



# Osteoporosis

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**MedNet21**  
Center for Continuing Medical Education

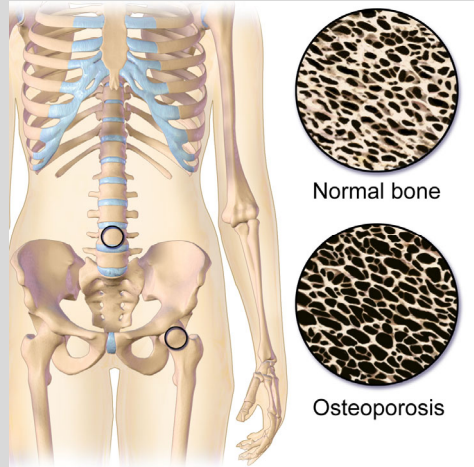
 **THE OHIO STATE UNIVERSITY**  
WEXNER MEDICAL CENTER

## Objectives

- Discuss Basics and Scope of Osteoporosis Problem
- Review Fracture Risk Evaluation including clinical tips

# Osteoporosis - Definition

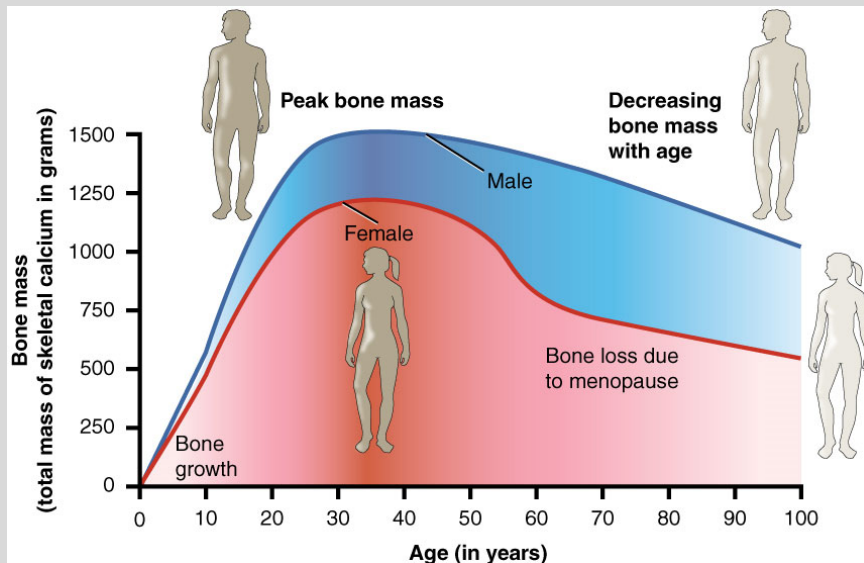
- Disease characterized by:
  - Low bone density
  - Deterioration of bone tissue
  - Disrupted bone microarchitecture
  - Compromised bone strength
  - Predisposing to fracture(s)



Osteoporosis International 2022;33:2049-2102

[https://en.wikipedia.org/wiki/Osteoporosis#/media/File:Osteoporosis\\_Locations.png](https://en.wikipedia.org/wiki/Osteoporosis#/media/File:Osteoporosis_Locations.png)

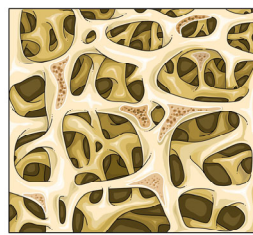
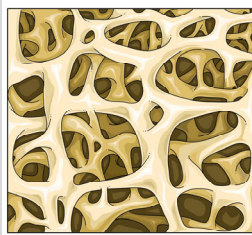
# Bone Mass by Age



[https://en.wikipedia.org/wiki/Osteoporosis#/media/File:615\\_Age\\_and\\_Bone\\_Mass.jpg](https://en.wikipedia.org/wiki/Osteoporosis#/media/File:615_Age_and_Bone_Mass.jpg)

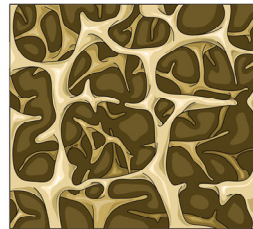
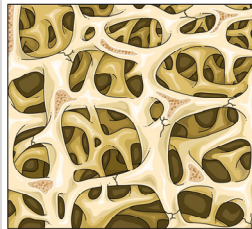
# Disrupted Microarchitecture

Normal Trabecular Bone



Trabecular Bone with Resorption Areas

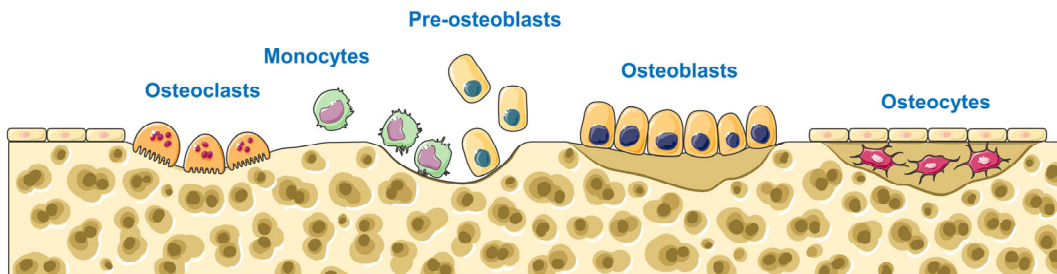
Trabecular Bone with Microcracks



Osteoporotic Trabecular Bone

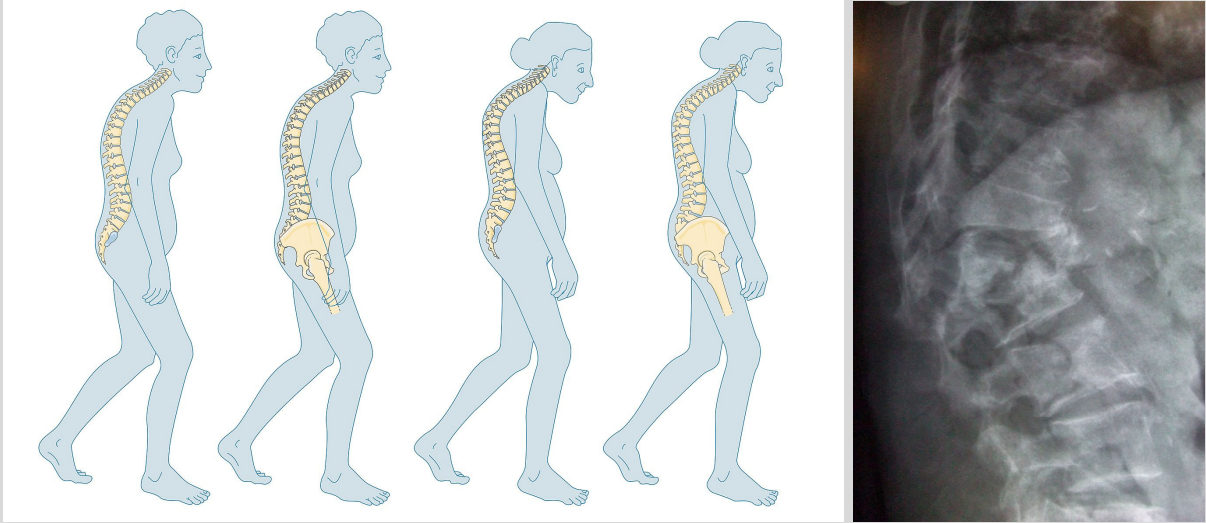
[https://en.wikipedia.org/wiki/Trabecula#/media/File:Spongy\\_bone\\_-\\_Trabecular\\_bone\\_-\\_Normal\\_trabecular\\_bone\\_Trabecular\\_bone\\_etc\\_--\\_Smart-Servier\\_\(cropped\).jpg](https://en.wikipedia.org/wiki/Trabecula#/media/File:Spongy_bone_-_Trabecular_bone_-_Normal_trabecular_bone_Trabecular_bone_etc_--_Smart-Servier_(cropped).jpg)

# Bone Remodeling



[https://en.wikipedia.org/wiki/Bone\\_remodeling#/media/File:Bone\\_regeneration\\_-\\_Bone\\_remodeling\\_cycle\\_III\\_-\\_Osteoclasts\\_Monocytes\\_Pre-osteoblasts\\_etc\\_--\\_Smart-Servier\\_\(cropped\).jpg](https://en.wikipedia.org/wiki/Bone_remodeling#/media/File:Bone_regeneration_-_Bone_remodeling_cycle_III_-_Osteoclasts_Monocytes_Pre-osteoblasts_etc_--_Smart-Servier_(cropped).jpg)

## A View of Osteoporosis



[https://en.wikipedia.org/wiki/Osteoporosis#/media/File:Menopause\\_-\\_Osteoporosis\\_-\\_Smart-Servier\\_\(cropped\).jpg](https://en.wikipedia.org/wiki/Osteoporosis#/media/File:Menopause_-_Osteoporosis_-_Smart-Servier_(cropped).jpg)  
[https://en.wikipedia.org/wiki/Osteoporosis#/media/File:L1\\_2 vertebral fracture.jpg](https://en.wikipedia.org/wiki/Osteoporosis#/media/File:L1_2 vertebral fracture.jpg)

## Scope of the Problem: US

	2010	2020	2030	
Osteoporosis	43.4	12.3	13.6	Millions
Osteopenia	10.2	52.3	57.8	

New osteoporotic fractures 2 million/year; 3.2 million in 2040  
\$95 billion/year by 2040

Wright NC et. al. JBMR 2014;29(11):2520-2526  
Lewiecki EM et al. JBMR Plus 3(9):e10192

## ***Scope of the Problem: Fractures***

<b>Among 1.5 million women in 2005</b>					
Age	Hip	Spine	Wrist	Pelvis	Other
50-64	13,420	57,562	136,624	5,532	159,043
65-74	25,288	85,020	88,072	15,596	84,963
75-84	84,274	142,892	70,317	43,059	105,394
85+	99,771	103,156	31,815	38,469	65,576
Total	222,753	388,630	326,828	102,656	414,976

@ age 50 lifetime fracture risk: 50% women, 20% men

Camacho PM Endocr Pract 2020;26(5):1-46

## ***Indications for BMD Testing***

1. Women  $\geq$  65, men  $\geq$  70
2. Younger postmenopausal women, in menopausal transition, men 50-69 with clinical risk factors
3. Fracture at  $\geq$  50
4. Condition/Medication associated with bone loss  
RA, organ transplant, steroid, AI, ADT

Osteoporosis International 2022;33:2049-2102

## ***Risk Factors for Osteoporotic Fracture***

Increasing age	Female sex	Postmenopause
Premature ovarian failure	Low body weight	White race
Prior fragility fracture	Clinical or morphometric spine fracture	Parental hip fracture
Rheumatoid arthritis	Current smoking	Alcohol ( $\geq 3$ drinks daily)
Low BMD	Vitamin D deficiency	Low calcium intake
Hyperkyphosis	Falls	Immobilization
Chronic steroids, aromatase inhibitors, GnRH agonists, anticonvulsants, chemotherapy		

Ann Intern Med 2023;176:224-238

## ***Risk Factors Included in Fracture Risk Assessment Model: FRAX<sup>®</sup>***

Age	Alcohol ( $\geq 3$ drinks qD)
Femoral neck BMD	BMI
Female sex	Prednisone ( $\geq 5$ mg qD x $>3$ M, [ever])
Parental hip fracture	Prior osteoporotic fracture (including morphometric spine )
Rheumatoid arthritis	Smoking (current)
2 <sup>o</sup> Causes: T1DM, OI, hyperthyroidism, hypogonadism/premature menopause, malnutrition, malabsorption, chronic liver disease	

**Tips: Include this list in clinical notes, in order to re-FRAX after DXA**

Osteoporosis International 2022;33:2049-2102

## Case

54 y.o. White woman  
No personal/parental h/o fracture  
PMH: rheumatoid arthritis  
Med: prednisone 10mg x 1 year  
HbA1c 7.5%  
Soc Hx: no cigarettes/alcohol  
Meets criteria for DXA: RA, pred, DM

Osteoporosis International 2022;33:2049-2102

## ***FRAX Limitations***

- Not all known risk factors are incorporated
  - e.g. falls, family history of non-hip fragility fractures, T2DM, CKD, frailty/multiple comorbidity
- Dose-response not included
  - multiple fractures
  - dose/duration of glucocorticoid
  - cigarettes, alcohol
- Clinical judgment necessary
  - consider patient preferences, cost, safety, and efficacy

Tip: For T2DM, enter “yes” for RA channel or ↓ T-score by 0.5

Tip: For prednisone ≥ 7.5mg qD, ↑ 20% to FRAX risk at hip

## Case

Meets criteria for DXA: RA, pred, DM

FN T-score -2.2; MOF 14%, Hip 2.9%

for high steroid: Add 20% to hip fracture risk:  $2.9\% + 1.2\% = 4.1\%$

Or for DM, ↓ T-score by 0.5: adjusted-FN -2.7: hip fracture risk = **5.5%**

Osteoporosis International 2022;33:2049-2102

## *Osteoporosis: Diagnostic Criteria*

1. Densitometric criteria: T-score  $\leq -2.5$  at lumbar spine, femoral neck, total hip, or distal radius
2. Fragility fracture of spine or hip regardless of BMD
3. Densitometric osteopenia and fragility fracture proximal humerus, pelvis, distal forearm
4. Densitometric osteopenia and high FRAX: Hip  $\geq 3\%$ , MOF  $\geq 20\%$

**Tips: State in clinical notes that Dx of osteoporosis is met based on these criteria, per Clinical Practice Guideline of AACE, NAMS.**

Camacho PM et al. Endocr Pract 2020;26(5):1-46  
Menopause 2021;28(9):973-997



## ***Indications for Spine Imaging***

1. Women  $\geq 65$  and men  $\geq 80$  if T-score  $\leq -1.0$
  2. Men 70-79 if T-score  $\leq -1.5$
  3. Postmenopausal women and men  $\geq 50$  with risks:
    - Fracture age  $\geq 50$
    - Historical height loss  $\geq 1.5$ "
    - Prospective height loss  $\geq 0.8$ "
    - Recent/ongoing glucocorticoid
    - Condition associated with bone loss, e.g. primary hyperparathyroidism
- Lateral spine x-rays or Vertebral Fracture Assessment (VFA)

**Tips: If spine fracture is found, osteoporosis if present (unless during trauma)**

Osteoporosis International 2022;33:2049-2102

## ***Tip: 3 Simple Messages after Fragility Fracture***

1. Likely underlying medical condition - "osteoporosis" - and increases risk for 2<sup>nd</sup> fracture, especially in next 1-2 years
2. Fractures Consequences:
  - Mobility (e.g. permanent use of cane, walker, or wheelchair)
  - Independence (e.g. moving a residential facility)
  - Participation in favorite activities
  - Life (e.g. higher risk of dying prematurely)
- 3. Medications lower the risk of future fractures with regular f/u to PCP or Bone Health specialist

Conley RB, et al. J Bone Miner Res 2020Jan;35(1):36-52

## **BMD T-score Categories**

WHO defined osteoporosis in terms of BMD for white postmenopausal female population.

T-score =  $\frac{\text{BMD of Individual} - (\text{Mean BMD of young adult women})}{\text{SD of BMD in young adult women}}$

SD of BMD in young adult women

BMD Classification	T-score
Normal	T-score $\geq$ -1.0
Osteopenia Low Bone Density	-2.5 < T-score < -1.0
Osteoporosis	T-score $\leq$ -2.5
<b>“Established” or “Severe” Osteoporosis</b>	<b>T-score <math>\leq</math> -2.5 + fragility fracture</b>

**Tip: State “Severe Osteoporosis” in your clinical note!**

JBMR 1994;9:1137-41

## **High vs. Very High-Risk**

High Risk	Very High Risk
Osteoporosis T-score $\leq$ -2.5	Recent fracture (within 12M) Fractures on osteoporosis Rx Multiple fractures Fracture on drug causing skeletal harm, e.g. steroids Very low T-score (< -3.0) Very high FRAX <sup>®</sup> (>30%, >4.5%) High risk for falls, history of injurious fall
Fragility fracture	
FRAX $\geq$ 3%, $\geq$ 20%	

**Tip: State “High” or “Very High Risk” for future fracture in your note**

Camacho PM et al. Endocr Pract 2020;26(5):1-46

## ***ACP & Treatment***

To reduce fracture risk in postmenopausal women and men with osteoporosis

1. Bisphosphonate is first-line
2. Denosumab is second-line
3. For very high risk of fracture, use romosozumab or PTH analogue
  - Very high: recent fracture, prior multiple fracture, multiple risk factors
4. Individualize approach for treatment of osteopenia

Ann Intern Med 2023;176:224-238

## ***May is Osteoporosis Awareness and Prevention Month***

About 54 million Americans have low bone density or osteoporosis!

# Bone Density in Children



## Treatment of Postmenopausal Osteoporosis

**Laura E. Ryan, MD**

*Clinical Associate Professor of Internal Medicine*

*Center for Women's Health*

*Division of Endocrinology, Diabetes and Metabolism*

*The Ohio State University Wexner Medical Center*

## True or False:

I would not start someone directly onto teriparatide or abaloparatide or romosozumab unless they had tried an anti-resorptive such as a bisphosphonate or denosumab:

- a) True
- b) False

## Treatment of Osteoporosis

- Calcium and vitamin D
- Estrogen and SERMs
- Bisphosphonates (alendronate, risedronate, ibandronate)
- RANKL inhibitor (denosumab)
- Anabolic therapy (teriparatide, abaloparatide, romosozumab)
- Physical therapy
  - Also fall prevention, including home safety assessment
- Tobacco cessation

# Calcium and vitamin D

• **NOF and IOM Recs:**

- Calcium:
  - Men 50-70: 1000mg cal/d
  - Women  $\geq$ 50, men  $\geq$ 70 consume 1200mg calcium/d
  - Increasing dietary calcium is preferred over calcium supplements
- Vitamin D recommendations:
  - NOF: adults  $\geq$  50: 800-1000u/d
  - IOM: <70, 600 units/day;  $\geq$ 70 800 units/day
  - Safe upper limit: 4000 units/day
  - Goal:  $\geq$  30ng/mL serum level



Milk 8 oz: 300mg



Yogurt 6oz: 250mg



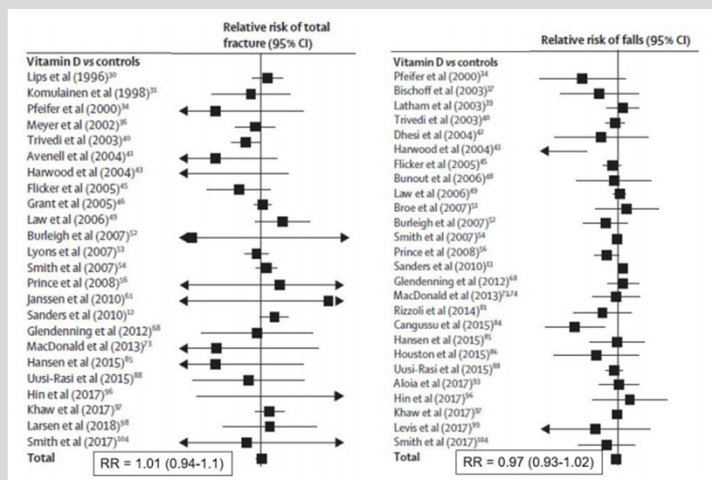
Cheese 1": 150mg

[www.nof.org](http://www.nof.org); Clinician's Guide to Prevention and Treatment of Osteoporosis, updated 6/2022

[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov) Reference intakes for calcium and vitamin D

Giustina A, et al. Controversies in vitamin D: Summary Statement. *J Clin Endocrinol Metab* (2019) 104(2):234-240

## Meta-analysis of trials supplementing vitamin D on total fracture and risk of falls



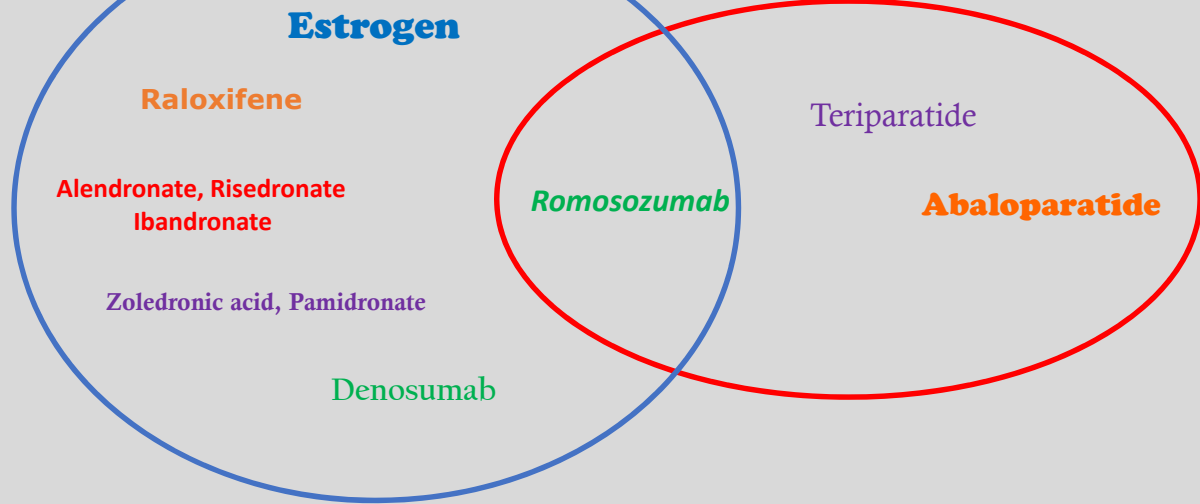
Boland, et al. *Lancet Diabetes Endocrinol* 2018, 6: 847-858

US Preventive Services Task Force: Screening for Vitamin D Deficiency in Adults; Recommendation Statement. *JAMA* April 2021;325(14):1436-1442

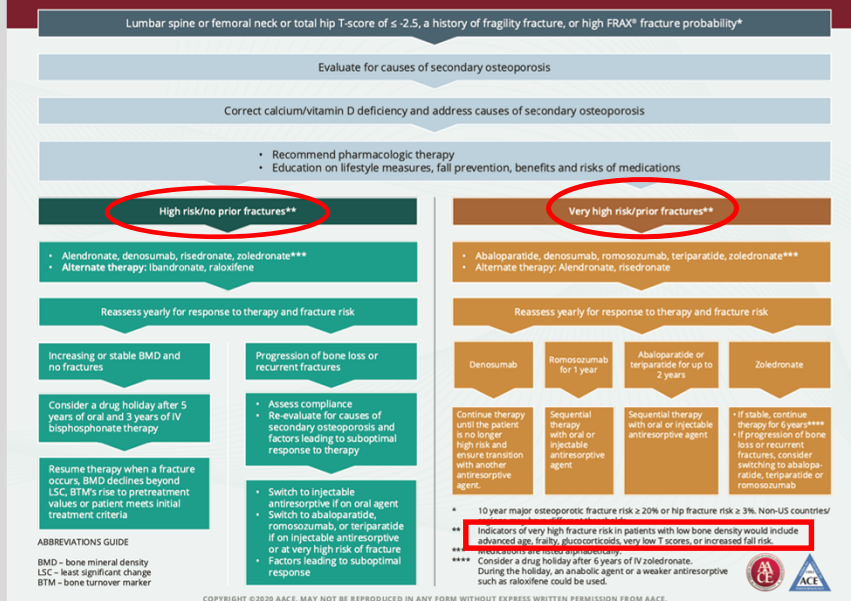
# Treatment of Osteoporosis

Anti-Resorptive Therapy

Anabolic therapy

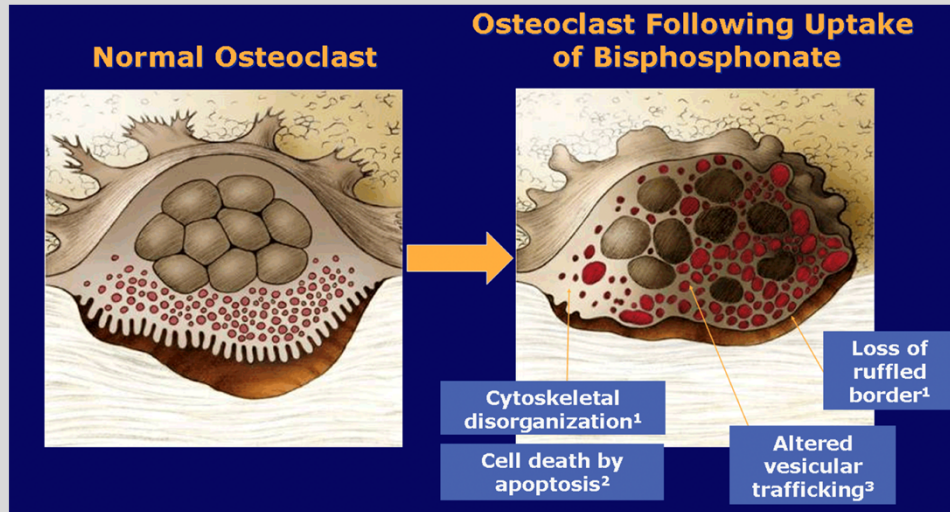


## AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM



Camacho PM, Petak SM, et al. *Endocr Pract* 2020; 26(Suppl 1)

## Effects of bisphosphonates on osteoclast function



Sato M, et al. *J Clin Invest.* 1991;88:2095-2105  
 Hughes DE, et al. *J Bone Miner Res.* 1995;10:1478-1487

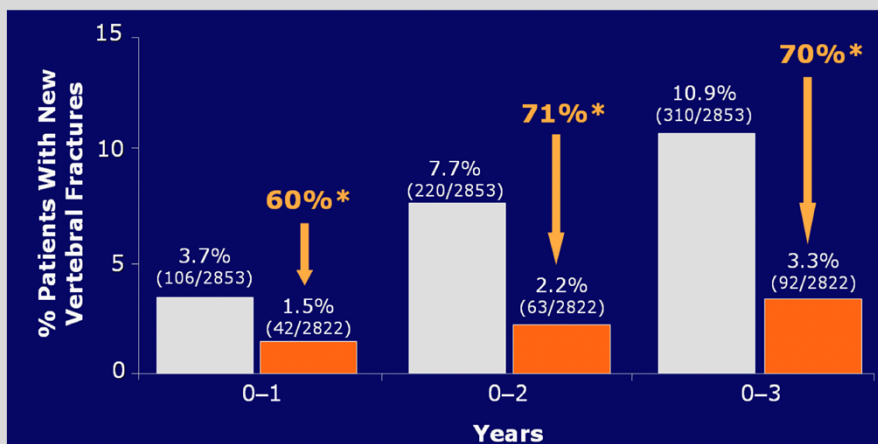
## Continuous increases in Lumbar Spine BMD with alendronate over 10 years

- This placebo controlled trial randomized postmenopausal women to Aln of varying doses vs. placebo, continued for 10 years
- The active alendronate group (10mg daily), showed ongoing improvements in bone density at the lumbar spine over 10years
- The group that received Aln 10mg daily x 5 years then stopped therapy for the next 4-5 years showed:
  - **Stable bone mass at the lumbar spine**
  - **Gradual decline in bone mass at the femoral neck and total hip, but NOT back to baseline**
- This established our understanding of the concept of a drug holiday

Bone HG, Hosking D, Dovogelaer JP, et al. Ten Years' Experience with Alendronate for Osteoporosis in Postmenopausal Women. *N Engl J Med* 2004; 350:1189-1199



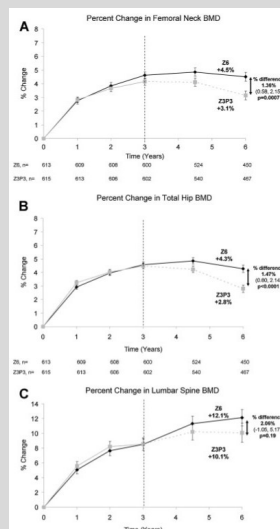
## Zoledronic acid reduces 3-year risk of morphometric vertebral fractures



Black DM, Delmas PD, et al. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis: the HORIZON Pivotal Fracture Trial *N Engl J Med.* 2007; 356:1809-1822

## Zoledronic acid: 3-year risk of hip fractures

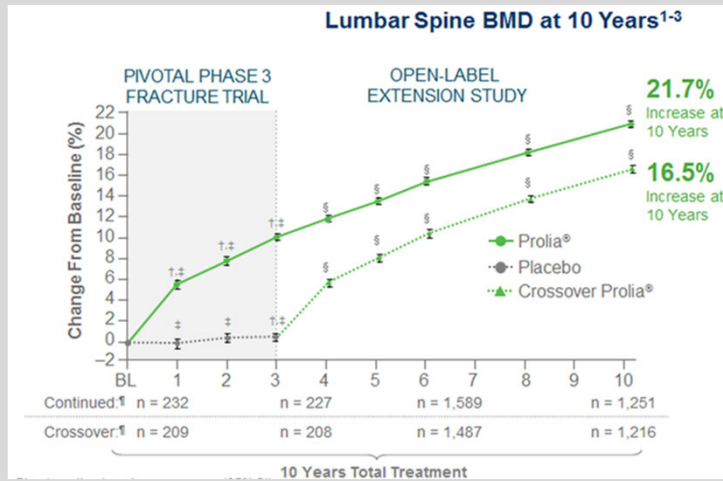
- Annual infusion of Zoledronic acid for 3 years significantly reduced the risk of all types of fractures
- Hip fractures were reduced by 41% over 3 years
- The difference in hip fractures between Zol and placebo became evident as early as 12 months after the first infusion of zoledronic acid



Black DM, Delmas PD, Eastell R, et al. *N Engl J Med.* 2007; 356:18: 1809-1822

Black DM, Reid IR, et al. *J Bone Miner Res* 2012, 27(2):243-254

## Denosumab 10 year Lumbar spine BMD Open-Label Study

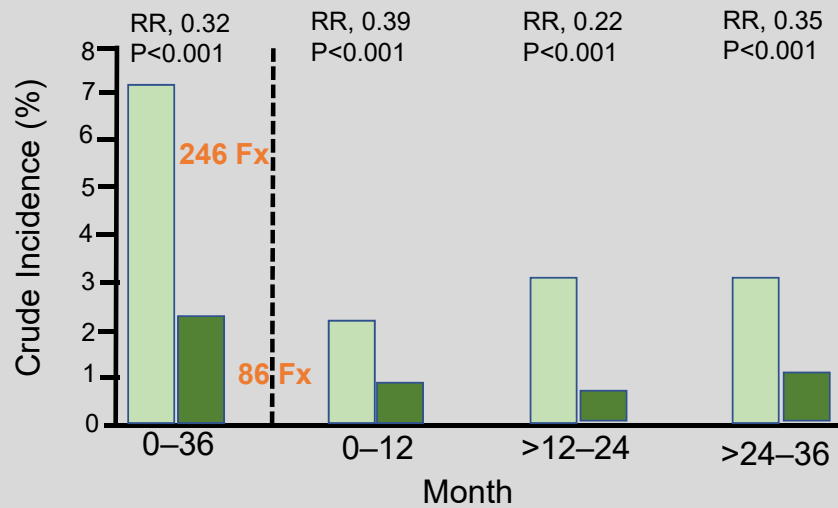


- ONJ: six in the cross-over group; none in the original 3 year trial; 7 cases in the cross over group.
- Atypical Fem Fracture: One in extension and one in cross-over group
- One serious skin infection (erysipelas) in the extension trial

Bone HG, Wagman RB, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: Results from the phase 3 randomized FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol.* 2017;5:513-23

## FREEDOM Trial: Incidence of new Vertebral Fracture

**New Vertebral Fracture**    □ Placebo    ■ Denosumab



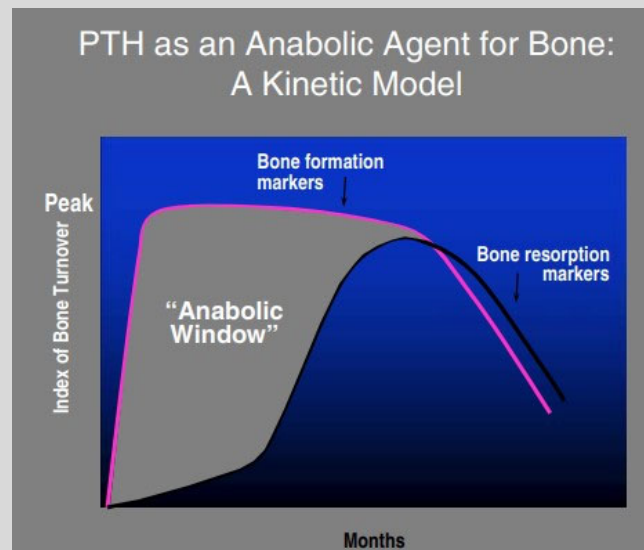
Cummings S et al, NEJM, August 2009, 756 - 765

## Teriparatide (Forteo)

- 1-34 PTH, synthetic
- Anabolic agents – main action is to stimulate osteoblasts
- Daily subcut injection, 20mcg
- Use for two years, then follow with bisphosphonate
- Currently FDA approved for:
  - Postmenopausal osteoporosis
  - Senile or hypogonadal osteoporosis in men
  - Glucocorticoid-induced osteoporosis



## Parathyroid hormone analogues: mechanism



Girotra M, Rubin MR, Bilezikian JP. The use of parathyroid hormone in the treatment of osteoporosis.  
*Rev Endocr Metab Disord* 2006 Jun;7(1-2):113-21

## 64 Year-Old Woman (M H)

**Before PTH(1-34)**

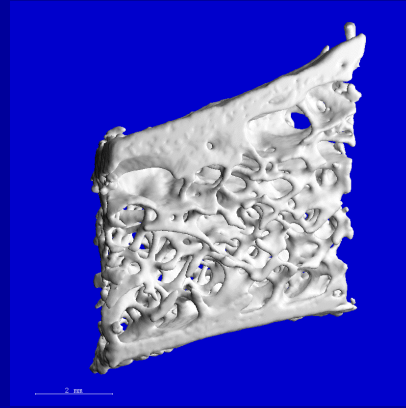
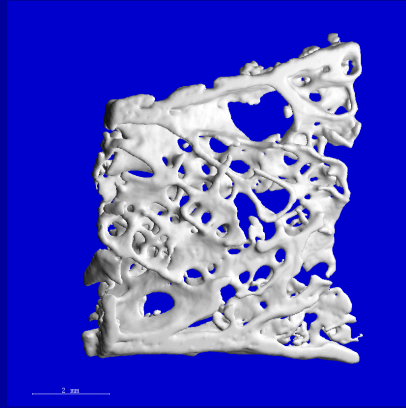
Ct.Th: 0.32 mm

CD: 2.9/mm<sup>3</sup>

**After PTH(1-34)**

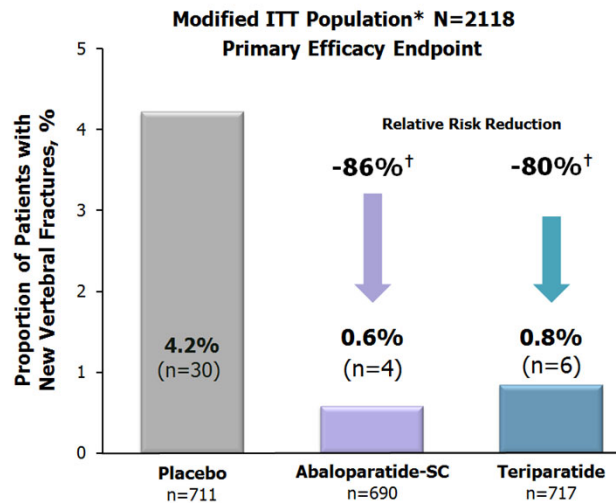
Ct.Th: 0.42 mm

CD: 4.6/mm<sup>3</sup>



3-D Bone biopsy reconstructions used with permission by D. Dempster

## Risk Reduction of New Vertebral Fractures



\*Includes all ITT patients who had pretreatment and postbaseline evaluable radiologic assessments. <sup>†</sup>P < 0.001 vs placebo.

Miller et al. *JAMA*. 2016;316:722-733.

P values were not adjusted for multiple comparisons

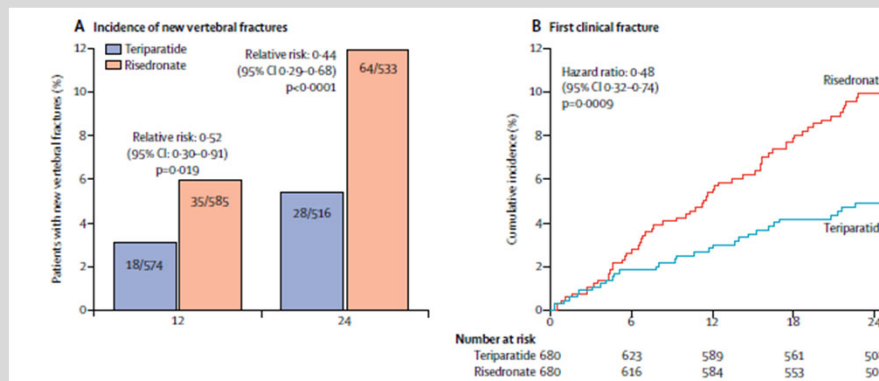
ABLSC-US-01580

Used with permission, Radius Health, Inc

## Anabolic therapy – first line?

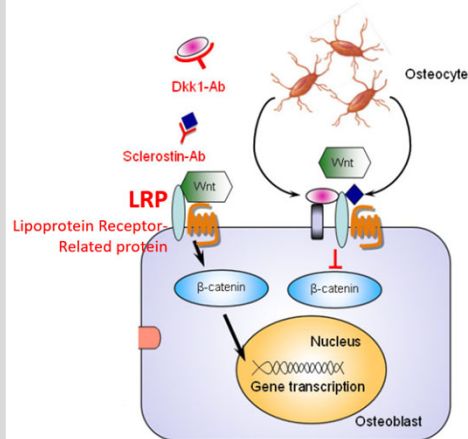
- Expensive, daily subcutaneous route of administration, osteosarcoma
  - Should not be first line for most patients
- But these are the drugs that show fracture prevention (vertebral) earliest (6mo) and most robust increase in bone density at all sites measured in the first month
- Consider using first in severe osteoporosis:
  - T-score  $\leq -3.5$
  - T-score  $\leq -2.5$  + fragility fracture

## Teriparatide versus oral bisphos: Better fracture results VERO Trial results



Kendler DL, Marin F, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a Multicentre, double-blind, double-dummy, randomized controlled trial. *Lancet* 2018;391:230-40

## Romosozumab: Anti-sclerostin antibody



- The binding of Wnt to its receptors induces association with LRP,  $\beta$ -catenin is stabilized and target genes are activated, resulting in osteoblastic formation
- Sclerostin is a circulating inhibitor of the Wnt-signaling pathway, which binds to LRP 5 and 6
- High bone density was seen in nature with an inactivating mutation in the SOST gene which causes formation of sclerostin by osteocytes

McClung MR. Endocrinology and Metabolism, Sept 2015(30): 429-435  
Ng KW, Martin TJ. ASBMR Primer on Metabolic Bone Disease, 8<sup>th</sup> Ed, Ch 56, 461-467

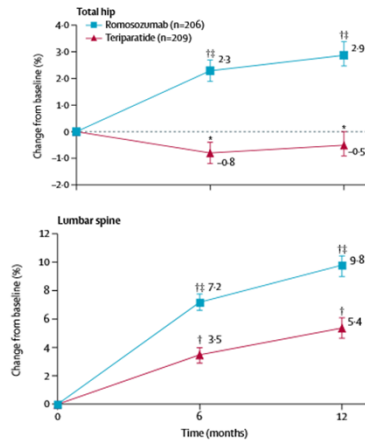
## Romosozumab BMD and Fracture Data

- FRAME: romosozumab vs. placebo in women with PMO, treatment naïve (n=7180) –
  - 73% reduction in Vertebral fracture risk after 12 months on romosozumab
- ARCH: romosozumab vs. alendronate in treatment naïve (n=4093)
  - 50% relative risk reduction of vertebral fractures vs. alendronate
  - 38% RR reduction in hip fractures after 36 months of therapy
- Structure: after 3+ years of bisphosphonates, randomized to romosozumab or teriparatide (n=436)

Cosman F, Crittenden DB, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016; 375:1532-1543  
Saag KG, Petersen J, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; 377:1417-1427

## STRUCTURE Trial:

teriparatide vs. romosozumab after 3+ years of alendronate



- Small study – 218 patients in each group
- “real-life”: transitioning from bisphosphonate therapy
- BMD data – no fracture data

Langdahl BL, Libanati C, et al. Lancet 2017;390:1585-94

## Romosozumab

- FDA approved April 2019
- 210mg (two 105mg injections) monthly in provider’s office x 12 months
- Indicated for treatment of postmenopausal osteoporosis
- Follow with antiresorptive therapy

Evenity (romosozumab-aqqg) package insert, Amgen, 4/2019

- Contraindication: hypocalcemia
- AR: arthralgia, headache most common
- One case each ONJ AFF

**WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH**  
See full prescribing information for complete boxed warning.

- EVENTY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)
- EVENTY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)
- If a patient experiences a myocardial infarction or stroke during therapy, **EVENTY should be discontinued.** (5.1)

# Risks of developing MRONJ

- In cancer patients, where ZA and Dmab are used more frequently, or in those on anti-angiogenesis medications, incidence:

20-100/10,000



[www.aaoms.org/docs/position\\_papers.mronj](http://www.aaoms.org/docs/position_papers.mronj)  
BMJ 2007 Jan 13;334(7584):103

- PMO?
- Oral Bisphosphonates
  - 1-10 cases/10,000 users
  - Up to 21 cases/10,000 when use exceeds 5 years
- IV Bisphosphonates and Denosumab
  - 1.7 cases – 4 cases/10,000 users

**The risk for ONJ among pts treated with ZA or denosumab approximates cases seen in placebo**

# AFF: Radiographs of fractures of the femoral shaft showing the “Simple with Thick Cortices” Pattern

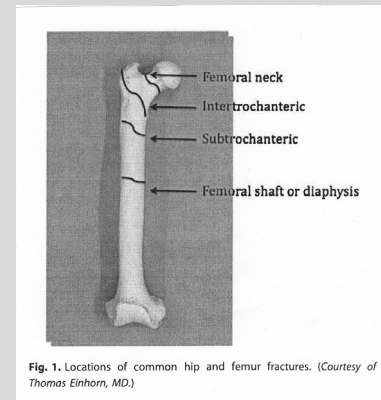


Lenart B et al. N Engl J Med 2008;358:1304-1306



## Atypical Femoral Fractures

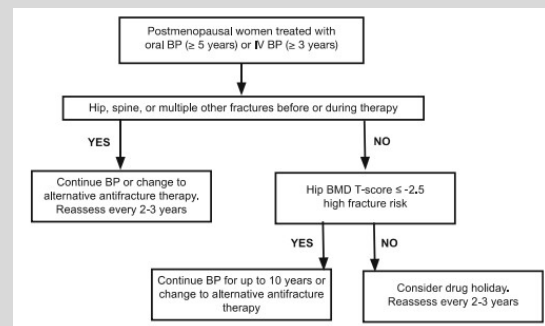
- Most commonly in the proximal 1/3 of femoral shaft
- Usually occur in the setting of no or minimal trauma
- Complete fractures extend through both cortices; incomplete involve only lateral cortex
- ***Often there is a prodrome of pain in the groin or thigh***



Report of a Task Force of the ASBMR:  
Shane E, Burr D, Ebeling PR et al. J of Bone and Miner Res, Nov 2010;25:2267-2294.

## Bisphosphonate holiday

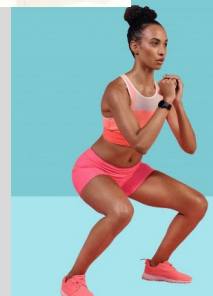
- Temporary suspension of therapy (2-5 years)
- Prolonged skeletal retention of bisphosphonate will confer antifracture benefits
- This may reduce the overall risk of ONJ and/or AFF
- Decisions about timing, time off of therapy, or even whether a holiday is appropriate must be tailored to the individual
- ‘Holiday’ is not appropriate in medications other than bisphosphonates



LeBoff MS, Greenspan SL, et al. 2022 The Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* 33:2049-2102

## Exercise and Osteoporosis

- Weight bearing
  - Walking, jogging, stair climbing
- Resistance training
  - Yoga, pilates
- Weight lifting
  - Has been shown to actively improve bone density
- AVOID: spine flexion
  - Crunches, sit ups, Russian twists



Kemmler W, Shojaa M, et al. Effects of Different Types of Exercise on Bone Mineral Density in Postmenopausal Women: A Systematic Review and Meta-analysis *Calcif Tissue Int.* 2020 Nov;107(5):409-439  
 LeBoff MS, Greenspan SL, etc. The Clinician's guide to prevention and treatment of Osteoporosis. *Osteoporos Int.* 2022 Oct;33(10):2049-2102

## Serial Monitoring

- Spine – significant gains from treatment can usually be seen in one year
  - Hip often takes over 24 months
- See changes (↑ or ↓) in six months with patients on glucocorticoids
  - Can see rapid changes starting or stopping glucocorticoids, aromatase inhibitors and progestin-only birth control
- BHOFF recommends using DXA for monitoring, generally every 2 years, potentially more or less frequently depending upon clinical situation