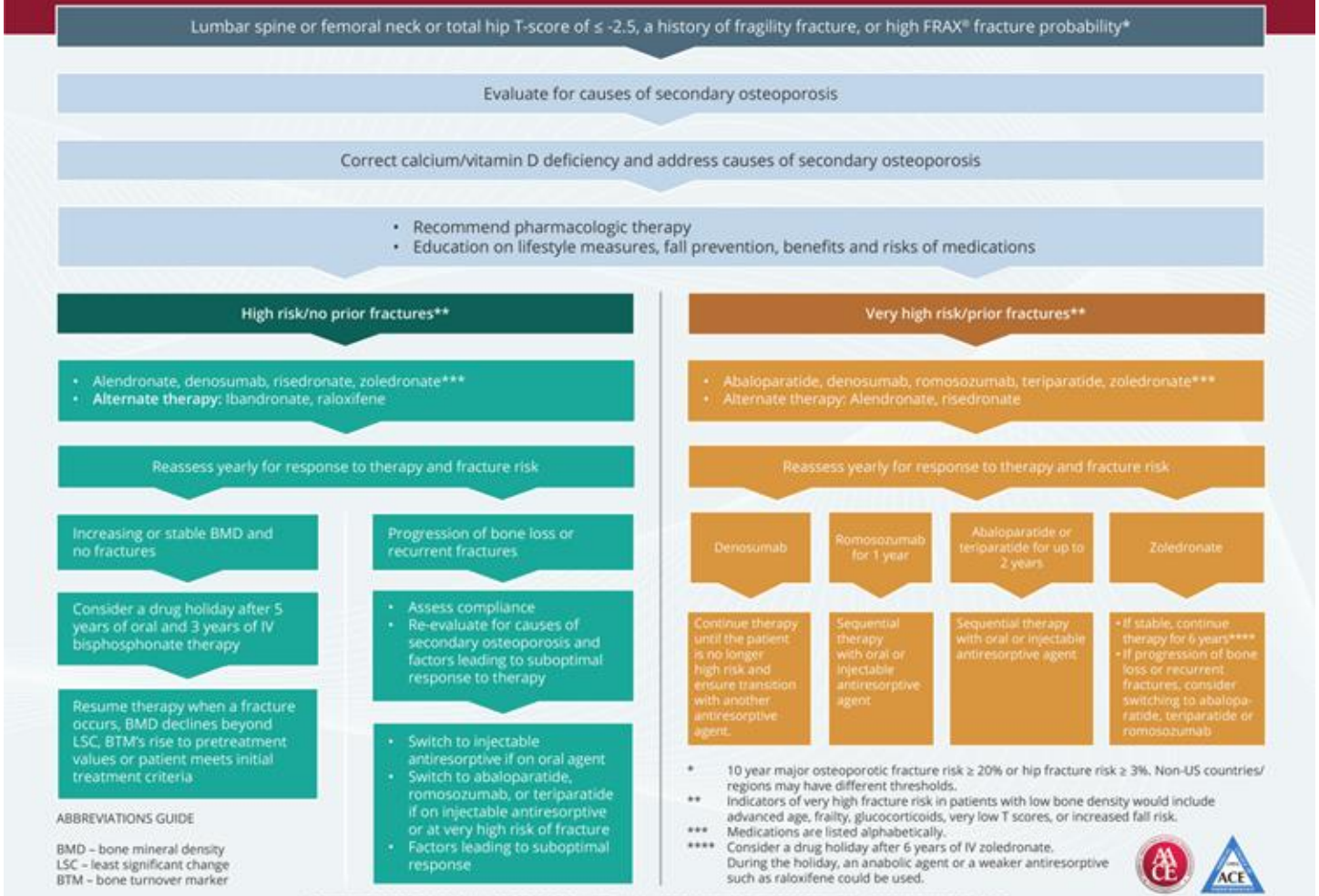
- Vertebroplasty and kyphoplasty are not recommended as first line treatment of vertebral fractures given the unclear benefit on overall pain and the potential risk for vertebral fractures in adjacent vertebrae

# Fracture Liaison Services

**Follow-up and coordination of care**

- ***Most patients with a hip fracture leave the hospital without osteoporosis treatment
- Fracture Liaison Service (FLS): a coordinator identifies fracture patients and makes sure they're evaluated and treated
- Nursing home and frail patients: annual IV zoledronate avoids adherence problems; focus on fall prevention

# AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM




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# References


1. Williams Textbook of Endocrinology
2. Greenspan’s Basic and Clinical Endocrinology
3. Bone Health and Osteoporosis Foundation (BHOF, formerly the National Osteoporosis Foundation) - 2022 Clinician’s Guide
4. American Association of Clinical Endocrinologists
5. Camacho PM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis.
6. Watts NB, Alder RA, Belezikian JP, et al. Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline. Journal of Clin Endo and Metab. 2012 June. 97(6):1802-1822.

# References

7. Tannenbaum C. Yield of Laboratory Testing to Identify Secondary Contributors to Osteoporosis in Otherwise Healthy Women. JCEM. 2002. 87(10):4431-4437.

8. Khosla S, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007 Oct;22(10):1479-91.

9. Dell RM. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res. 2012 Dec;27(12):2544-50.

10. Imaging from Santa Fe Bone Symposium slides