



Osteoporosis

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Objectives

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

Osteoporosis - Definition

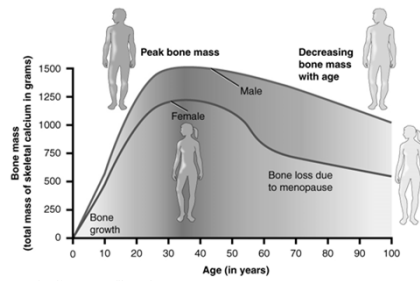
- Disease characterized by:
 - Low bone density
 - Deterioration of bone tissue
 - Disrupted bone microarchitecture
 - Compromised bone strength
 - Predisposing to fracture(s)



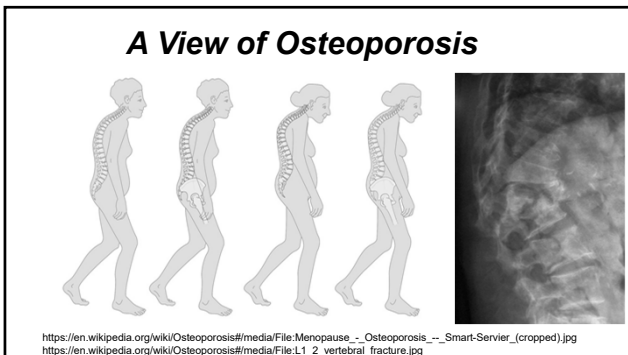
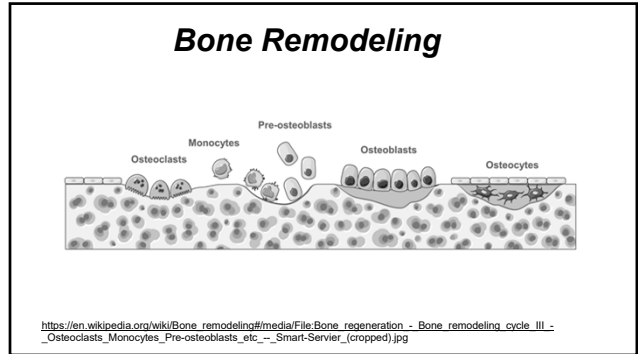
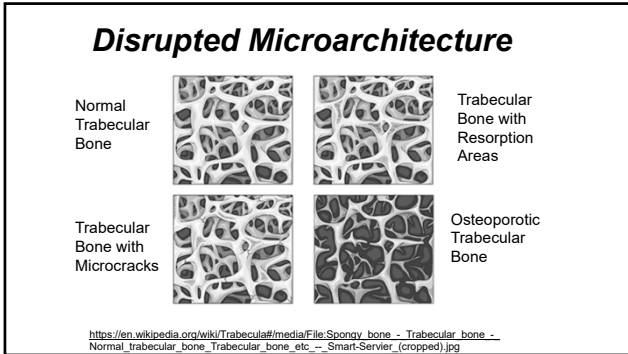
Osteoporosis International 2022;33:2049-2102

https://en.wikipedia.org/wiki/Osteoporosis#/media/File:Osteoporosis_Locations.png

Bone Mass by Age



https://en.wikipedia.org/wiki/Osteoporosis#/media/File:615_Age_and_Bone_Mass.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

Among 1.5 million women in 2005					
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[®]

Age	Alcohol (\geq 3 drinks qD)
Femoral neck BMD	BMI
Female sex	Prednisone (\geq 5mg qD x >3M, [ever])
Parental hip fracture	Prior osteoporotic fracture (including morphometric spine)
Rheumatoid arthritis	Smoking (current)
2 ^o 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 ≤ -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 ≥ 3%, MOF ≥ 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 ≥ 65 and men ≥ 80 if T-score ≤ -1.0
 2. Men 70-79 if T-score ≤ -1.5
 3. Postmenopausal women and men ≥ 50 with risks:
 - Fracture age ≥ 50
 - Historical height loss ≥ 1.5"
 - Prospective height loss ≥ 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 2nd 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 2020;Jan;35(1):36-52

BMD T-score Categories

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

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

BMD Classification	T-score
Normal	T-score ≥ -1.0
Osteopenia Low Bone Density	-2.5 < T-score < -1.0
Osteoporosis	T-score ≤ -2.5
"Established" or "Severe" Osteoporosis	T-score ≤ -2.5 + fragility fracture

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 ≤ -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® (>30%, >4.5%) High risk for falls, history of injurious fall
Fragility fracture	
FRAX ≥3%, ≥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

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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:

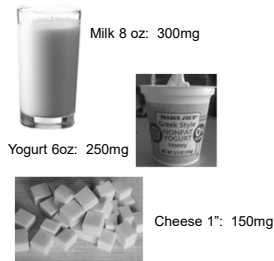
- a) True
- b) False

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

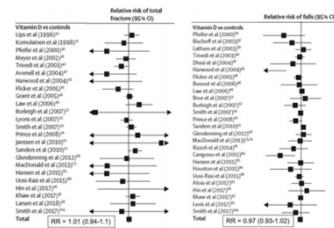
Calcium and vitamin D

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

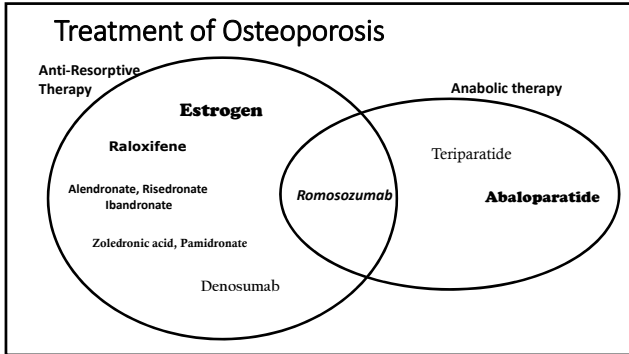


www.nof.org Clinician's Guide to Prevention and Treatment of Osteoporosis, version 10/2022
 Giustina A, et al. Controversies in vitamin D. Summary Statement. J Clin Endocrinol Metab (2019) 104(3):234-240

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



AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Consider spine or femoral neck or total hip T-scores if a history of fragility fracture, or high FRAX fracture probability

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Evaluation on lifestyle measures, fall prevention, benefits and risks of medications

High fracture risk treatment

- 1. Add bisphosphonate treatment (oral or intravenous)
- 2. Add anabolic treatment (teriparatide, abaloparotide)

Very high fracture risk treatment

- 1. Add anabolic treatment (teriparatide, abaloparotide)
- 2. Add bisphosphonate treatment (oral or intravenous)

Reasons justify for regimen to therapy and fracture risk

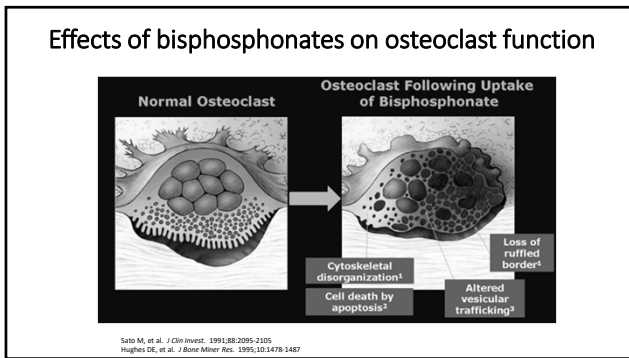
Consider a drug holiday after 3 years of oral bisphosphonate or 2 years of intravenous therapy

Review therapy after 3 years of oral bisphosphonate or 2 years of intravenous therapy to assess if a patient may still need treatment

ADDITIONAL GUIDANCE

Refer to the AACE/ACE 2020 Postmenopausal Osteoporosis Treatment Algorithm for more information on the management of osteoporosis.

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

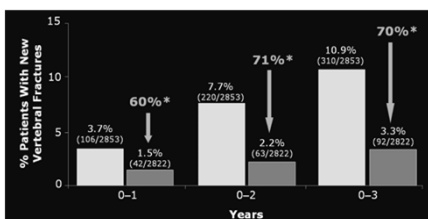


Continuous increases in Lumbar Spine BMD with alendronate over 10 years

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

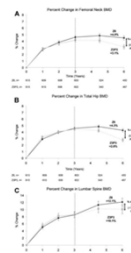
Zoledronic acid reduces 3-year risk of morphometric vertebral fractures



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

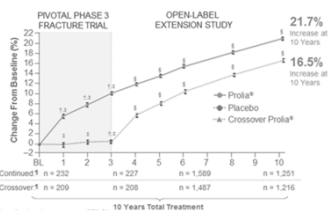


Black DM, Delmas PD, Eastell R, et al. *N Engl J Med.* 2007; 356:18: 1809-1822

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

Denosumab 10 year Lumbar spine BMD Open-Label Study

Lumbar Spine BMD at 10 Years¹⁻³

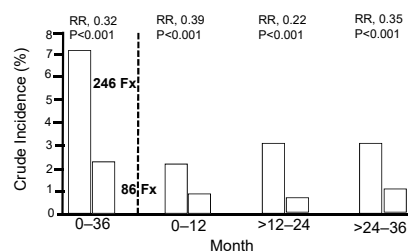


- ONJ: six in the cross-over group; none in the original 3 year trial; 7 cases in the cross over group.
- Atypical Fem Fracture: One in extension and one in cross-over group
- One serious skin infection (erysipelas) in the extension trial

Bone HD, 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;5:513-21

FREEDOM Trial: Incidence of new Vertebral Fracture

New Vertebral Fracture □ Placebo □ Denosumab



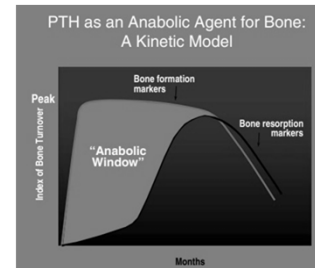
Cummings S et al, NEJM, August 2009, 756 - 765

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



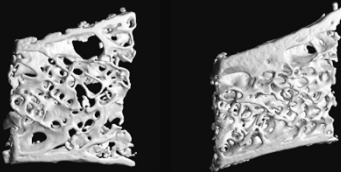
Parathyroid hormone analogues: mechanism



Grotra M, Rubin MR, Bleckman JP. The use of parathyroid hormone in the treatment of osteoporosis. *Am J Med Sci*. 2009;338(1):113-21.

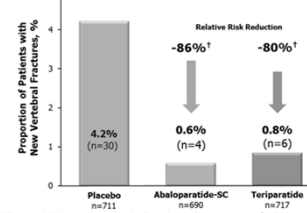
64 Year-Old Woman (M H)

Before PTH(1-34) After PTH(1-34)
 Ct.Th: 0.32 mm Ct.Th: 0.42 mm
 CD: 2.9/mm³ CD: 4.6/mm³



Risk Reduction of New Vertebral Fractures

Modified ITT Population* N=2118
 Primary Efficacy Endpoint



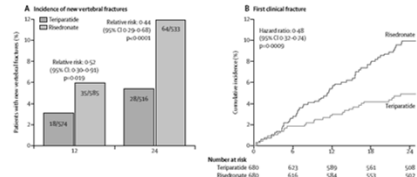
*Includes all ITT patients who had pretreatment and postbaseline evaluable radiologic assessments. †P < 0.001 vs placebo. Miller et al. JAMA. 2016;316:722-731. P values were not adjusted for multiple comparisons. ABISC-05-01580

Used with permission, Radius Health, Inc

Anabolic therapy – first line?

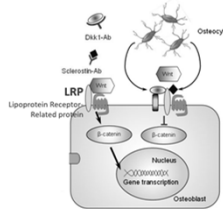
- Expensive, daily subcutaneous route of administration, osteosarcoma
 - Should not be first line for most patients
- But these are the drugs that show fracture prevention (vertebral) earliest (6mo) and most robust increase in bone density at all sites measured in the first month
- Consider using first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

Teriparatide versus oral bisphos: Better fracture results VERO Trial results



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

Romozosumab: Anti-sclerostin antibody



- The binding of Wnt to its receptors induces association with LRP5/6, β -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

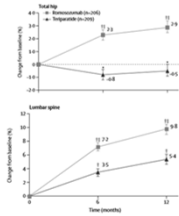
Mitchell MR. *Endocrinology and Metabolism*, Sept 2015(30): 429-435
Ng KY, Martin TJ. *ASBMR Primer on Metabolic Bone Disease*, 8th Ed, Ch 56, 461-467

Romozosumab BMD and Fracture Data

- FRAME: romozosumab vs. placebo in women with PMO, treatment naïve (n=7180) –
 - 73% reduction in Vertebral fracture risk after 12 months on romozosumab
- ARCH: romozosumab 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 romozosumab or teriparatide (n=436)

Cosman F, Crittenden DB, et al. Romozosumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016; 375:1532-1543
Saag KG, Petersen J, et al. Romozosumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 2017; 377:1413-1427

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

Lanquar H, Liberman 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

- 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.

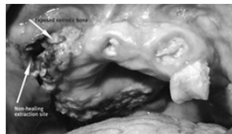
- EVENTY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)
- EVENTY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular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

Eventy (romosozumab) package insert, Amgen, 4/2019

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.aoms.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**

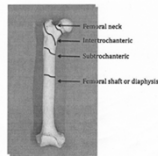
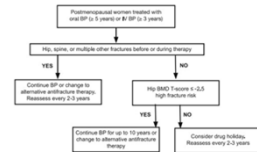


Fig. 1. Locations of common hip and femoral fractures. (Courtesy of Roméo Gohari, MD)

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



Kemmer 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(3):409-439. LeBoff MS, Greenspan SL, et al. 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
- BHOE recommends using DXA for monitoring, generally every 2 years, potentially more or less frequently depending upon clinical situation