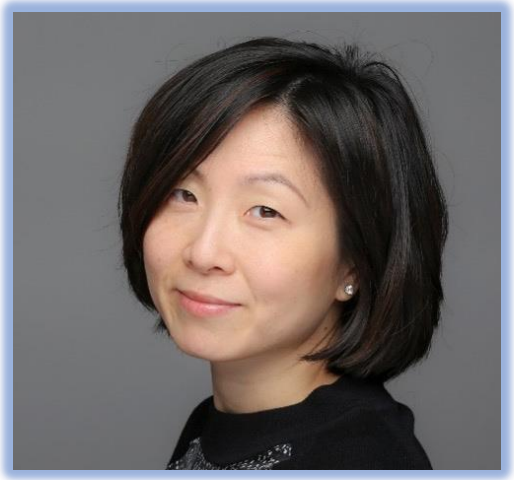
Bothersome Bones: Challenging Osteoporosis Cases

A CSEM Knowledge Transfer Activity

Tuesday, June 18, 2024

7:00 pm ET

Faculty



Dr. Sandra Kim
Women's College Hospital, Toronto, ON
Speaker

Dr. Sabrina Gill
St. Paul's Hospital, Vancouver, BC
Speaker

Dr. Xin Feng
Royal Jubilee Hospital, Victoria, BC
Royal Columbian Hospital, Vancouver, BC
Speaker

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The Ottawa Hospital, Ottawa, ON
Moderator

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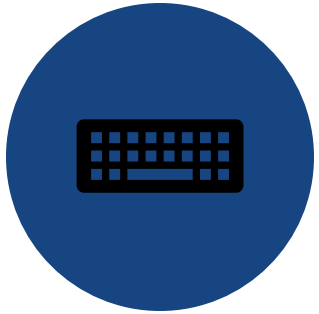

SIGN IN TO SLIDO

PRE-TEST

POST-TEST

REVIEW AND REFLECT

Agenda

7:00 pm	Welcome and Introductions	Dr. Christopher Tran
7:05 pm	Topic #1: Osteoporosis in CKD	Dr. Sandra Kim
7:25 pm	Topic #2: Denosumab transition	Dr. Sandra Kim
7:40 pm	Topic #3: Treatment failure, Sequences of therapy	Dr. Xin Feng
8:00 pm	Topic #4: Premenopausal osteoporosis	Dr. Sabrina Gill
8:25 pm	Q&A	
8:55 pm	Wrap Up	

CONFLICT OF INTEREST DECLARATION – Dr. Christopher Tran

I **DO/DO NOT** have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria		
Membership on advisory boards or speakers' bureaus		
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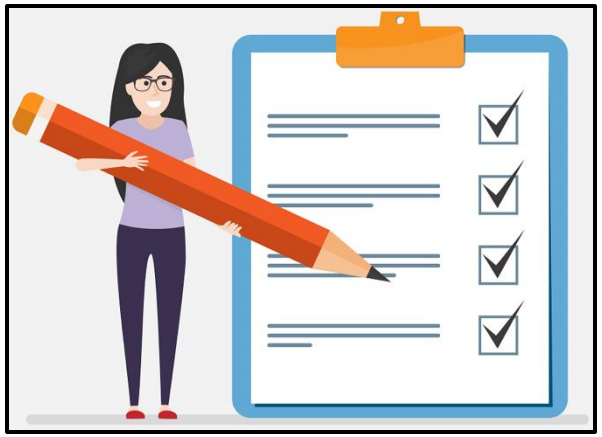
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

Learning Objectives

- Incorporate guidelines, investigations, and fracture risk to **individualize management of osteoporosis in chronic kidney disease**
- Formulate an approach to "treatment order matters", including **key considerations when transitioning off denosumab** and when **switching between anabolic to anti-resorptive therapies**
- Define osteoporosis pharmacotherapy **treatment failure** and review the evidence for **when to repeat BMD after treatment initiation**
- Describe an approach to **premenopausal osteoporosis**, including **pregnancy and lactation-associated** osteoporosis



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Pre-Test Question #1: Osteoporosis in CKD

Incorporate guidelines, investigations, and fracture risk to **individualize management** of **osteoporosis in chronic kidney disease**

Pre-test Question #1

- According to 2017 KDIGO guidelines for assessment and management of fracture risk in CKD-MBD, which of the following is **TRUE**?

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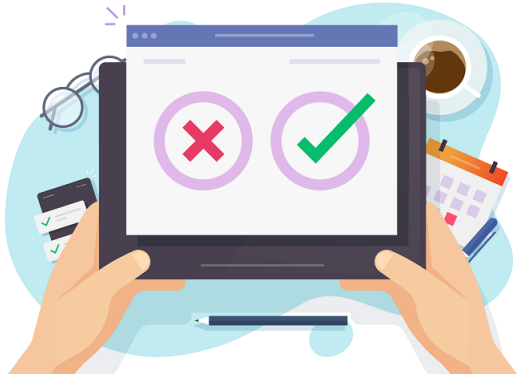
A) BMD cannot be used in advanced CKD (eGFR < 45) to assess fracture risk, if there are biochemical abnormalities of CKD-MBD

B) Osteoporosis treatment can be used in stage 3 CKD (eGFR >30), if no biochemical abnormalities of CKD-MBD

C) Bone biopsy to assess for underlying renal osteodystrophy should be done prior to initiating osteoporosis treatment in stage 4-5 CKD (eGFR <30)

D) None of the above



KDIGO: Kidney Disease Improving Global Outcomes
CKD-MBD: Chronic Kidney Disease - Mineral and Bone Disorder

Ketteler, Kidney Int 2017

Case 1: Osteoporosis in CKD

- 84-year-old female, recurrent fragility fractures (both wrists, humerus, pelvis)
- Presents with new forearm fracture
- CKD Stage 3b/4 (eGFR 25-34)
- Remote short-term bisphosphonate use in her 60s
- Meds: pravastatin, amlodipine, candesartan, vitamin D 1000 IU daily
- BMI 20
- Bone mineral density:

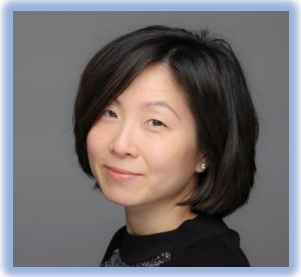
L-spine	**–1.1**
L fem neck	**–3.9**
L total hip	**–4.6**

Questions:

- **How do you assess osteoporosis versus renal bone disorders in CKD?**
- **Would you treat her with osteoporosis medication? If so, with what agent?**

Osteoporosis in Chronic Kidney Disease

Incorporate guidelines, investigations, and fracture risk to **individualize management** of **osteoporosis in chronic kidney disease**



CONFLICT OF INTEREST DECLARATION – Dr. Sandra Kim

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Any direct financial payments including receipt of honoraria	Non-profit organizations: • Osteoporosis Canada • AMEQ, Pri-Med Canada, CSEM	• Volunteer (SAC, Guidelines work) • Speaker honoraria
Membership on advisory boards or speakers' bureaus		
Funded grants or clinical trials		
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

Stages of CKD

GFR categories (ml/min/1.73 m^2), description and range			
	G1	Normal or high	≥90
	G2	Mildly decreased	60–89
	G3a	Mildly to moderately decreased	45–59
	G3b	Moderately to severely decreased	30–44
	G4	Severely decreased	15–29
	G5	Kidney failure	<15

Early CKD Stage 2

- Age-related / older patients
- Normal PO_4, PTH, ALP

CKD Stage 3

- 3a: GFR 45-59
- 3b: GFR 30-44
  - ↑ FGF-23 with ↓ GFR (prior to ↑ PTH)

Late Stage 4-5 CKD (eGFR < 30)

- Abnormal Ca, PO_4, PTH, 25OHVitD
- Mineral and Bone Disorder (MBD)
- Renal osteodystrophy

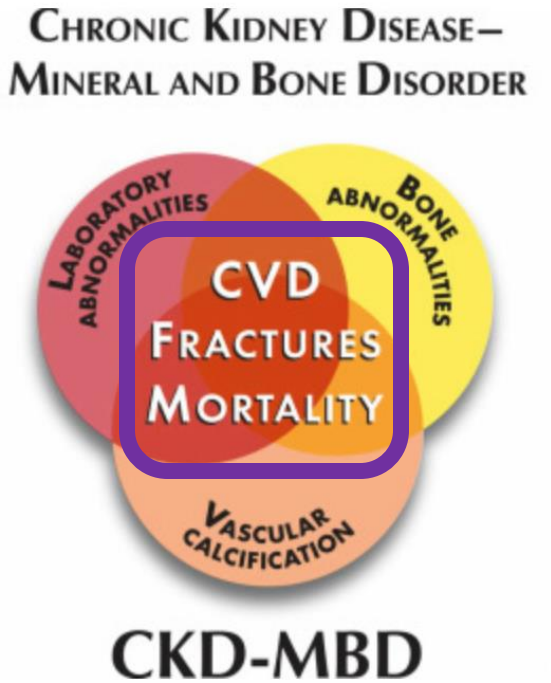
Ketteler, Kidney Int 2017

CKD-MBD (Mineral and Bone Disorder)

- Different from previously recognized "renal osteodystrophy"
- **Systemic disorder** of mineral and bone metabolism due to CKD
- Manifested by one or combination of the following:

LAB abnormalities

Ca, PO_4, PTH
Vitamin D, (FGF-23)



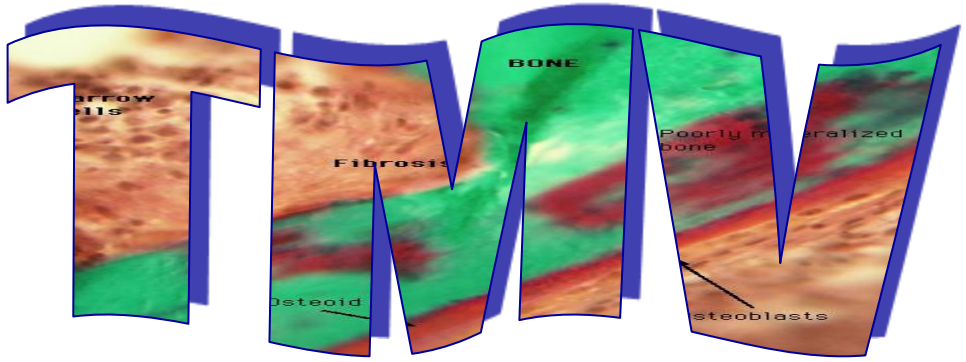
BONE abnormalities in turnover, mineralization, volume, linear growth or strength

Vascular or Extraskeletal Calcification

Moe, Kidney Int 2006

Renal Osteodystrophy: Classification

- Alteration of bone morphology in CKD-MBD
- Quantifiable by histomorphometry on bone biopsy
- Usually late stages of CKD (e.g. stage 4-5)



Turnover	Mineralization	Volume (mass)
High	Normal	High
Normal	Abnormal	Normal
Low		Low

Major Types

Osteitis fibrosa cystica

- High bone turnover
- Due to secondary ↑ PTH

Adynamic bone disease

- Low bone turnover

Osteomalacia

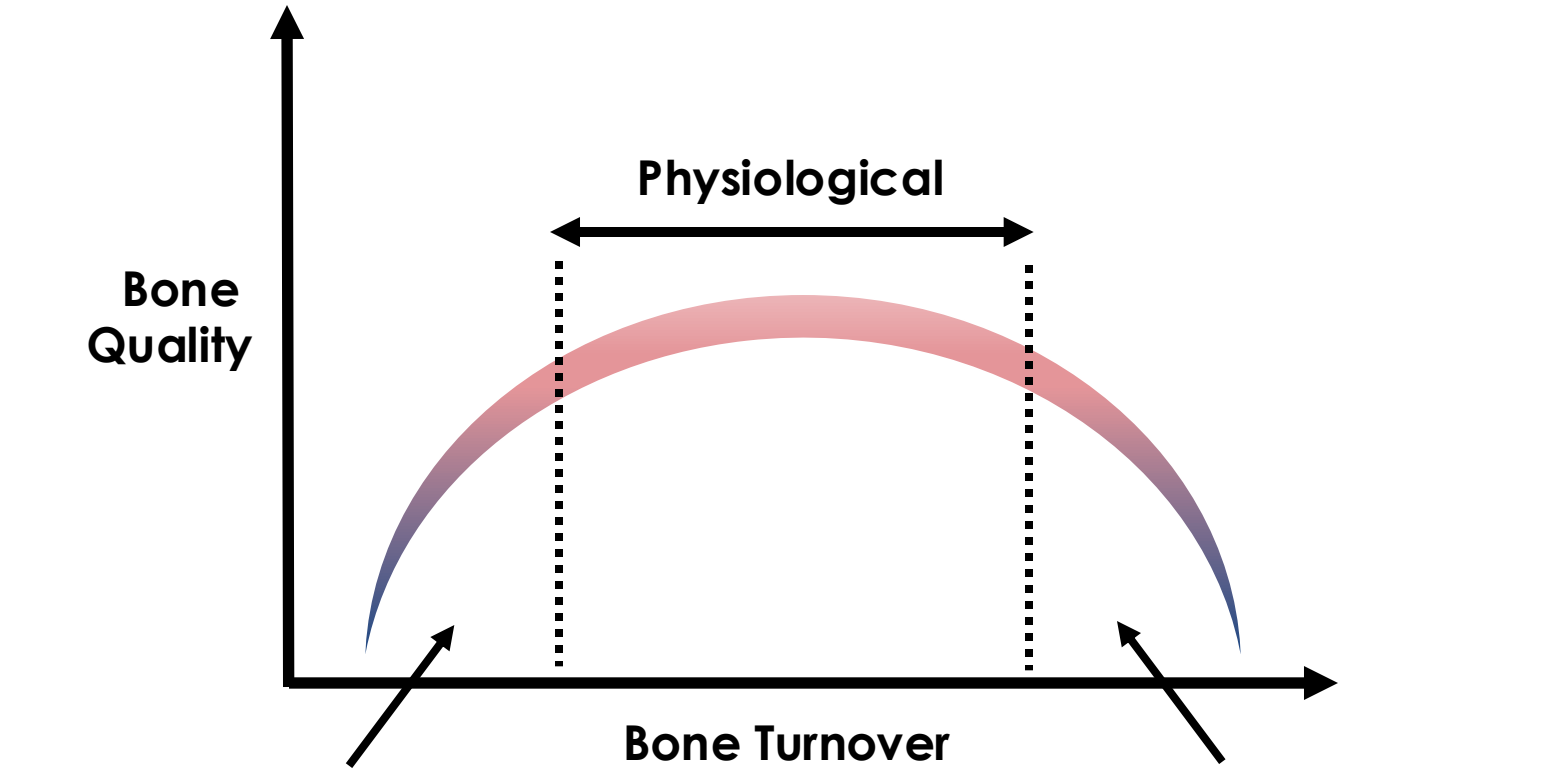
- Abnormal mineralization

Mixed uremic osteodystrophy

- Variable bone turnover
- Abnormal mineralization

Moe, Kidney Int 2006

Renal Bone Disease: May Have Altered Bone Turnover



Biomarkers for Bone Turnover

PTH

- > 2-9x ULN: suggests high turnover
- > 9x ULN: high specificity for high turnover

ALP and bsALP

- Biomarkers of bone formation
- Not affected by eGFR
- ↓ bsALP consistently associated with low bone turnover

C-telopeptide, N-telopeptide

- Associated with high turnover
- However, affected by renal clearance
- Unclear if cleared by dialysis

Hampson, Endocrine 2021; Ginsberg, Am J Kidney Dis 2022

Osteoporosis versus CKD-MBD

- Difficult to diagnose osteoporosis in advanced CKD
  - May coexist with CKD-MBD or renal osteodystrophy
- All spectrums of renal bone disease increase fracture risk
  - But etiology and management may be different
- CKD: independent risk factor for fracture
  - Likely multifactorial
  - ↑ 2.5x hip fracture (↑ 5x on dialysis)
  - ↑ fracture-related mortality with severity of CKD
- FRAX risk does not account for eGFR
  - Proposal: consider doubling absolute fracture risk if CKD Stage 3b-5

Coco, Am J Kidney Dis 2000, Ensrud, Arch Int Med 2007
Pimental, Kidney Int 2017; Hampson, Endocrine 2021; Ginsberg, Am J Kidney Dis 2022

Bone Density by DXA in CKD

KDIGO 2017

Multiple new prospective studies: Lower DXA BMD predicts incident fractures in CKD G3a-G5D

3.2.1. In patients with **CKD G3a-G5D** with **evidence of CKD-MBD, and/or risk factors for osteoporosis**, we **suggest BMD testing** to assess fracture risk **if results will impact treatment decisions (2B)**

Limitations:

- No info on bone turnover
- No info on bone mineralization
- Does not directly assess microarchitecture
  - Cannot distinguish cortical vs trabecular bone
- Cannot distinguish osteoporosis from renal bone disease

Nickolas, J Am Soc Nephrol 2010; Ketteler, Kidney Int 2017; KDIGO, Kidney Int Supp 2017

Diagnosing Osteoporosis in CKD

CKD Stage 1-3 (eGFR > 30)

- Renal bone disease is less common
- Can use WHO T-score -2.5
- Can apply FRAX to assess fracture risk
  - As long as **no biochemistry abnormalities** suggesting CKD-MBD

CKD Stage 4-5 (eGFR < 30)

- CKD-MBD and renal osteodystrophy become more prevalent and profound
- **Cannot** apply BMD WHO criteria
- **Cannot** apply FRAX
- Need to exclude CKD-MBD (including renal osteodystrophy)
  - Labs: Ca, PO_4, PTH, bsALP, VitD
  - Bone biopsy may be considered

Isakova, Am J Kidney Dis 2017; Ketteler, Kidney Int 2017; KDIGO, Kidney Int Supp 2017

Bone Biopsy: Gold Standard for Ruling out Renal Bone Disease

KDIGO 2017

Growing experience with osteoporosis medications in CKD, low BMD, and high risk for fracture

Inability to perform bone biopsy may not justify withholding antiresorptive therapy from patients with high fracture risk

3.2.2. In patients with **CKD G3a-G5D**, it is **reasonable to perform a bone biopsy if** knowledge of the **type of renal osteodystrophy** will **impact treatment decisions** (not graded)

Limitations:

- Invasive, specialized expertise, costly, "fluid"

When uncertain if underlying adynamic bone disease:

- bsALP > median reference range or high: adynamic bone disease very unlikely
- Low PTH: strongly correlates with adynamic bone disease

Isakova, Am J Kidney Dis 2017; Ketteler, Kidney Int 2017

Treatment of Osteoporosis in CKD

CKD Stage 1-3 (eGFR > 30)

Same as for osteoporosis without CKD, IF no evidence for CKD-MBD

If abnormal biochemistry of CKD-MBD:

- Manage secondary ↑ PTH and mineral metabolism prior to considering osteoporosis drug
  - Prevent renal osteodystrophy
  - Control secondary hyperparathyroidism
  - Avoid over-suppression of PTH (risk of adynamic bone disease)
  - Manage acidosis, vitamin D deficiency

CKD Stage 4-5 (eGFR < 30)

- If no history of fragility fracture, no treatment is recommended
- If high risk based on fractures (not BMD alone), AND excluded renal bone disease (labs or biopsy), then may consider pharmacotherapy
- If GFR <15, consider bone biopsy
  - Only treat if clearly high risk of mortality from recurrent fracture
- Must always rule out adynamic bone disease
  - Linked to increased vascular calcification
  - Unlikely if ↑ bsALP and ↑ PTH

Miller, Semin Nephrol (2009); NOF. Osteoporosis and CKD Updates (2010); Ginsberg, Am J Kidney Dis 2022

Treatment of Osteoporosis in CKD

- Data for fracture risk reduction in CKD (up to stage 3/4):
  from post-hoc secondary analyses
  of pivotal osteoporosis drug trials
  with **no evidence of CKD-MBD**

- Bisphosphonates
- Denosumab
- Teriparatide
- Raloxifene

Miller, Semin Nephrol (2009); Ginsberg, Am J Kidney Dis 2022

North American / European Labelling: Bisphosphonates

- **Oral bisphosphonates:** not recommended if GFR < 30 (Stage 4-5)
- **IV zoledronic acid:** not recommended if GFR < 35

- Bisphosphonate data in CKD:
  - Post-hoc analyses, otherwise healthy women, short-term duration
  - Bisphosphonate retention in bone over time with low GFR is unknown
    - Excreted by kidneys; expect longer bone retention in CKD

- Low dose oral bisphosphonate has been suggested when GFR <30
  - Expert opinion / controversial

Miller, Semin Nephrol (2009); Eveneopeol, Nephrology Dialysis Transplantation 2021
Hampson, Endocrine 2021; Ginsberg, Am J Kidney Dis 2022

Caution with denosumab in CKD

- Not cleared by kidneys (benefit)
- Limited experience in advanced CKD (GFR <30)

- Potent anti-resorptive, risk of profound suppression of bone turnover
- Risk of symptomatic hypocalcemia
  - Especially with vitamin D insufficiency and/or inadequate calcium

- Unclear effect on vascular calcification
- Risk of rapid bone loss and rebound VCFs when delayed or stopped

VCFs: vertebral compression fractures

Block, JBMR 2012; Eveneopeol, Nephrology Dialysis Transplantation 2021
Hampson, Endocrine 2021; Ginsberg, Am J Kidney Dis 2022

Anabolics in CKD

- May be beneficial with low bone turnover state (adynamic bone disease)

Teriparatide:

- Does not appear to increase risk of renal impairment
- Efficacy and safety in GFR to 30 (small sample size)
  - Trial only included normal PTH

Romosozumab:

- Dual action of bone formation and anti-resorptive
- Risk of hypocalcemia (especially if GFR<30 or dialysis)
- Black box warning: increased CV events

Millar, Osteo Int 2007; Eveneopeol, Nephrology Dialysis Transplantation 2021
Hampson, Endocrine 2021; Pazianas, Am J Kidney Dis 2021; Ginsberg, Am J Kidney Dis 2022

Osteoporosis treatment in CKD-MBD?

KDIGO 2017

4.3.3. In patients with **CKD G3a-G5D** with **biochemical abnormalities of CKD-MBD** and **low BMD and/or fragility fractures,** we suggest that **treatment choices take into account** the **magnitude and reversibility of the biochemical abnormalities** and the **progression of CKD**, with consideration of bone biopsy (2D)

- Off-label use (limited evidence)
- Priority: **optimize underlying CKD-MBD derangements** that adversely affect bone quality first
  - E.g. ↑ PTH, ↑ PO_4, vitamin D insufficiency

Ketteler, Kidney Int 2017; Eveneopeol, Nephrology Dialysis Transplantation 2021

Case 1 Revisited

- 84-year-old female, recurrent fragility fractures (both wrists, humerus, pelvis)
- Presents with new forearm fracture
- CKD Stage 3b/4 (eGFR 25-34)
- Remote short-term bisphosphonate use in her 60s
- Meds: pravastatin, amlodipine, candesartan, vitamin D 1000 IU daily
- BMI 20
- Bone mineral density:

L-spine	**–1.1**
L fem neck	**–3.9**
L total hip	**–4.6**

Labs

- Ca = 2.23 normal
- Phos = 1.2 (normal)
- PTH = 5.9 pmol/L (ref 1.6-7.2)
- Cr = 137 (eGFR 29)
- ALP = 127 (normal)
- 25OHD = 99
- bsALP = 32.8 (ref 8.1-22)
- C-telopeptide = 1560 (H)

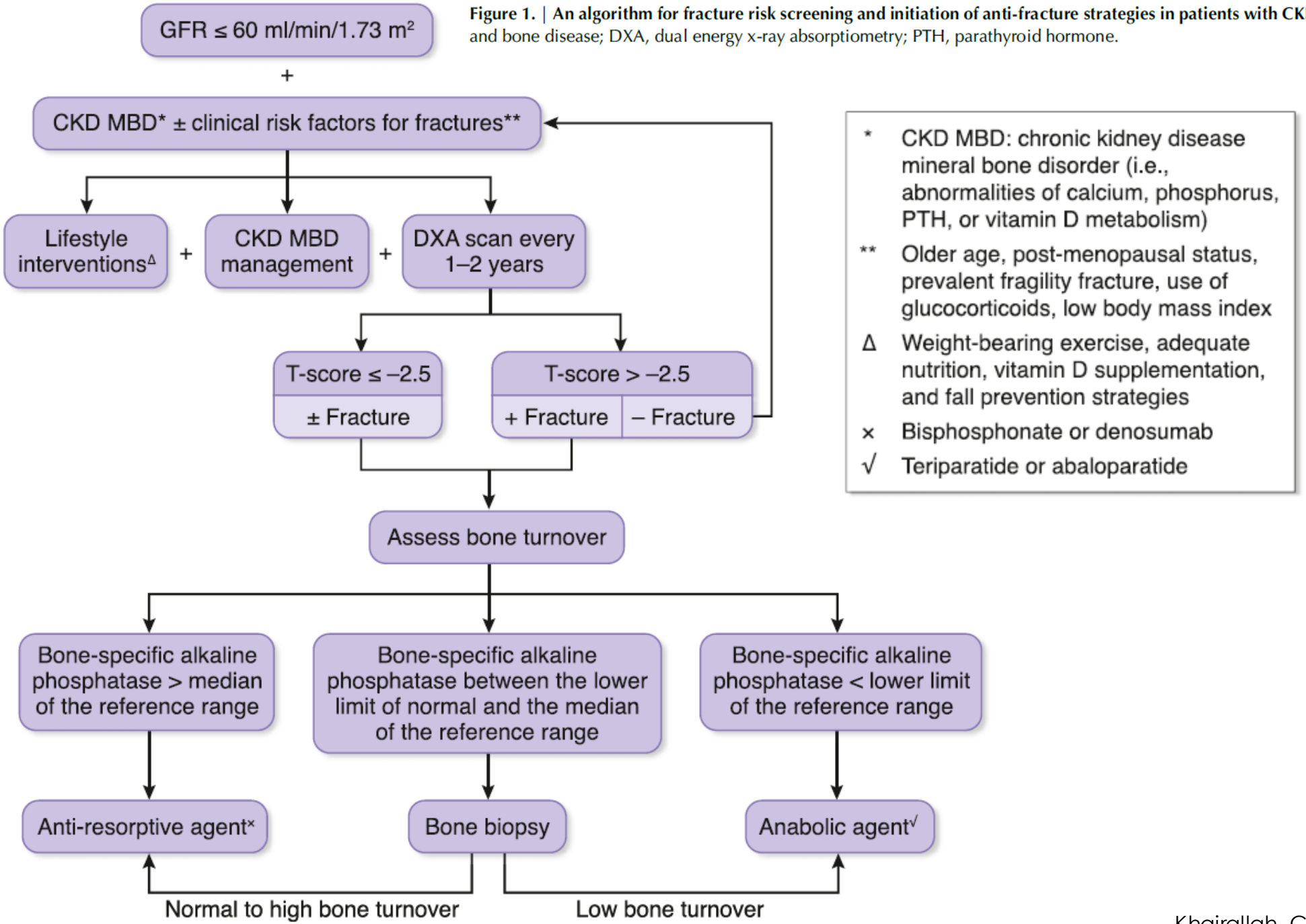


Figure 1. | An algorithm for fracture risk screening and initiation of anti-fracture strategies in patients with CKD. CKD-MBD, CKD mineral and bone disease; DXA, dual energy x-ray absorptiometry; PTH, parathyroid hormone.

Khairallah, Clin J Am Soc Nephrol 2018

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Post-Test Question #1

Pre-Test Question #2

Post-test Question #1

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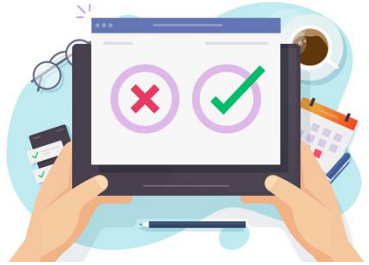

KDIGO: Kidney Disease Improving Global Outcomes
CKD-MBD: Chronic Kidney Disease - Mineral and Bone Disorder

Ketteler, Kidney Int 2017

Pre-test Question #2

- A 71yo woman sustains an acute T8 vertebral fracture after missing her denosumab dose 8 months ago. Which of following management options would be considered acceptable?

Choose all acceptable answer(s):

A) Offer vertebroplasty and/or teriparatide if experiencing retractable pain

B) Prompt re-initiation of denosumab

C) IV zoledronic acid or oral bisphosphonate

D) Combination of denosumab and teriparatide for 2 years, followed by a potent anti-resorptive agent

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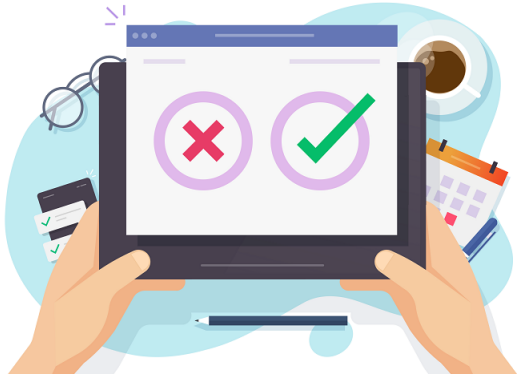


Leder, Lancet 2015; Ramchand, JCEM 2020; Tsourdi, JCEM 2021

Case 2: Denosumab Transition

- 72 yo Asian female
- Wrist fracture age 61
- Maternal hip fracture age 60
- Meds: denosumab x 9.5 yrs, vitamin D 1000 units/day
- Was on oral bisphosphonate x 5 yrs before denosumab
- Asymptomatic, but worried about higher risk of AFF in Asian women
- Favourable BMD response over time

	2016	2018	2020	Now
L-spine	–1.8	–1.5	–1.3	–1.0
L fem neck	–2.5	–2.2	–2.0	–1.7
L total hip	–2.0	–1.8	–1.5	–1.3

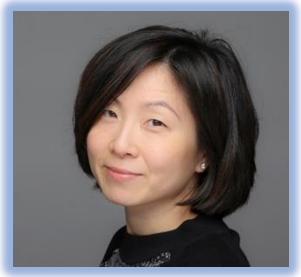
AFF: atypical femoral fracture

Questions:

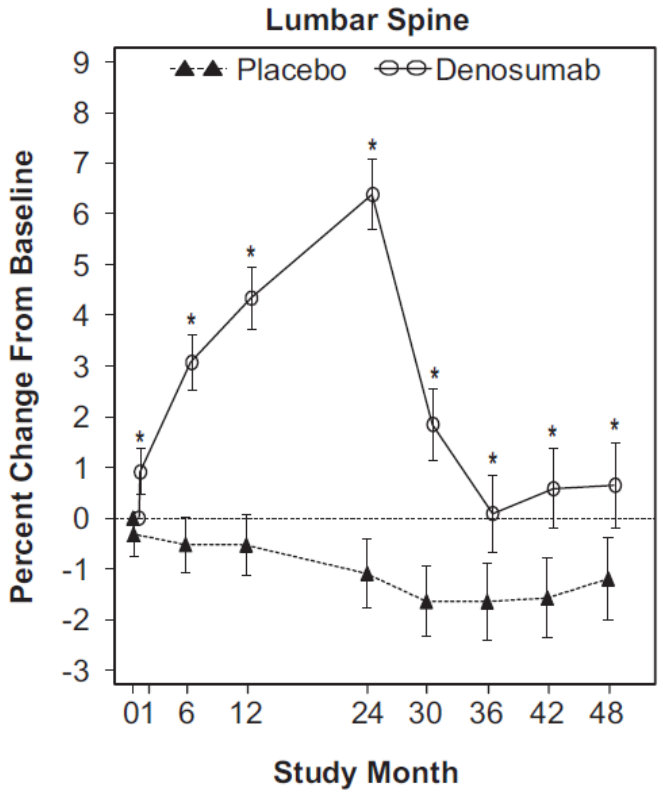
- **Would you suggest continuing denosumab indefinitely or transitioning off?**
- **What approach would you propose in transitioning off denosumab?**

Management of Discontinuation of Denosumab

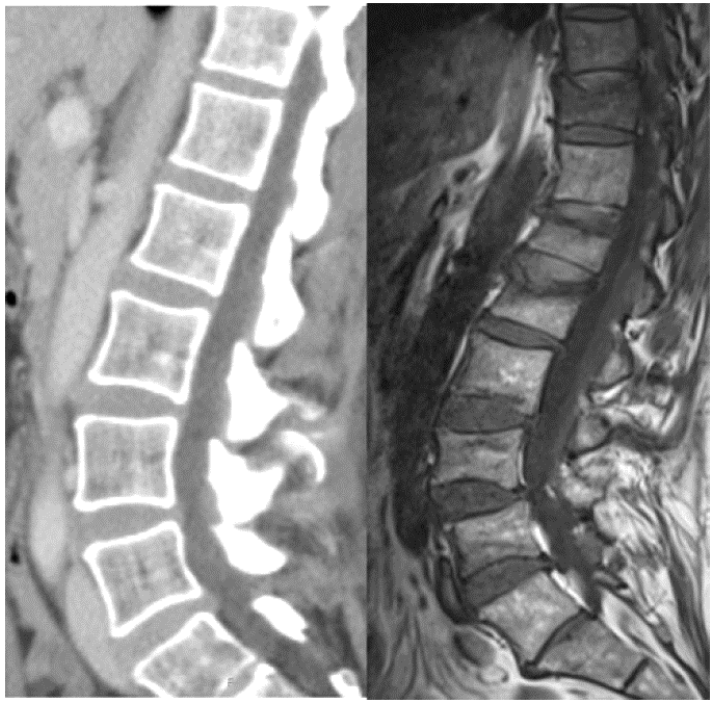
Formulate an approach to “treatment order matters”, including **key considerations when transitioning off denosumab** and when switching between anabolic to anti-resorptive therapies



Drug Holiday: Does NOT apply to denosumab



Rapid drop to baseline BMD within 1-2 years



Risk of rebound vertebral fractures

Higher risk with:
- **Longer DMAB duration e.g. > 2.5 yr**
- **Prevalent vertebral fracture**

Prior bisphosphonate therapy may mitigate risks

- Do NOT delay q6mo doses
- Switch to another agent if patient cannot receive next dose

Bone, JCEM 2011; Popp, Osteo Int 2016

Denosumab discontinuation

- Transition to anti-resorptive **six months after final DMAB dose**
  - Good results if prior DMAB was only 1-2 years

Goals are to try and:

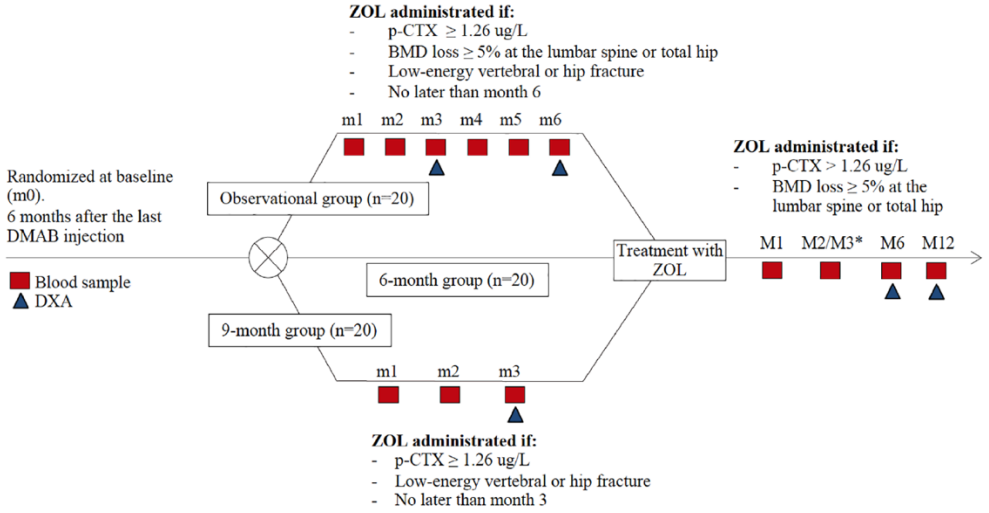
- Minimize BMD drops after DMAB stopped
- Offset risk of rebound vertebral fractures

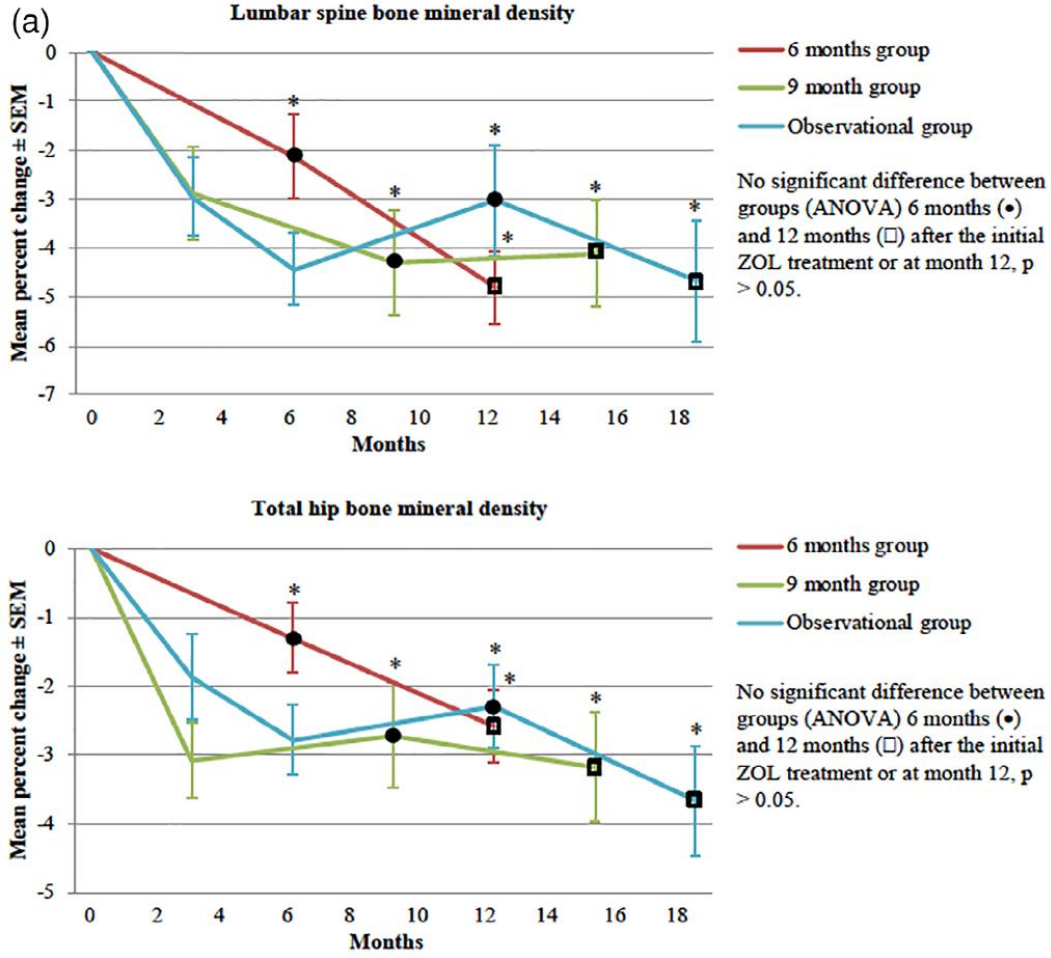
- Best study = Sølling, JBMR 2020
  - Only partial protection with zoledronic acid in all groups
  - Repeat dose needed in many

Lamy, JCEM 2016; Ferrari, JBMR 2020; Sølling, JBMR 2020; Tsourdi, JCEM 2021

Zoledronic acid after denosumab

- N = 61, average DMAB duration = 4.6 yr
- RCT: IV zoledronic acid after denosumab
  - 6 mo, 9 mo, or based on c-telopeptides





Treatment with ZOL post-DMAB:
- **Did not fully prevent BMD losses**
- **Irrespective of timing of ZOL**

Only partial protection in all groups; repeat dose needed in many

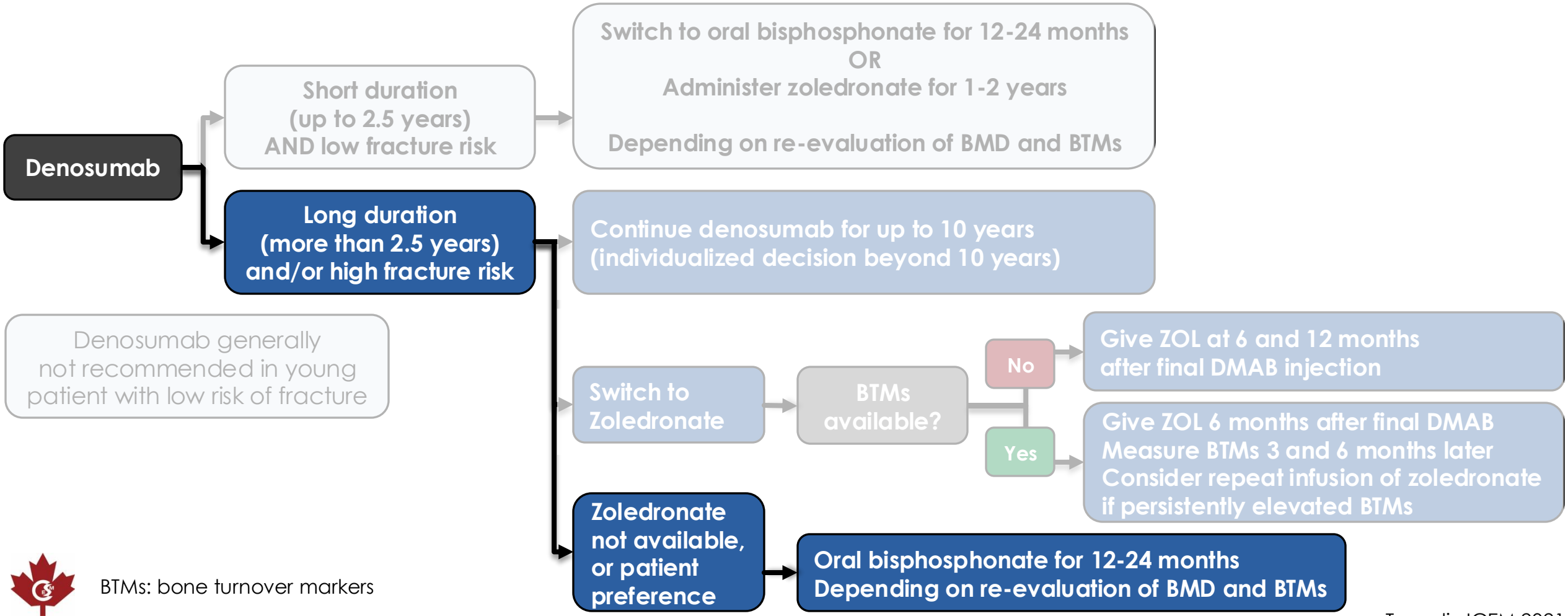
Sølling, JBMR 2020

European Calcified Tissue Society: Position Statement

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 1, 264–281
doi:10.1210/clinem/dgaa756
Reports and Recommendations

Reports and Recommendations

Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement



BTMs: bone turnover markers

Tsourdi, JCEM 2021

European Calcified Tissue Society: Position Statement

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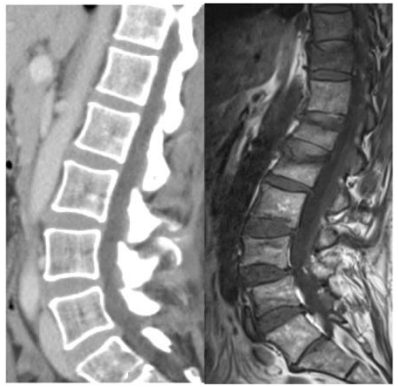
Reports and Recommendations

Reports and Recommendations

Fracture Risk and Management of Discontinuation of Denosumab Therapy: A Systematic Review and Position Statement

Vertebral fracture(s) occurring within 1-2 years after DMAB discontinuation



→ **Avoid vertebroplasty and/or monotherapy with teriparatide**

→ **Prompt re-initiation of denosumab**

OR

IV zoledronate or PO bisphosphonate

OR

Consider combination of denosumab and teriparatide for 2 years, followed by zoledronate

Tsourdi, JCEM 2021

Low dose denosumab

Endocrine
https://doi.org/10.1007/s12020-022-03230-5

ORIGINAL ARTICLE

Effect of low dose denosumab on bone mineral density in postmenopausal women with osteoporosis after a transition from 60 mg dose: a prospective observational study

- Denosumab 60 mg SC q6months → **30 mg** SC q6months
- Postmenopausal women, moderate risk for fracture
- **Maintained BMD without clinical fractures** observed

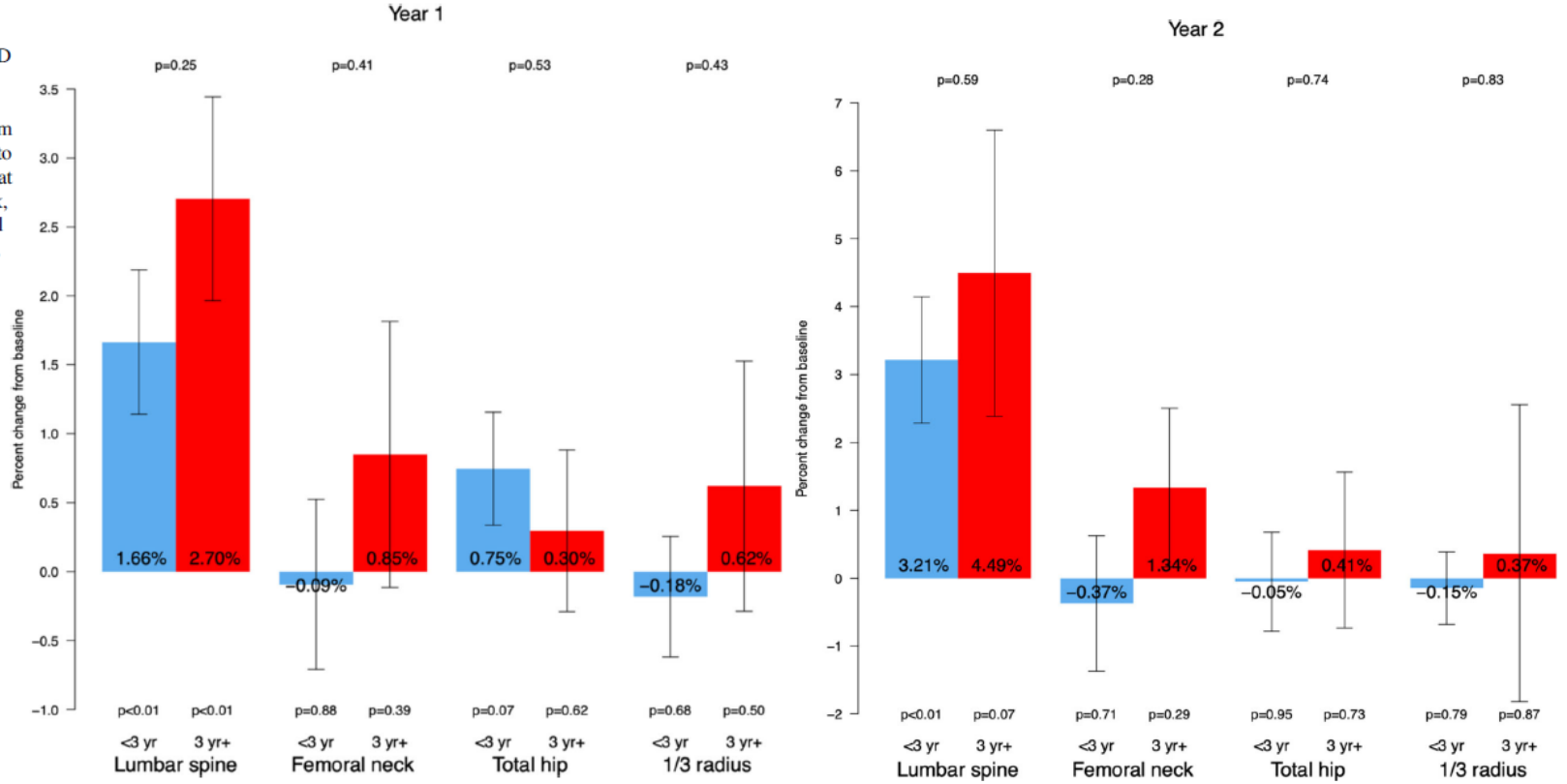


Fig. 1 Mean % change in BMD at 12 months describes the changes in BMD values 12 months after the switch from denosumab 60 mg q 6 months to denosumab 30 mg q 6 months at the lumbar spine, femoral neck, total hip, and distal third radial sites. Blue: group A ($N = 78$), red: group B ($N = 36$)

Khan, Endocrine 2023

Case 2 Revisited: Denosumab transition

- 72 yo Asian female
- Wrist fracture age 61
- Maternal hip fracture age 60
- Meds: denosumab x 9.5 yrs, vitamin D 1000 units/day
- Was on oral bisphosphonate x 5 yrs before denosumab
- Asymptomatic, but worried about higher risk of AFF in Asian women
- Favourable BMD response over time
- Most recent BMD:

L-spine	**–1.0**
L fem neck	**–1.7**
L total hip	**–1.3**

Imaging

- Thoracolumbar XR: no VCF
- Bilateral femoral XR: no AFF

Options:

1. Continue denosumab
2. Transition to IV zoledronic acid
3. Half dose denosumab x 24 month, then transition to IV zoledronic acid
   - Monitor BTM and BMD

AFF: atypical femoral fracture

VCF: vertebral compression fracture

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Post-Test Question #2

Pre-Test Question #3

Post-test Question #2

- A 71yo woman sustains an acute T8 vertebral fracture after missing her denosumab dose 8 months ago. Which of following management options would be considered acceptable?

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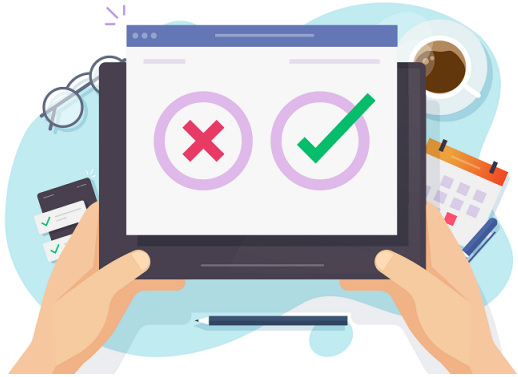
Choose all acceptable answer(s):

A) Offer vertebroplasty and/or teriparatide if experiencing retractable pain

B) Prompt re-initiation of denosumab

C) IV zoledronic acid or oral bisphosphonate

D) Combination of denosumab and teriparatide for 2 years, followed by a potent anti-resorptive agent



Leder, Lancet 2015; Ramchand, JCEM 2020; Tsourdi, JCEM 2021

Pre-Test Question #3

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Osteoporosis Canada 2023 guidelines define inadequate response to treatment as which of the following despite adherence to adequate course of treatment for at least 1 year?

A) At least 1 fracture AND ≥5% BMD drop from baseline

B) More than 1 fracture OR ≥5% BMD drop from baseline

C) At least 1 fracture AND any BMD drop from baseline

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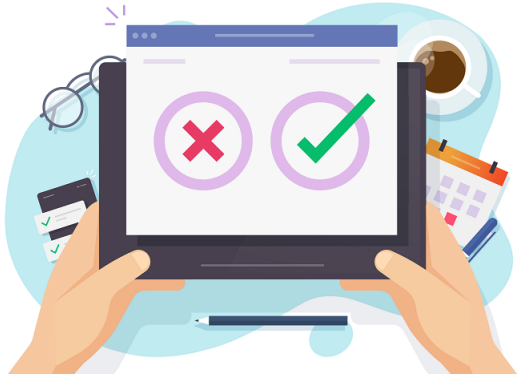


Morin, CMAJ 2023

Case 3

- 70 year old female with osteoporosis
- Alendronate x 2 years
- Recent fall: distal radius fracture

Questions:

- **Does this 'count' as a treatment failure?**
- **Would you change her medications?**

Treatment Failures and Sequences of Therapy

Formulate an approach to "treatment order matters", including **key considerations when switching between anabolic to anti-resorptive therapies**

Define osteoporosis pharmacotherapy **treatment failure** and review the evidence for **when to repeat BMD after treatment initiation**

CONFLICT OF INTEREST DECLARATION – Dr. Xin Feng

I **DO/DO NOT** have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria		
Membership on advisory boards or speakers' bureaus	Amgen Bayer Sandoz Esai	Speaker fees and advisory board fees
Funded grants or clinical trials		
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

Treatment Failure: Definition

British Columbia

Fragility fracture, AND
BMD decline ≥5%,
despite ≥1 yr bisphosphonate

Manitoba

Fragility fracture, AND/OR
BMD decline below baseline,
despite ≥1 yr adherence

Ontario

Fragility fracture, OR
BMD decline below baseline,
despite ≥1 yr adherence

Treatment Failure: Definition

OSTEOPOROSIS CANADA

- Remark: Inadequate response to treatment should be considered when **> 1 fracture or substantial bone density decline (e.g., ≥ 5%) occurs despite adherence to an adequate course of treatment (typically > 1 yr)**.
- However, fractures or bone density decline during therapy do not always indicate inadequate response to treatment (e.g., secondary causes of osteoporosis, falls, BMD imprecision errors).

Morin, CMAJ 2023

Monitoring for treatment response

2020	ENDOCRINE SOCIETY	**Repeat BMD every 1-3 years**
2020	AACE® American Association of Clinical Endocrinology	**Repeat BMD in 1-2 years**
2022	BHOF Bone Health & Osteoporosis FOUNDATION™	**Repeat BMD in 1-2 years**
2023	OSTEOPOROSIS CANADA	**Repeat BMD in 3 years***

*shorter interval if secondary causes of osteoporosis, new fracture, or new risk factors associated with rapid bone loss

Shoback, JCEM 2020; Camacho, Endocr Pract 2020
LeBoff, Osteoporos Int 2022; Morin, CMAJ 2023

Trouble with serial BMD

- Serial BMD done in quick succession can:
  - Magnify error
  - Lead to incorrect conclusion on treatment effect
- Leading to:
  - Erroneous adjustments on medication
  - Additional investigations
  - Patient distress
  - Physician confusion

Observational Study > J Clin Endocrinol Metab. 2022 May 17;107(6):1662-1666.
doi: 10.1210/clinem/dgac051.

Apparent "Rapid Loss" After Short-Interval Bone Density Testing in Menopausal Women Is Usually a Measurement Artifact

Gregory A Kline [1], Suzanne N Morin [2], Lisa M Lix [3], William D Leslie [4 5]

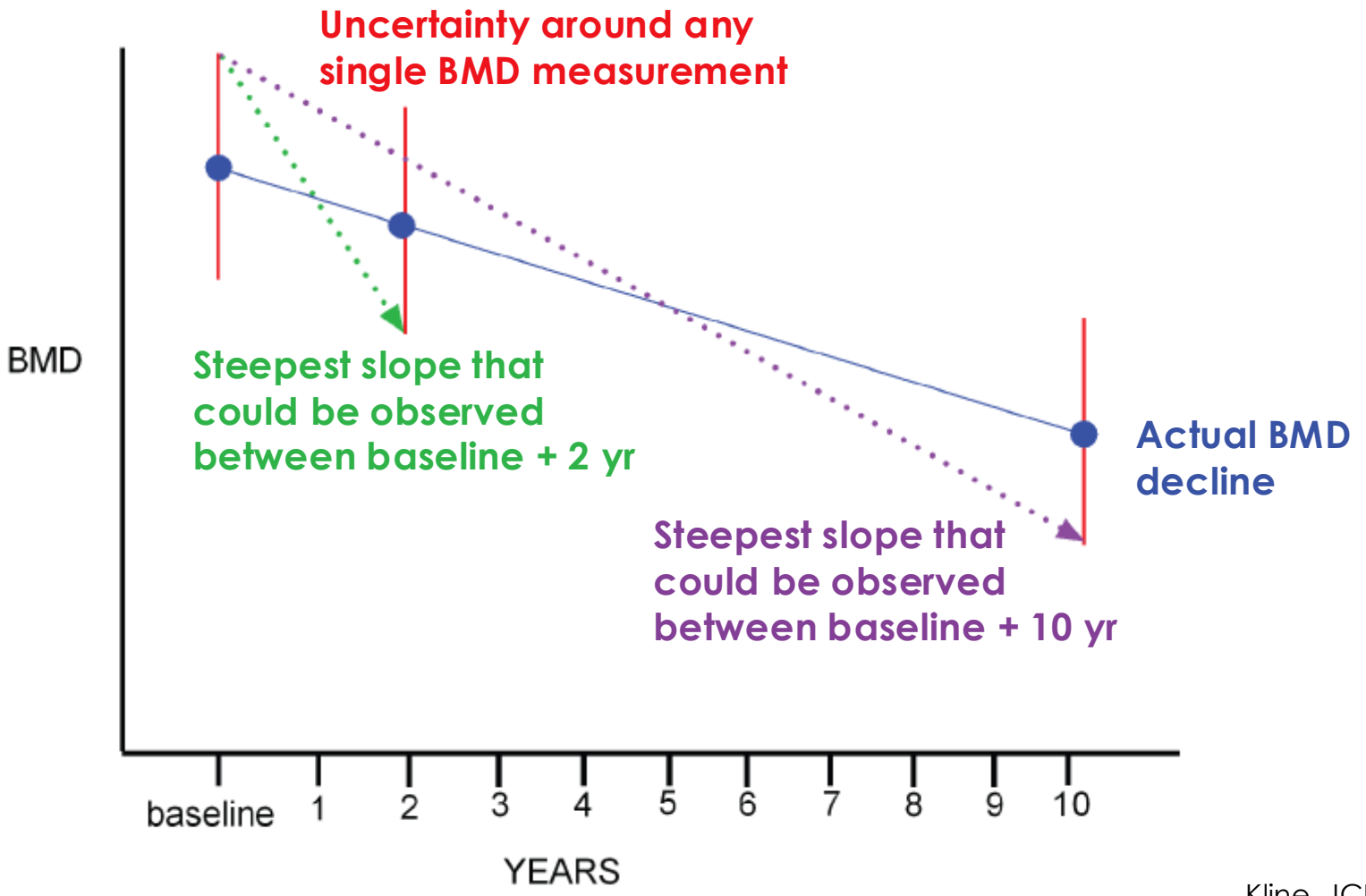
Affiliations + expand

PMID: 35134963 DOI: 10.1210/clinem/dgac051

Kline, JCEM 2022

Trouble with serial BMD

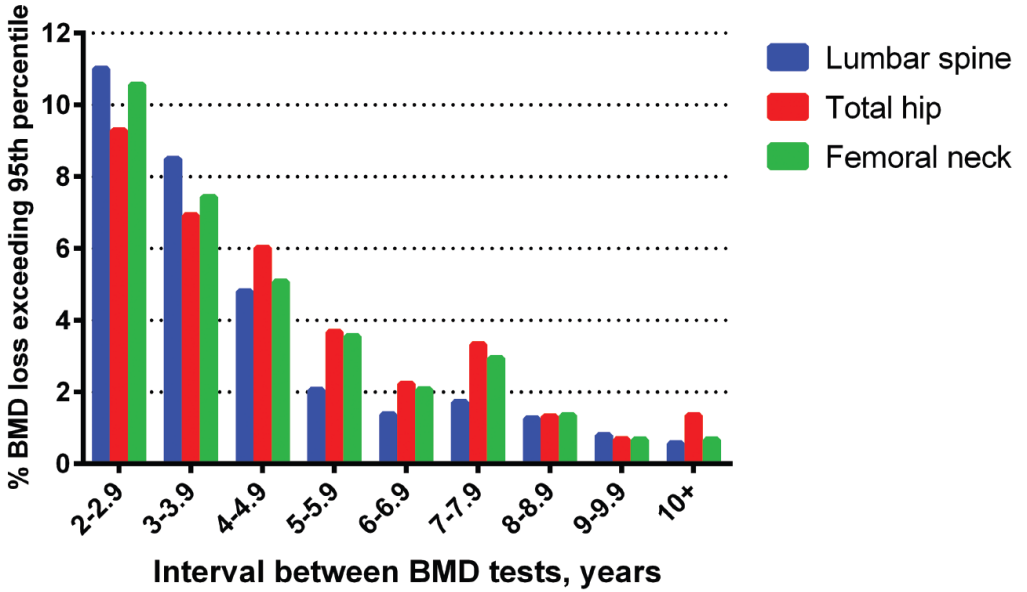
- Measurement error (slope of green vs blue line) magnifies at shorter versus longer intervals
- Steepest slope will always be greater for a shorter time interval



Kline, JCEM 2022

Trouble with serial BMD

- Odds ratio for 'rapid bone loss' (> 95th %ile) highest at 2-2.9 years, declining from there
- Population BMD loss per year: steady across cohort
- Suggests people with more frequent BMDs may be more likely to have a magnified conclusion on treatment effect (or lack thereof)



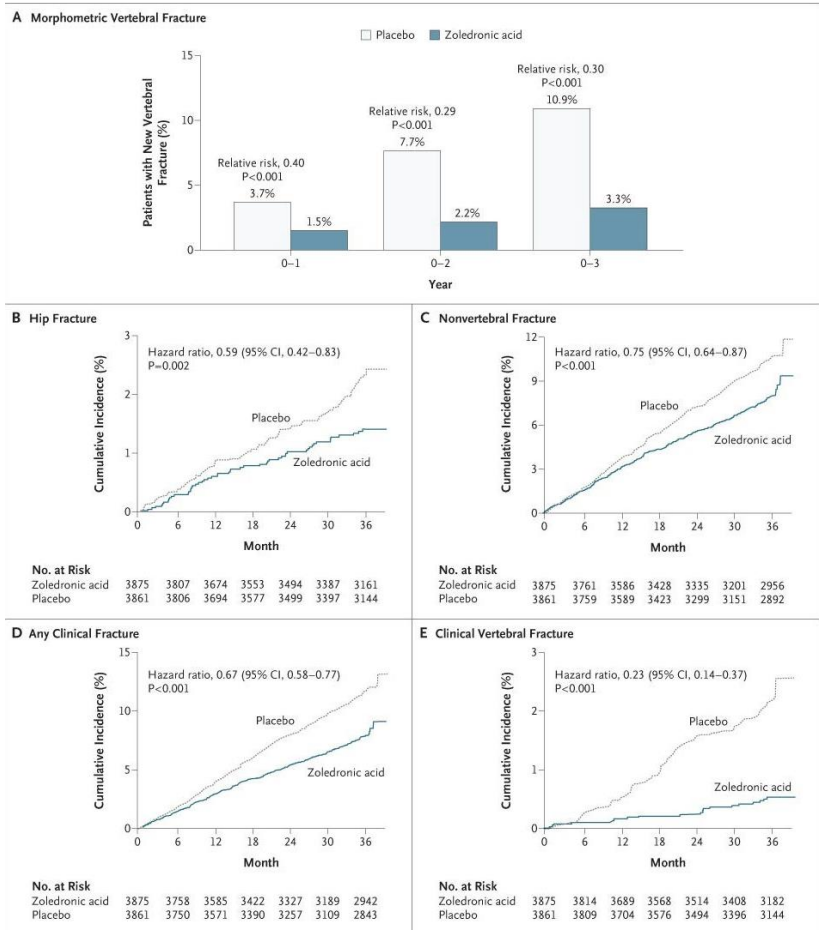
		Lumbar spine BMD % loss per year			Total hip BMD % loss per year			Femoral neck BMD % loss per year		
Interval, years	Number of BMD pairs	Mean	SD	95th percentile	Mean	SD	95th percentile	Mean	SD	95th percentile
2-2.9	947	-0.1	1.9	-2.8	-0.6	1.5	-3.1	-0.6	1.8	-3.1
3-3.9	1762	-0.2	1.5	-2.6	-0.7	1.2	-2.6	-0.7	1.4	-2.6
4-4.9	1163	-0.2	1.1	-2.0	-0.7	1.0	-2.3	-0.7	1.1	-2.3
5-5.9	844	-0.1	1.0	-1.6	-0.7	0.9	-2.2	-0.7	1.0	-2.2
6-6.9	628	-0.2	0.9	-1.6	-0.7	0.7	-2.0	-0.7	0.8	-2.0
7-7.9	511	-0.1	0.9	-1.5	-0.7	0.8	-2.0	-0.7	0.8	-2.0
8-8.9	378	-0.2	0.8	-1.5	-0.7	0.6	-1.8	-0.7	0.7	-1.8
9-9.9	296	-0.1	0.8	-1.3	-0.7	0.6	-1.7	-0.7	0.7	-1.7
≥10	593	-0.1	0.7	-1.4	-0.7	0.6	-1.8	-0.7	0.7	-1.8

Kline, JCEM 2022

Trouble with fractures on therapy

- Can't prevent all fractures
  - E.g. ↓ 15-20% non-vertebral fracture (and not 100%)
  - Yet they are within the definition of 'treatment failure'
- Patients have "residual fracture risk" while on therapy
- Fractures provide an opportunity to assess the patient
  - Adherence
  - Appropriate administration
  - New/worsened medical conditions (e.g. inflammatory)
  - Glucocorticoids
  - Malabsorption or other GI concerns
  - Weight loss

HORIZON



Black, NEJM 2007

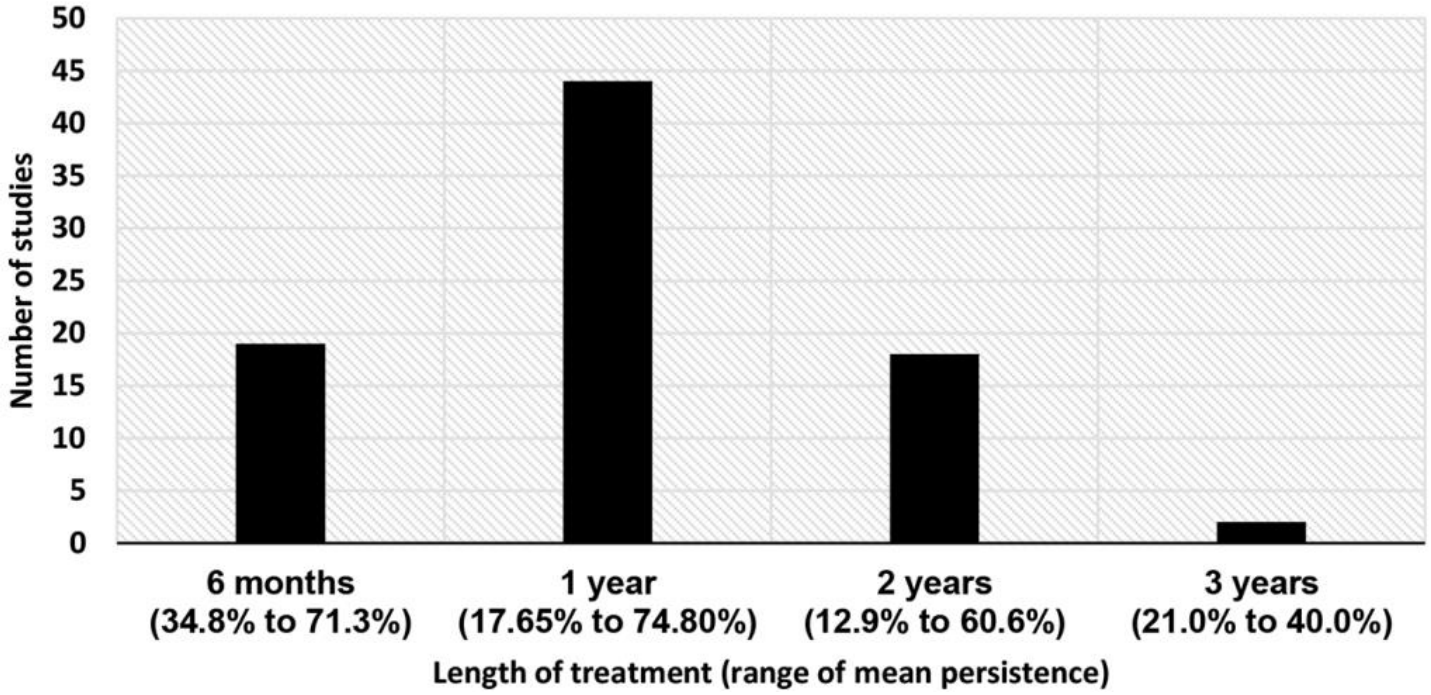
Persistence of oral bisphosphonates

BMJ Open

Real-world persistence and adherence with oral bisphosphonates for osteoporosis: a systematic review

F Fatoye, P Smith, T Gebrye, G Yeowell

- "Patient persistence and adherence with oral bisphosphonates was poor and reduced notably over time"
- Important to assess adherence and appropriate administration



Fatoye, BMJ Open 2019

Back to the Case: After 'failure'

- 70 year old female with osteoporosis
- Alendronate x 2 years
- Recent fall: distal radius fracture

Question:

- **What is the sequence of therapy after 'failure' ?**

Answer:

- **Depends on the current course of therapy**

If starting on an oral bisphosphonate:

- **Switch to zoledronic acid?**
- **Switch to denosumab?**
- **Switch to an anabolic agent?**

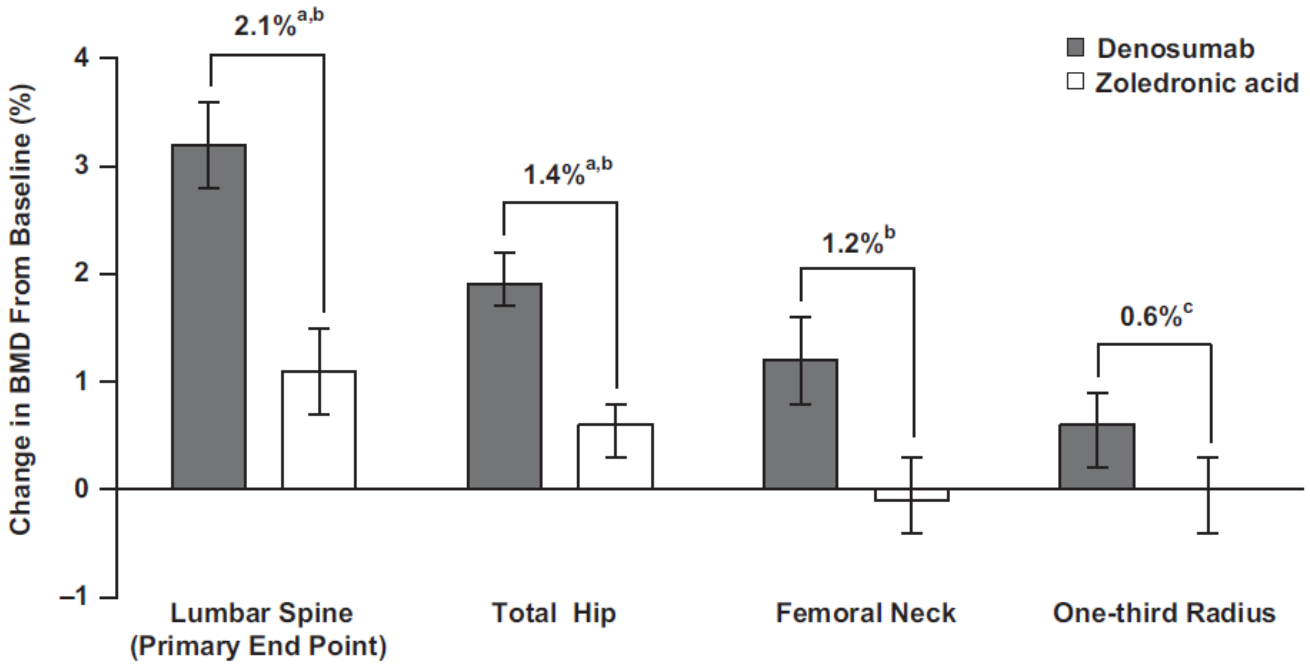
Oral bisphosphonate to ZOL or DMAB

Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates

P. D. Miller, N. Pannacciulli, J. P. Brown, E. Czerwinski, B. S. Nedergaard, M. A. Bolognese, J. Malouf, H. G. Bone, J.-Y. Reginster, A. Singer, C. Wang, R. B. Wagman, and S. R. Cummings*

- International multicenter RCT
- N = 643, women age ≥ 55
- ≥2 years oral bisphosphonate (average 6 years)
- Switched to either ZOL or DMAB
- BMD and BTMs at 12 months

- DMAB: greater BMD increases and greater inhibition of bone remodeling versus ZOL



RCT = randomized control trial
BTM = bone turnover markers

ZOL = zoledronic acid
DMAB = denosumab

Miller, JCEM 2016

Sequence of therapy matters

- Ideally start patients who are treatment naïve on anabolic agents first (if indicated) before transitioning to antiresorptive therapy
  - Greater BMD gains

- Certain 'transition' combinations are important to know

PERSPECTIVE

Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

Felicia Cosman,[1,2] Jeri W Nieves,[1,3] and David W Dempster[1,4]

[1]Regional Bone Center and Clinical Research Center, Helen Hayes Hospital, West Haverstraw, NY, USA
[2]Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA
[3]Department of Epidemiology, Columbia University College of Physicians and Surgeons, New York, NY, USA
[4]Department of Pathology, Columbia University College of Physicians and Surgeons, New York, NY, USA

Cosman, JBMR 2017

Antiresorptive before Teriparatide

PERSPECTIVE

Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis

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[3]Department of Epidemiology, Columbia University College of Physicians and Surgeons, New York, NY, USA
[4]Department of Pathology, Columbia University College of Physicians and Surgeons, New York, NY, USA

- Although there is a decline in response with antiresorptive therapy before anabolic agent, there is still a residual effect (with oral bisphosphonate)

Table 1. Hip BMD Effect of Switching From Potent Antiresorptive Therapy to TPTD

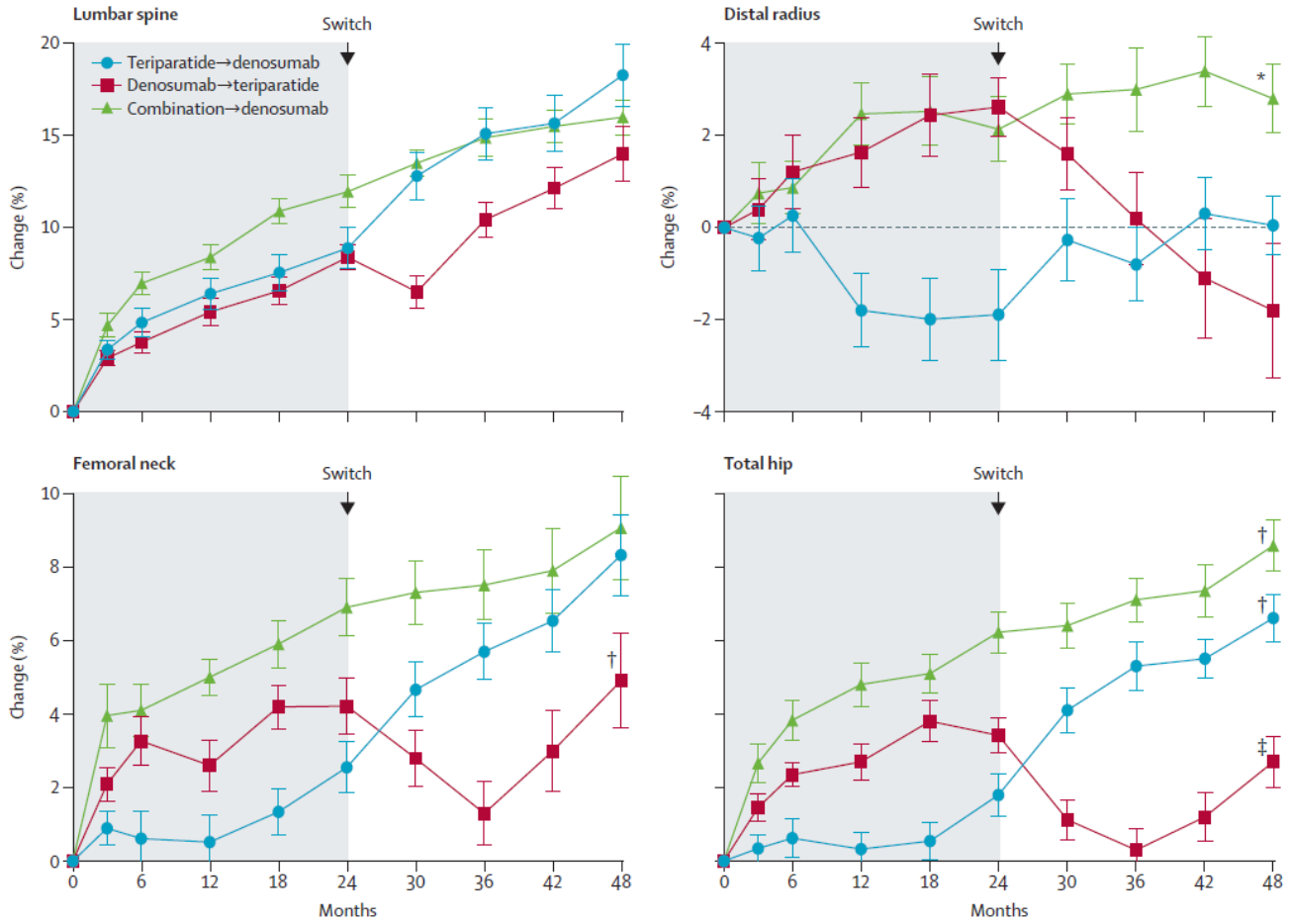
Study	Sample size	Treatment paradigm	% Change in total hip BMD during TPTD/PTH treatment			
			6 mo	12 mo	18 mo	24 mo
Ettinger et al.[27]	33	Alendronate (mean 29.3 mo) → TPTD (18 mo)	−1.8%	−1.0%	+0.3%	–
Boonen et al.[24]	107	Alendronate (median 29.2 mo) → TPTD (24 mo)	−1.2%	−0.6%	+0.6%	+2.1%
Boonen et al.[24]	59	Risedronate (median 23.4 mo) → TPTD (24 mo)	−1.6%	−0.4%	+0.9%	+2.9%
Miller et al.[30]	158	Risedronate (mean 37.2 mo) → TPTD (12 mo)	−1.2%	−0.3%	–	–
Miller et al.[30]	166	Alendronate (mean 38.0 mo) → TPTD (12 mo)	−1.9%	−1.7%	–	–
Cosman et al.[26]	50	Alendronate (mean 45.7 mo) → TPTD (18 mo)	−0.8%	–	+0.9%	–
Leder et al.[28]	27	Denosumab (24 mo) → TPTD (24 mo)	−1.7%	−2.7%	−1.7%	−0.7%

mo = months.
In some cases, numbers are estimated by extrapolation from graph in article.

Cosman, JBMR 2017

Denosumab before Teriparatide

- Caveat to previous slide is denosumab → teriparatide
- DATA-Switch:
  - Decline in BMD after switching from DMAB → TPTD



DMAB = denosumab
TPTD = teriparatide

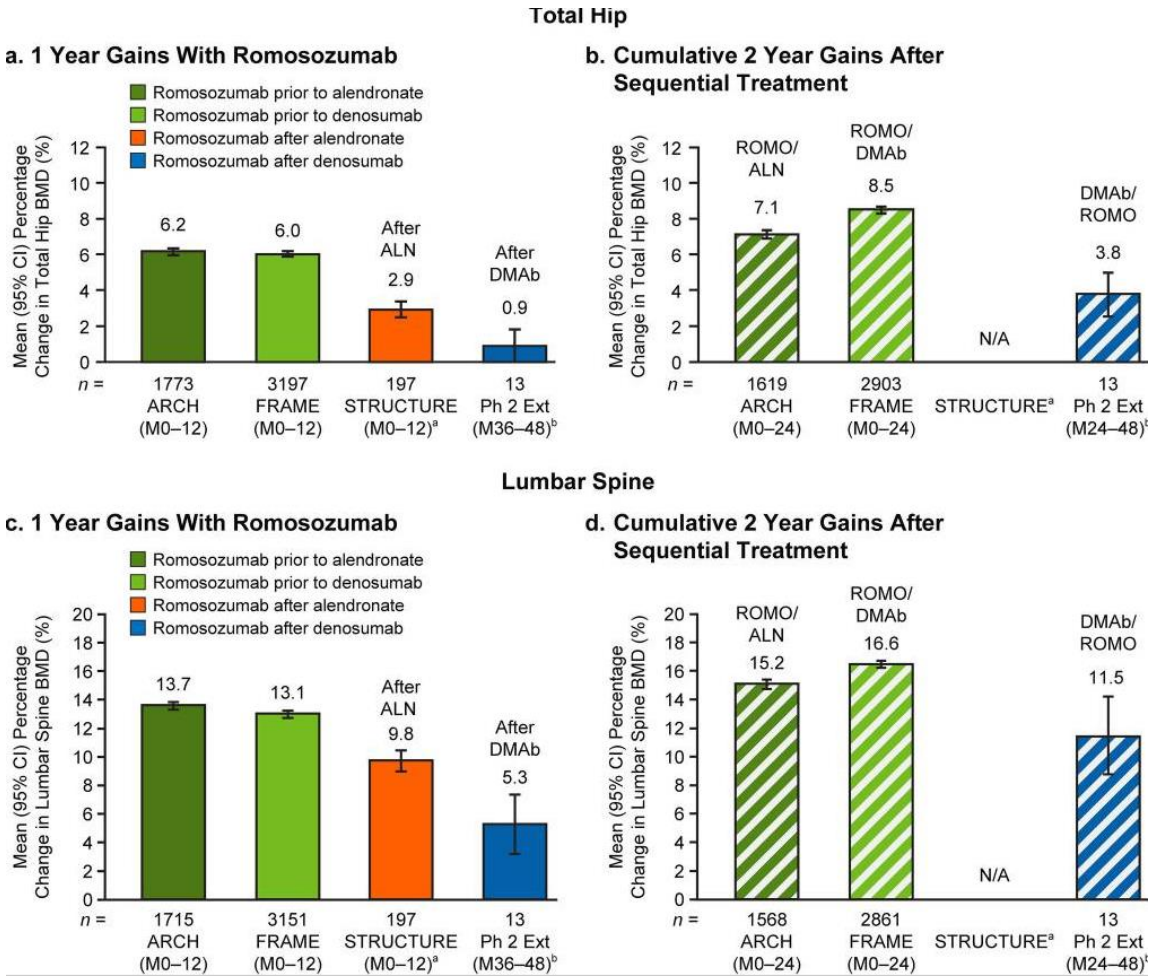
Leder, Lancet 2015

Antiresorptive before Romosozumab

Romosozumab and antiresorptive treatment: the importance of treatment sequence

Felicia Cosman[1] · David L. Kendler[2] · Bente L. Langdahl[3] · Benjamin Z. Leder[4] · E. Michael Lewiecki[5] · Akimitsu Miyauchi[6] · Maria Rojeski[7] · Michele McDermott[7] · Mary K. Oates[7] · Cassandra E. Milmont[7] · Cesar Libanati[8] · Serge Ferrari[9]

- Less BMD gains if romosozumab started AFTER antiresorptive therapy
- However there is still a BMD gain



Cosman, Osteo Int 2022

Antiresorptive before Romosozumab

Effects of prior osteoporosis treatment on 12-month treatment response of romosozumab in patients with postmenopausal osteoporosis

Kosuke Ebina[a,b,*], Hideki Tsuboi[c], Yoshio Nagayama[d], Masafumi Kashii[e],

- Prospective, observational, multicentre Japan study
- BMD gains after starting or switching to Romosozumab
  - Not as much as pretreatment
  - But still an increase

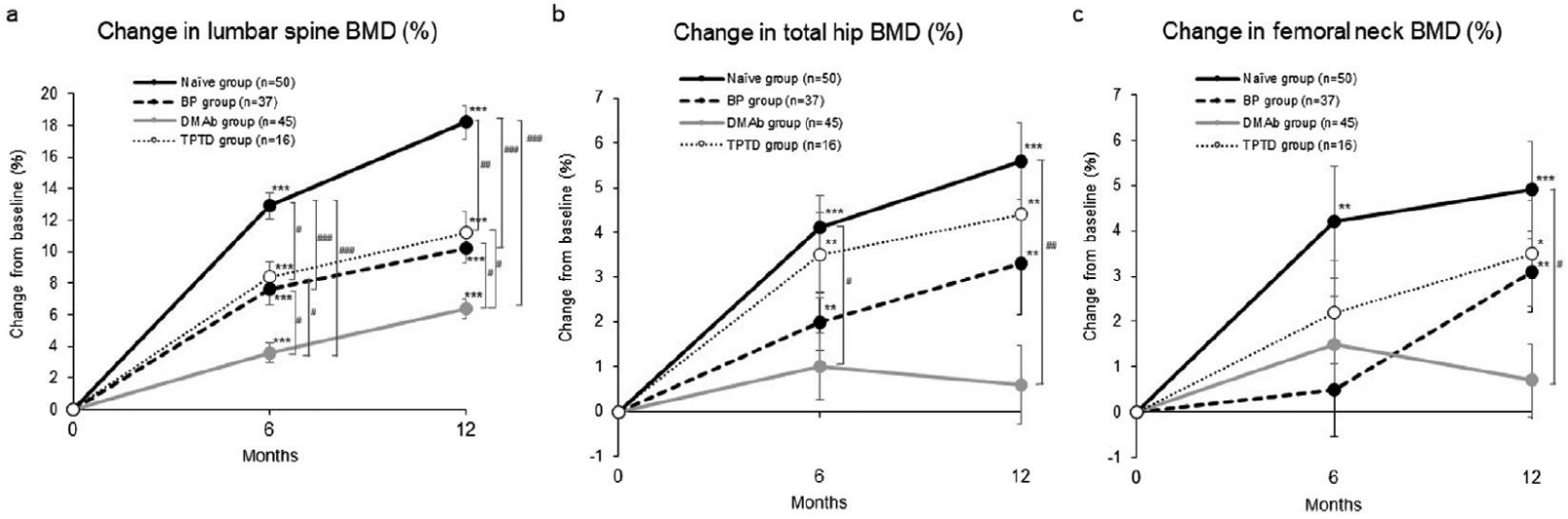


Table 1. Patients' clinical characteristics at baseline.

Variable	Naïve group (n=50)	BP group (n=37)	DMAb group (n=45)	TPTD group (n=16)
Duration of prior treatment (months)	0	28.1±23.3	24.1±15.8	11.6±8.0[a]

ROMO = romosozumab

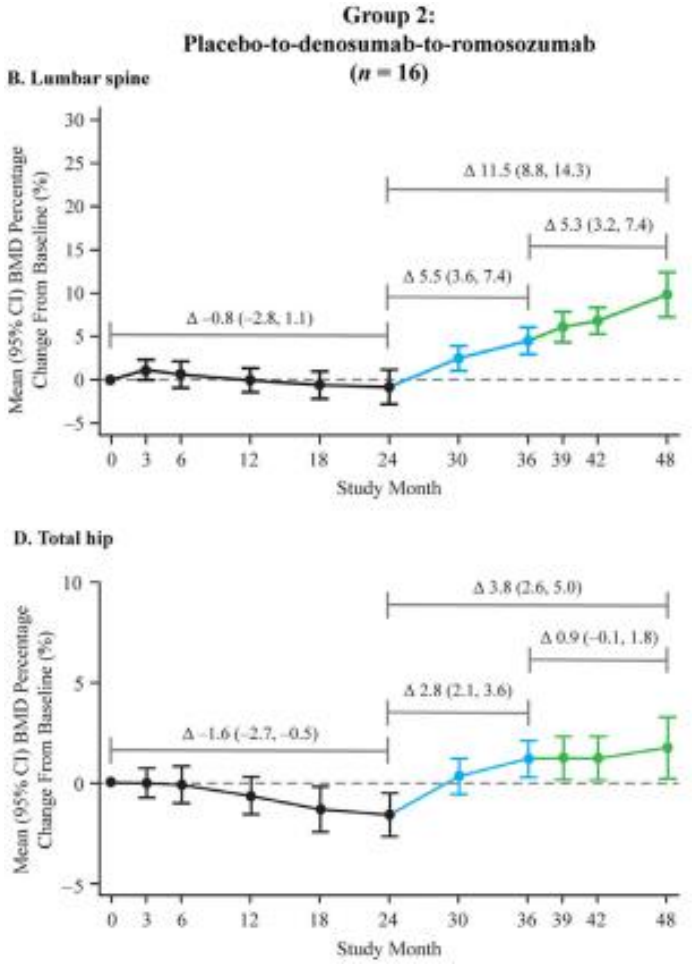
Ebina, Joint Bone Spine, 2021

Switching from DMAB to ROMO

Skeletal responses to romosozumab after 12 months of denosumab

Michael R. McClung,[1,2] Michael A. Bolognese,[3] Jacques P. Brown,[4] Jean-Yves Reginster,[5,6] Bente L. Langdahl,[7] Yifei Shi,[8] Jen Timoshanko,[9] Cesar Libanati,[9] Arkadi Chines,[8] and Mary K. Oates[8]

- N = 16
- Placebo → DMAB → ROMO
- No comparator to teriparatide
- BMD gain seen, but small study
  Unclear if generalizable to longer duration of DMAB



DMAB = denosumab
ROMO = romosozumab

McClung, JBMR Plus, 2021

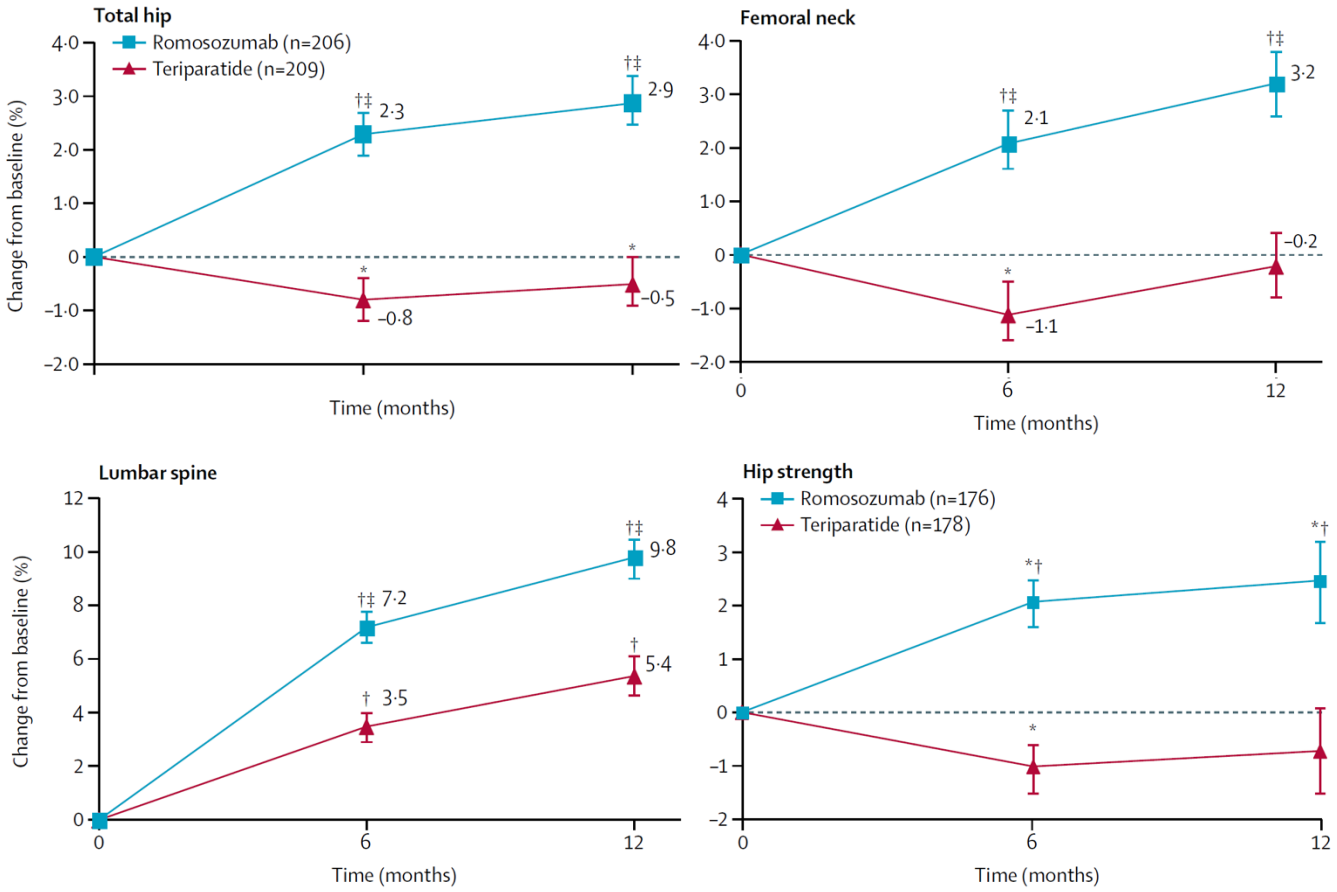
Which anabolic after antiresorptive?

Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial

Bente L Langdahl, Cesar Libanati, Daria B Crittenden, Michael A Bolognese, Jacques P Brown, Nadia S Daizadeh, Eva Dokoupilova, Klaus Engelke, Joel S Finkelstein, Harry K Genant, Stefan Goemaere, Lars Hyldstrup, Esteban Jodar-Gimeno, Tony M Keaveny, David Kendler, Peter Lakatos, Judy Maddox, Jorge Malouf, Fabio E Massari, Jose Fernando Molina, Maria Rosa Ulla, Andreas Grauer

- 436 postmenopausal women
- ≥ 3 years of oral bisphosphonate
- Alendronate for the year before screening
- Randomized to ROMO or TPTD

- % BMD change with ROMO was greater versus TPTD



ROMO = romosozumab
TPTD = teriparatide

Langdahl, Lancet 2017

Repeat anabolic therapy

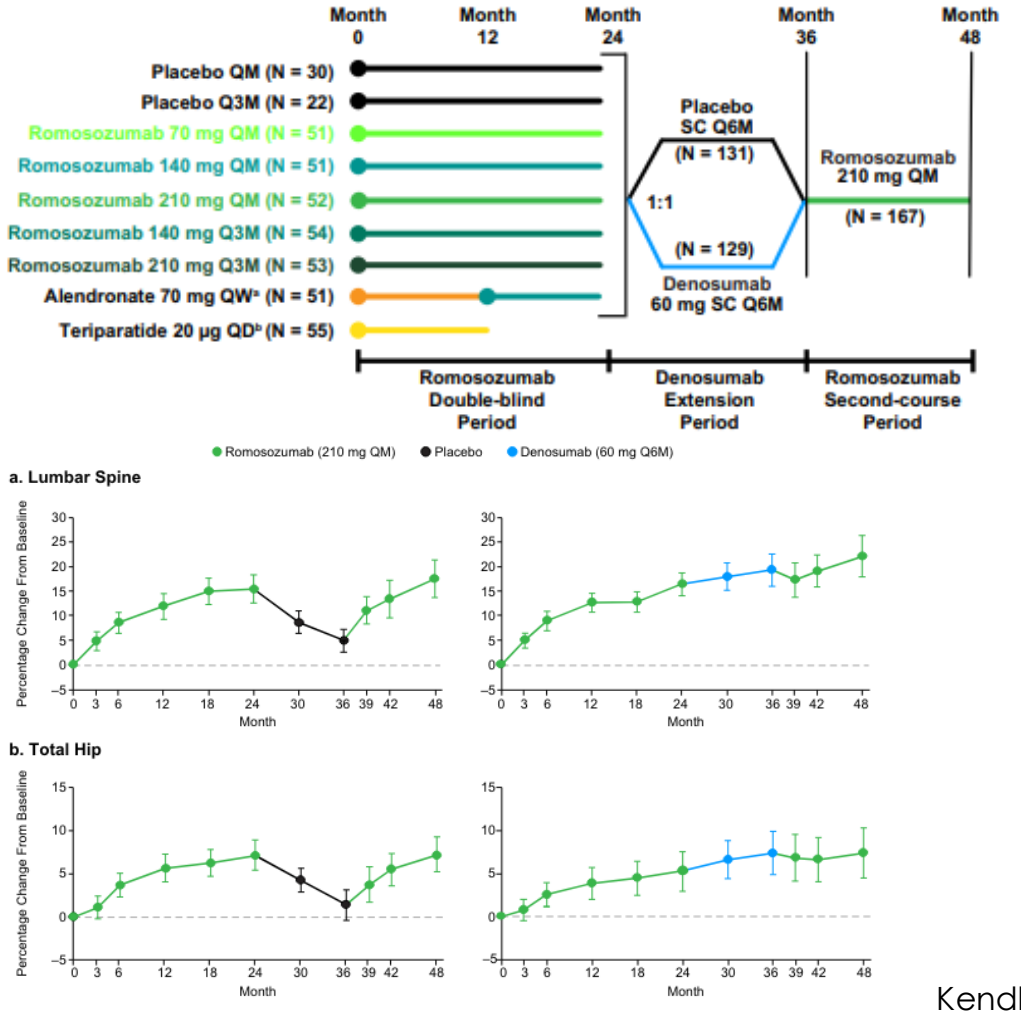
- Limited data on repeat romosozumab after initial course of therapy
- Teriparatide black box warning lifted November 2020
  - No longer restricted for 24 months lifetime exposure
- Repeat therapy not currently approved for use
  - Perhaps consider in very high risk fracture patients?

Repeat anabolic therapy

- Second course of ROMO after 1 year of placebo or DMAB
- Stability to slight BMD gain with continued treatment
- No safety concerns noted

Bone mineral density gains with a second 12-month course of romosozumab therapy following placebo or denosumab

D.L. Kendler[1] · H.G. Bone[2] · F. Massari[3] · E. Gielen[4] · S. Palacios[5] · J. Maddox[6] · C. Yan[7,8] S. Yue[6,9] · R.V. Dinavahi[6] · C. Libanati[10] · A. Grauer[6,11]



ROMO = romosozumab
DMAB = denosumab

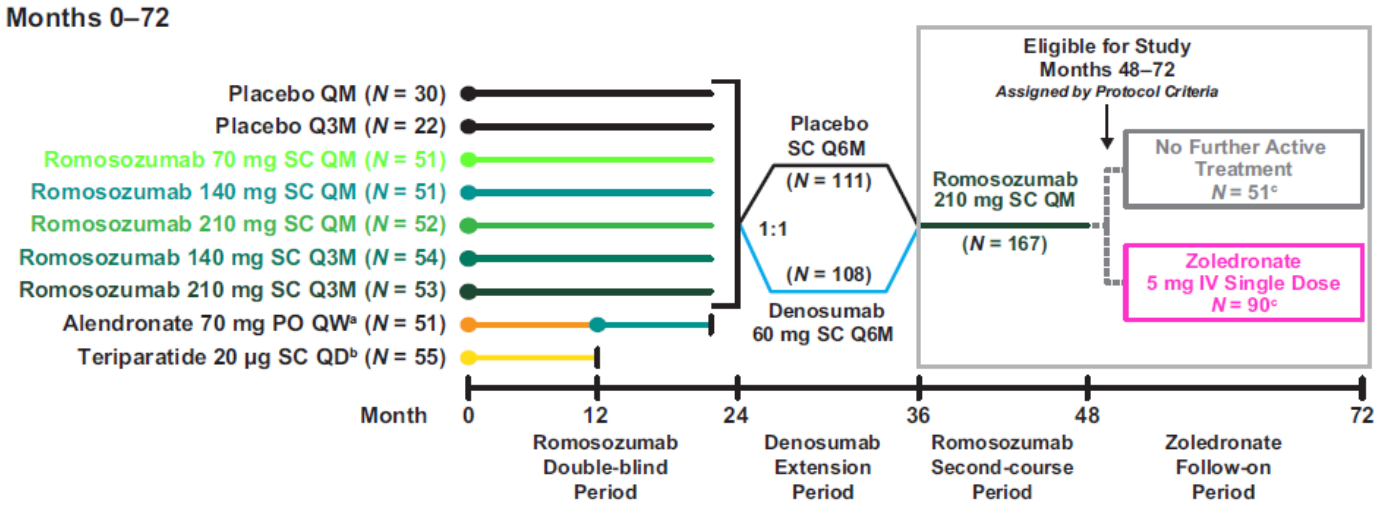
Kendler, Osteo Int 2019

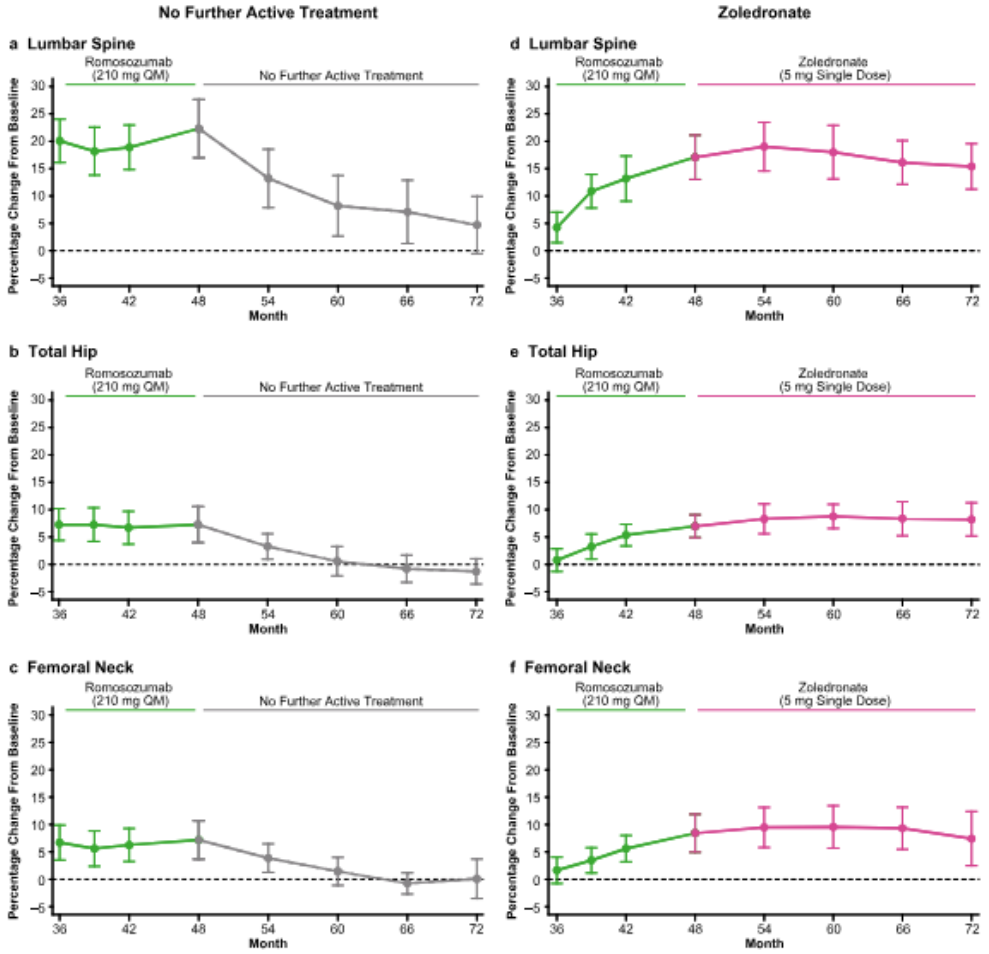
Repeat anabolic therapy

A single dose of zoledronate preserves bone mineral density for up to 2 years after a second course of romosozumab

M. R. McClung[1,2] · M. A. Bolognese[3] · J. P. Brown[4] · J.-Y. Reginster[5,6] · B. L. Langdahl[7] · J. Maddox[8] · Y. Shi[8] M. Rojeski[8] · P. D. Meisner[9] · A. Grauer[8]

- BMD preserved with single dose of zoledronic acid following second course of ROMO





ROMO = romosozumab

McClung, Osteo Int 2020

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Post-Test Question #3

Pre-Test Question #4

Post-Test Question #3

Sign in to Slido: Name, Email

Slido.com with code: **#2041940**

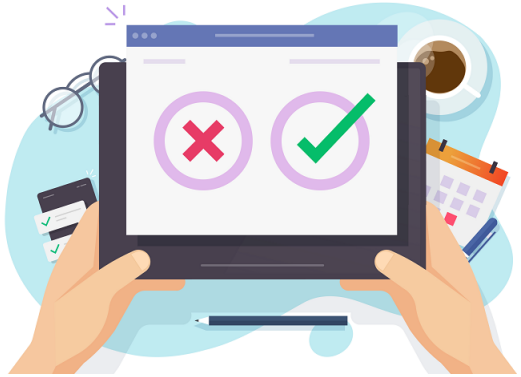
Osteoporosis Canada 2023 guidelines define inadequate response to treatment as which of the following despite adherence to adequate course of treatment for at least 1 year?

A) At least 1 fracture AND ≥5% BMD drop from baseline

B) More than 1 fracture OR ≥5% BMD drop from baseline

C) At least 1 fracture AND any BMD drop from baseline

D) More than 1 fracture OR any BMD drop from baseline



Morin, CMAJ 2023

Pre-Test Question #4

Regarding premenopausal osteoporosis, which of the following is **FALSE?**

A) Bisphosphonates have been shown to increase BMD in premenopausal women.

B) Bisphosphonate exposure in pregnancy has been shown to increase adverse neonatal outcomes above the general population.

C) Teriparatide followed denosumab has been shown to increase BMD in premenopausal women.

D) There is no published data with denosumab and anabolic therapy in pregnancy.

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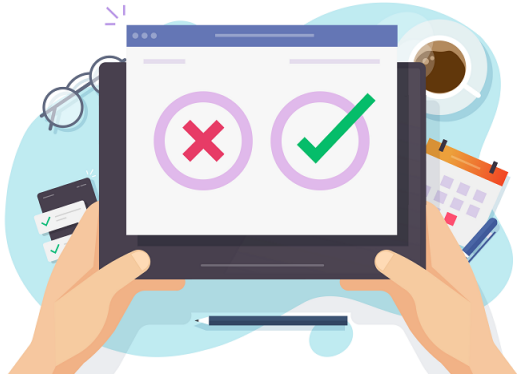


Bhardwaj, Cochrane Database Syst Rev 2016; Shane, JCEM 2022; de Campos, Eur J Clin Pharmacol 2024

Case 4

- 37 year old female
- Acute back pain 2 months postpartum
- X-rays: wedging at T8, T9, T12, L1
- MRI spine: T9 30% compression fracture with marrow edema
- Bone mineral density:

	Z
L-spine	–3.4
L fem neck	–0.8
L total hip	–1.5

Questions:

- **Do we start osteoporosis pharmacotherapy?**
- **What is our approach to premenopausal and pregnancy/lactation osteoporosis?**

Premenopausal Osteoporosis

Describe an approach to **premenopausal osteoporosis**, including **pregnancy and lactation-associated** osteoporosis

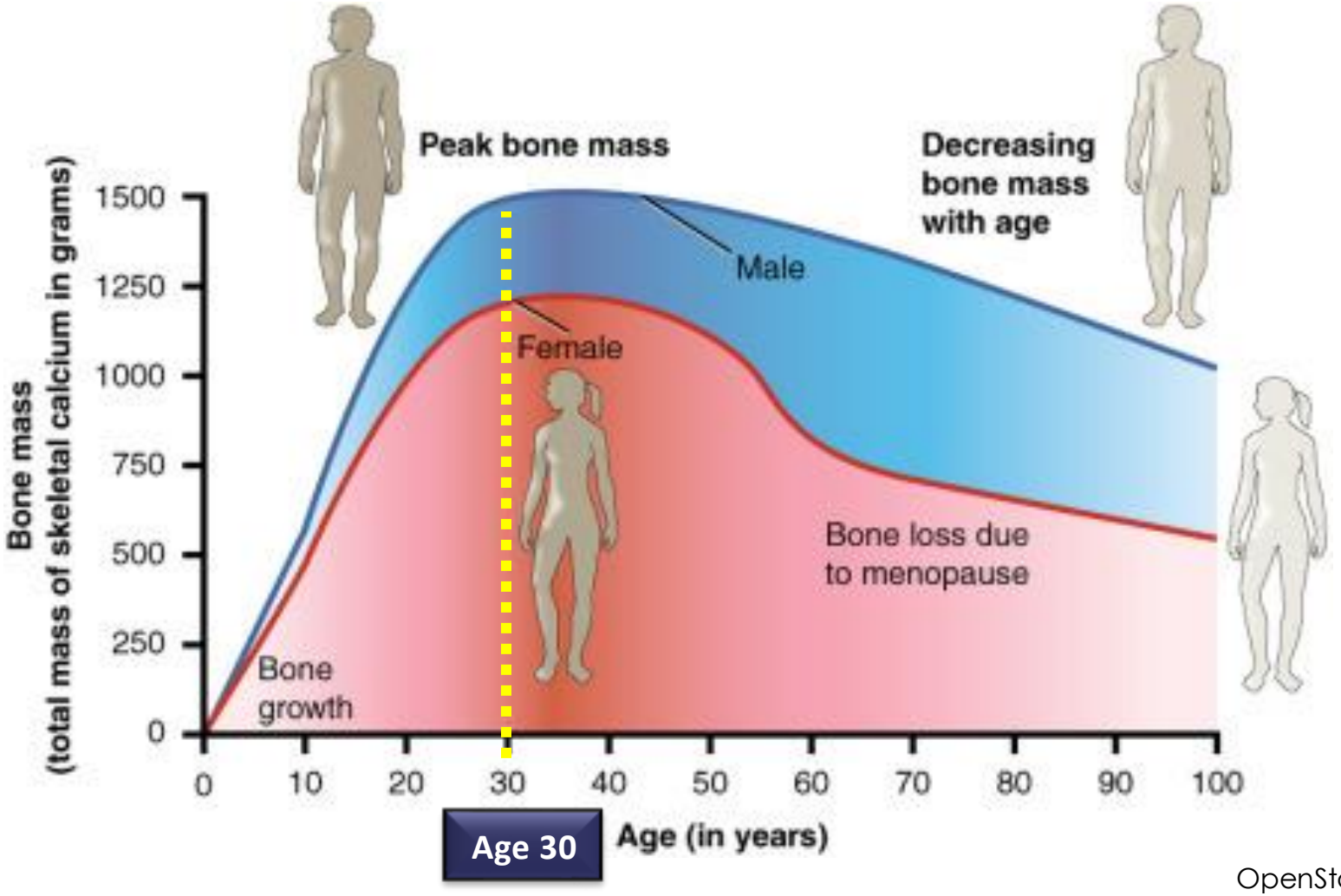
CONFLICT OF INTEREST DECLARATION – Dr. Sabrina Gill

I **DO/DO NOT** have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria	Amgen, BI, Lilly, GSK	Honorarium for presentations
Membership on advisory boards or speakers' bureaus	Amgen, BI, Lilly, GSK	Advisory boards
Funded grants or clinical trials		
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

Peak Bone Mass Accrual

- Childhood disorders
- Sexual development and function
- Birth Control
- Lifestyle factors



OpenStax College, 2013

Low Bone Mass in Premenopausal Women

- Rare, challenging

- Cannot extrapolate fracture risk from BMD
- Fracture risk calculators not standardized for premenopausal women

IOF International Osteoporosis Foundation

Z-score < –2 before age 20,
T-score ≤ –2.5 after age 20 AND
absence of delayed puberty

ISCD The International Society For Clinical Densitometry

Low bone mass
Z-score < –2 below the expected range for age

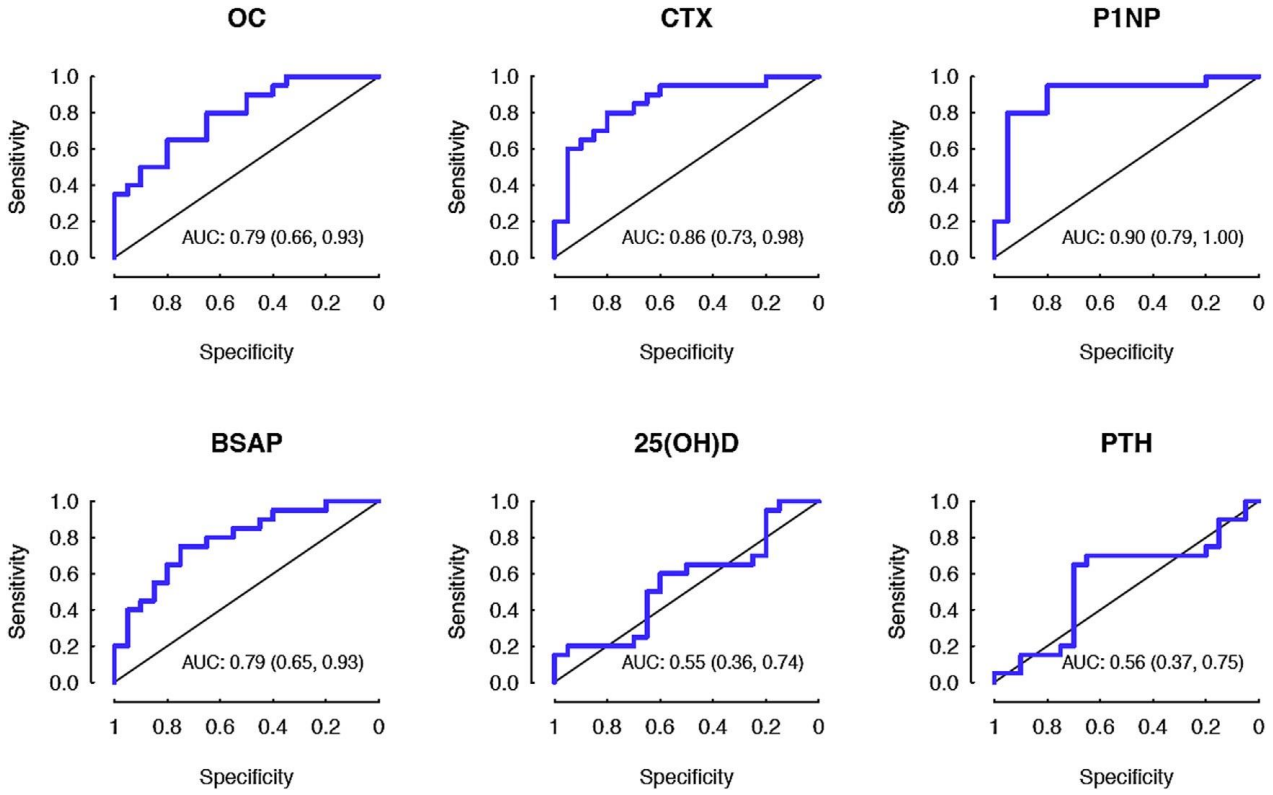
Predictors of Bone Loss and Fractures in Premenopausal Women

Elevated Bone Turnover Markers Are Associated With Distal Radius Fractures in Premenopausal Women

Beverlie L. Ting MD *, Kempland C. Walley BSc †, Thomas G. Travison PhD ‡, Tamara D. Rozental MD †

- FRAX only validated for age 40-90
- Further studies required to validate TBS and HRpQCT

- What about bone turnover markers?
  - N = 20, logistic regression
  - Only moderate performance of osteocalcin, P1NP, and CTX in predicting distal radius #



Ting, J Hand Surg 2017

Idiopathic Osteoporosis

- Low trauma fracture with T-score ≤ –2.5
- Possible mechanisms:
  - Microarchitectural deterioration + atypical regulation of bone and fat
  - Osteoblastic dysfunction
  - GH/IGF-1 abnormalities
  - Subclinical estrogen deficiency
  - Increased bone turnover
  - Hypercalciuria
- Potential genetic variants
  - LRP5, WNT1, PLS3, DKK1, COL1A1/COL1A2 , DKBP10, HGD, SLC34A3
  - 46% have no genetic variants

Reed, JBMR 1995; Rubin, Osteo Int 2005; Peris, Clin Exp Rheumatol 2008; Colett, JBMR Plus 2018
Cohen, JCEM 2011; Sturznickel, JBMR 2021; Cohen, Bone 2022; Goetz, Osteo Int 2022; Stringer, JCEM Case Rep 2024

Who Should be Evaluated?

ENDOCRINE SOCIETY

A Contemporary View of the Definition and Diagnosis of Osteoporosis in Children and Adolescents

Examples of supporting evidence needed to trigger a bone health evaluation

Physical/radiographic stigmata (ie, blue sclera, Wormian bones, joint hypermobility, etc)
Known increased risk for fracture (such as glucocorticoid exposure)
A positive family history of osteoporosis/osteogenesis imperfecta
Recurrent low-trauma fractures
Low** BMD

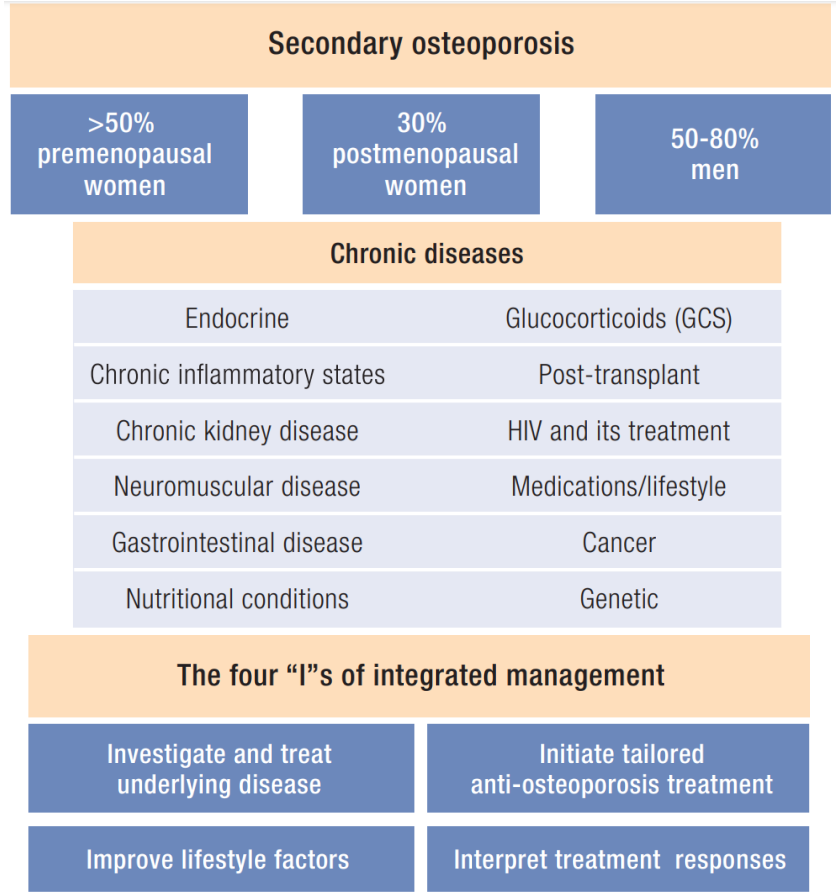
* Low trauma - defined as falling from a standing height or less, at no more than walking speed.

** Low BMD - a continuous, not a threshold, factor. The lower the BMD, the more likely to sustain a fragility fracture.

Ward, JCEM 2020

Notable Secondary Causes in Premenopausal Osteoporosis

- Anorexia Nervosa
  - ↑ osteoporosis (OR 12.6) and fractures (OR 1.84)
- Lifestyle alterations
  - Smoking (OR 2.6 if > 3 pack years)
  - Excess ETOH
  - Malnutrition
  - Vegetarian / vegan diet
    - ↓ 4-6% BMD versus omnivores (clinically insignificant)
  - Vitamin D deficiency
- Medications
  - Glucocorticoids
  - Hormone deprivation therapy

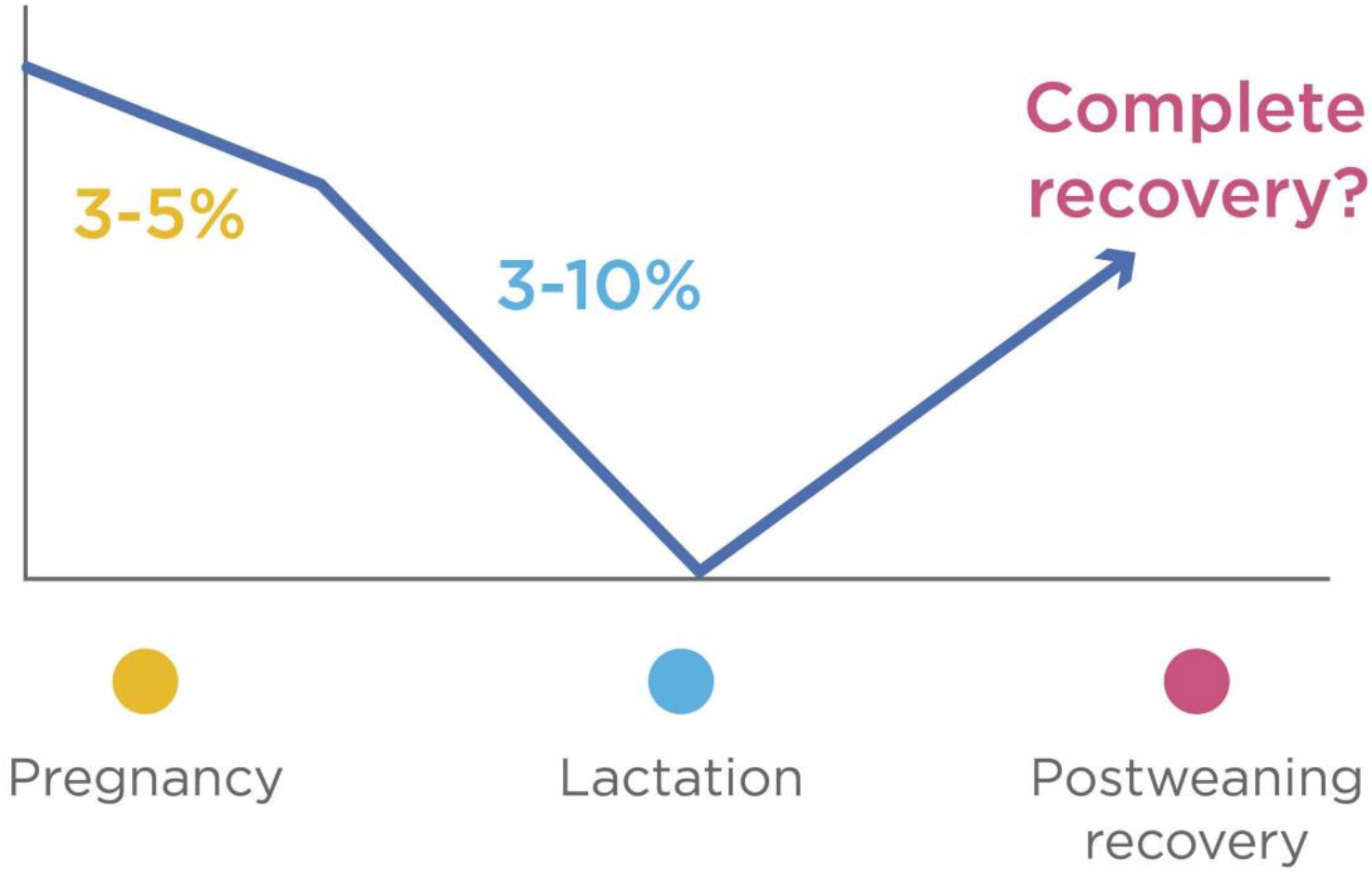


Ho-Pham, Am J Clin Nutr 2009; Salmi, Acta Psychiatr Scand 2016, Ebeling, Endocr Rev 2022

BMD Changes in Pregnancy and Lactation

Recent Insights into Pregnancy and Lactation-Associated Osteoporosis (PLO)

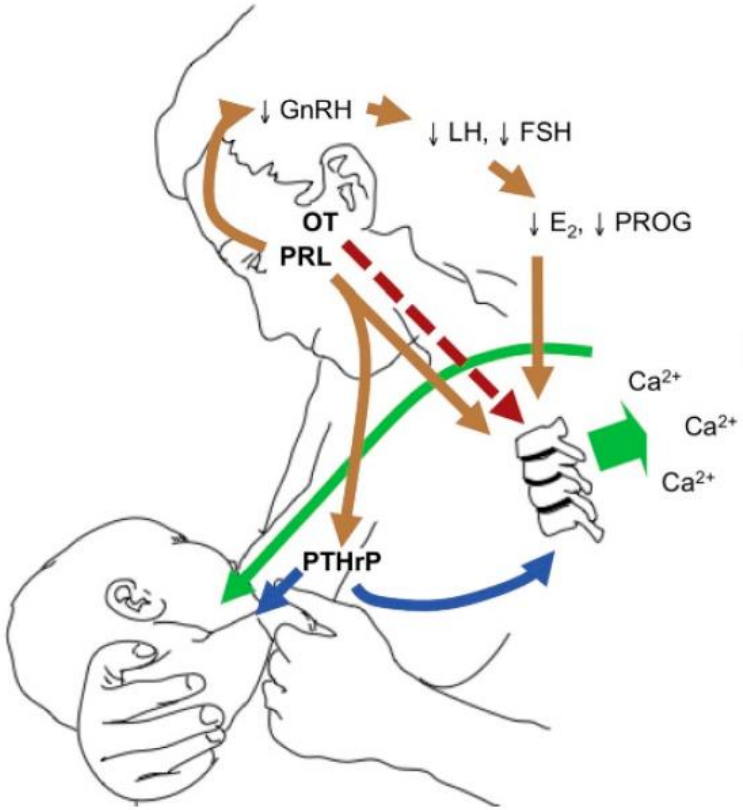
Maria Florencia Scioscia, Maria Belen Zanchetta



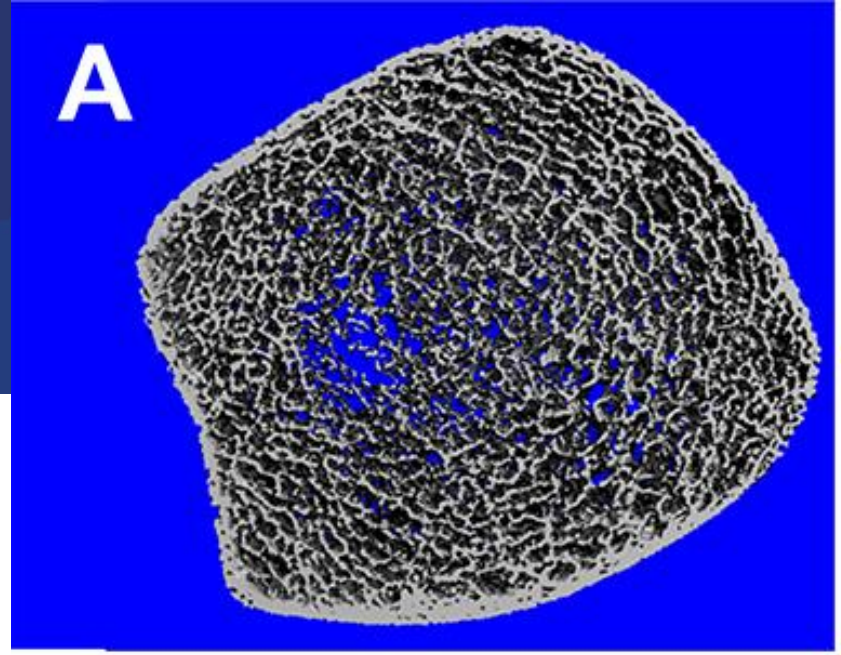
Scioscia, Int J Womens Health 2023

Bone loss in pregnancy and lactation

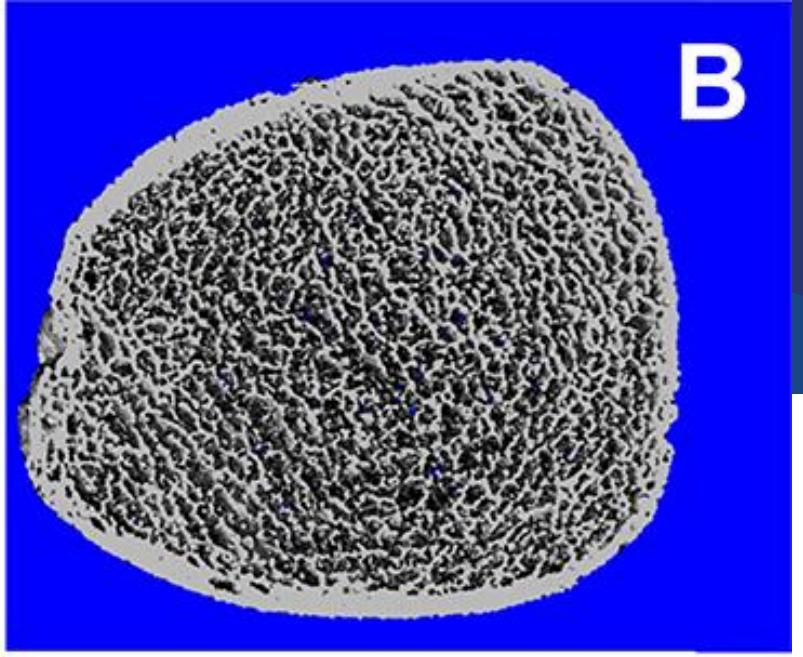
Period of life	Adaptation mechanisms	Effect	Bone loss?
Pregnancy	1-25 OH Vitamin D increase →	Doubled-up intestinal absorption of calcium	No
	PTHrp increase →	Mild bone resorption increase	
Lactation	Suckling>> HyperPRL>>(-) GnRH>> HypoE2 →	Increased bone resorption	Yes.
	PTHrp increase		
However, pregnancy and lactation do not increase the risk of fracture in the long term			



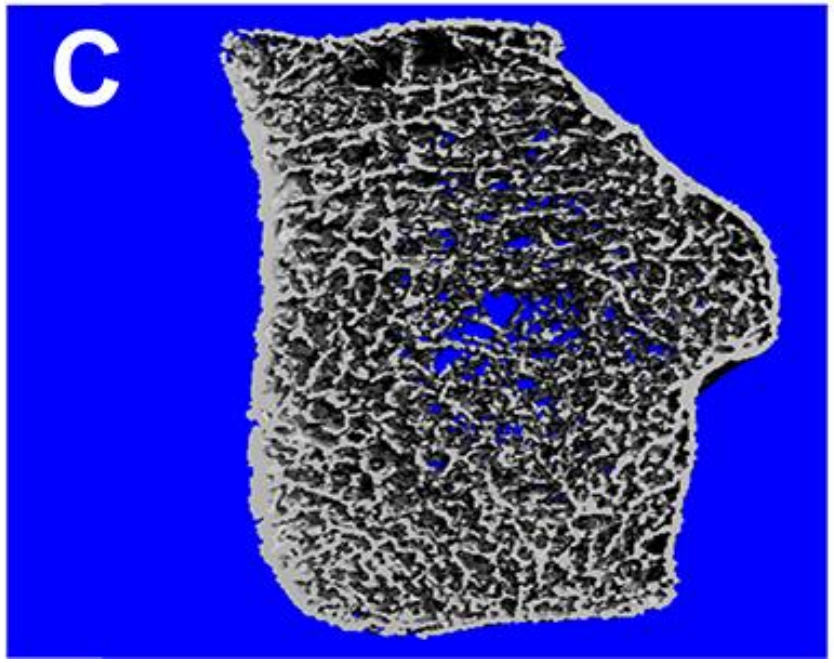
Kovacs 2020; Ali, J Clin Med 2021; Scioscia, Int J Womens Health 2023



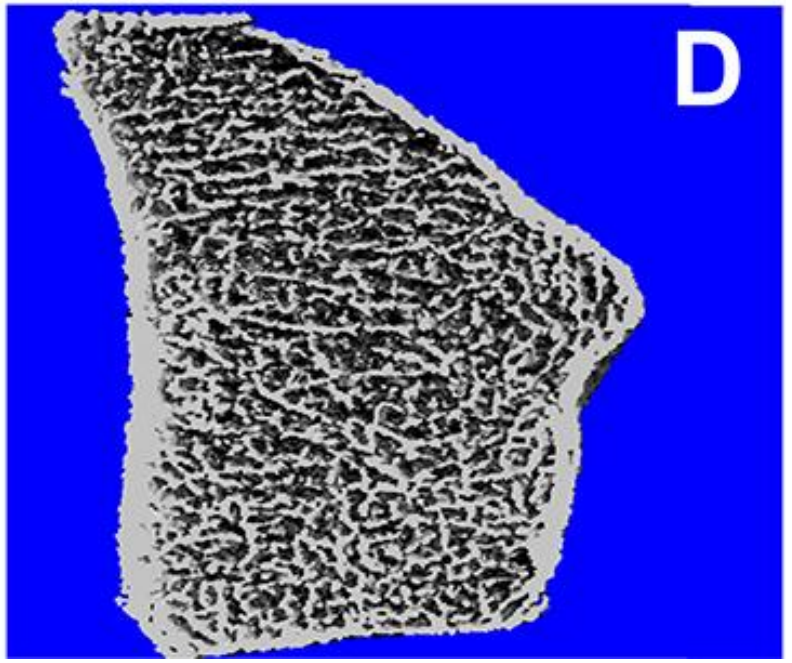
Distal radius in PLO



Distal radius, healthy lactating woman



Distal tibia in PLO



Distal tibia, healthy lactating woman

Scioscia,
J Endocr Soc 2021

Pregnancy and Lactation-associated osteoporosis

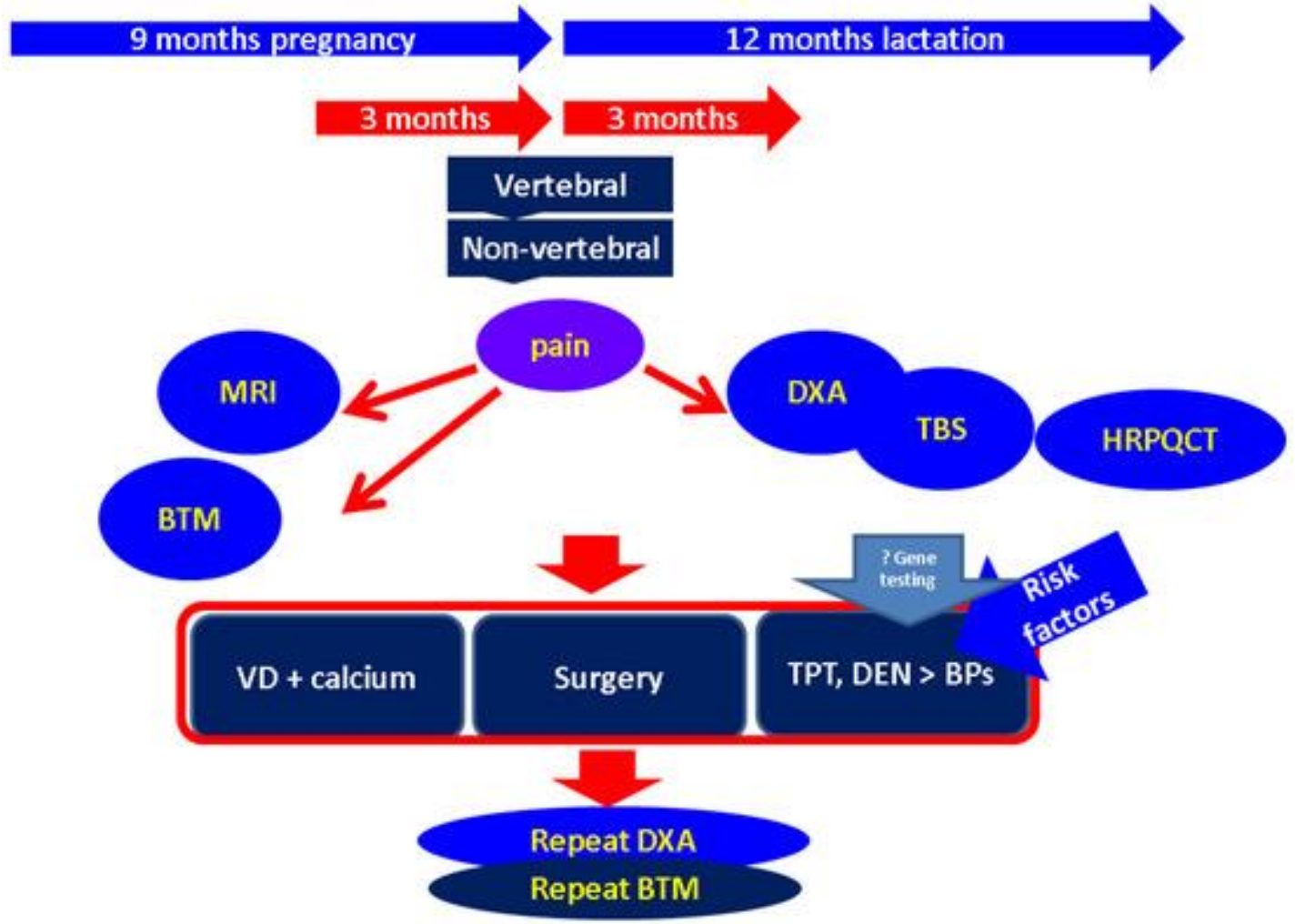
- Incidence: 4.5 per 10 000
- Fragility fractures in 3rd trimester or early postpartum
  - Vertebral, hip, pelvis/sacral fractures most common
- Severe back pain at presentation
  - Debilitating with chronic pain

Potential Risk Factors for PLO

- Maternal age > 30
- Smoking
- Family history of Osteoporosis
- Heparin or glucocorticoid use in pregnancy
- Vitamin D deficiency
- Gestational diabetes
- IVF
- Twin pregnancy
- Postpartum thyroiditis
- Autoimmune disease
- LRP5/WNT1, COL1A1/A2 mutations

Kovacs, Physiol Rev 2020; Carsote, Diagnostics 2023

Approach to PLO:



Carsote, Diagnostics 2023

Premenopausal Osteoporosis: Treatment options

- Treat underlying secondary cause if feasible
- Calcium 1000-1500 mg/day
- Target 25OHVitD ≥ 75 nmol/L
- Reasonable, non-excessive physical activity
- Analgesia ± vertebroplasty for vertebral #

- Bisphosphonates, denosumab, teriparatide
- SERMs: not indicated
- Nasal calcitonin: limited use
- Romosozumab: no data in premenopausal women

Arnala, Bone 1996; Scioscia, Int J Womens Health 2023

BMD Improvements by Treating Underlying Cause

Osteoporosis in Premenopausal Women: A Clinical Narrative Review by the ECTS and the IOF

Jessica Pepe,[1] Jean-Jacques Body,[2] Peyman Hadji,[3] Eugene McCloskey,[4] Christian Meier,[5] Barbara Obermayer-Pietsch,[6] Andrea Palermo,[7] Elena Tsourdi,[8,9] M.Carola Zillikens,[10] Bente Langdahl,[11,*] and Serge Ferrari[12,*]

Diseases	Patients	Study Design	Intervention	Findings Summary
PHPT	N = 10, median age 44.5 years (28-55)	Retrospective study	**Parathyroidectomy**	Approximately 12 ± 6 months after parathyroidectomy a percentage increase of BMD was observed at LS 2.2 ± 4.5, total hip + 2.6 ± 2.2, radius −0.8 ± 3.2.
IBD	anti-TNF-a N = 23 (90% premen women) Mean age 33.4 ± 12.1years vs control N = 48 (66.7% premen) Mean age 39.6 ± 11.6 years	Longitudinal prospective cohort	**Treatment with anti-TNF-a therapy**	After 7 years of follow-up, LS and FN BMD increased significantly in patients treated with anti-TNF-a. No difference in the number of incident fractures but new fractures were more common and more severe in the group not receiving anti-TNF-a therapy
Celiac disease	N = 26, mean age 31.1 ± 8.7 years (19-50)	Longitudinal prospective cohort	**Gluten-free diet for 1 year**	HR-pQCT revealed improvement at the distal radius of approximately 9% of trabecular volumetric density, BV/TV and trabecular thickness (all $P < 0.05$). A decrease of cortical thickness was reported (−3.6%, $P = 0.03$). At the distal tibia, all volumetric parameters, the total, trabecular and the cortical density increased significantly (3.6%, $P = 0.004$; 8.3%, $P < 0.0001$; and 1.54%, $P = 0.0004$, respectively). A BV/TV and trabecular thickness increase of approximately 8.3% (both $P < 0.05$) were reported. A decrease of cortical thickness was observed (−0.8%, $P < 0.05$).
Anorexia nervosa	N = 160, mean age 28.3 ± 10 years	Retrospective	**Body weight regain**	No significant changes in hip and LS BMD were observed after 3 years. However, fat mass gain was a significant factor associated with BMD improvement at follow-up (8.0 ± 9.1 vs 3.0 ± 3.5 kg, $P = 0.02$), as well as weight gain (7.7 ± 8.2 vs 3.2 ± 5.6 kg, $P = 0.10$).

Pepe, JCEM 2020

Osteoporosis Pharmacotherapy with Secondary Causes

Diseases	Patients	Study Design	Intervention	Findings Summary
RA	N = 167 women, 6% < 40 years, 20% < 50 years Premenopausal 27% in the ibandronate group, 20% in the placebo group	A 48-week double-blinded RCT	**Ibandronate 150 mg or placebo every 4 weeks for 48 weeks**	After 48 weeks, increased LS BMD changes (3.7% vs −1.9%, P < 0.0001and FN and total hip also showed similar results (P < 0.0073 and P< 0.0031, in ibandronate
Celiac disease	N = 28, mean age 26 years (14 female)	RCT open label	**calcium/vitamin (N = 13) vs zoledronic acid 4mg + calcium/vitamin D (N = 15)** **For One year**	Ca/vit D:T-score increase from -3.31 ± 1.46 to −2.12 ± 1.44 SD, (P< 0.05) Zol -2.82 ± 1.27 to −1.06 ± 1.84 SD, (P < 0.001). No difference in delta T scores
Anorexia nervosa	N = 21, mean age 47 years	RCT	**Teriparatide for 6 months (N = 10) placebo (N = 11).**	6.0% ± 1.4% increase in LS BMD compared to 0.2%± 0.7% all P < 0.01). No differences in femoral BMD.
People Living With HIV	N = 44 (2 women), median age alendronate 43 years placebo 47 years	RCT	**Alendronate group (N = 20) vs placebo group (N = 24) for 96 weeks**	6.1% (95% CI 2.8-9.3), P = 0.0003 difference improvement with a T-score <−2.5 SD in alendronate vs placebo
Cystic fibrosis	N = 171, female N = 84, mean age 14, years (range 5-30)	RCT	**Alendronate group (N = 65) vs placebo group (N = 63) for 12 months.**	Alendronate significantly increased BMD 16.3% vs 3.1% vs placebo group (P = 0.001).

Pepe, JCEM 2020

Premenopausal Osteoporosis: Bisphosphonates

- Limited data in premenopausal women
- ↑ BMD in cystic fibrosis, IBD, β-thalassemia

American College of Rheumatology
Empowering Rheumatology Professionals
Glucocorticoid-Induced Osteoporosis
2022

Moderate risk / consider treatment:
Women age < 40
Prednisone ≥7.5mg/day for ≥6 months, AND
Z-score < – 3 OR significant bone loss*

*above least significant change

Conwell, Cochr Database Rev 2014; Bhardwaj, Cochr Database Rev 2016; Yao Medicine 2017, Humphrey, Arthritis Rheumatol 2023

Premenopausal Osteoporosis: Denosumab

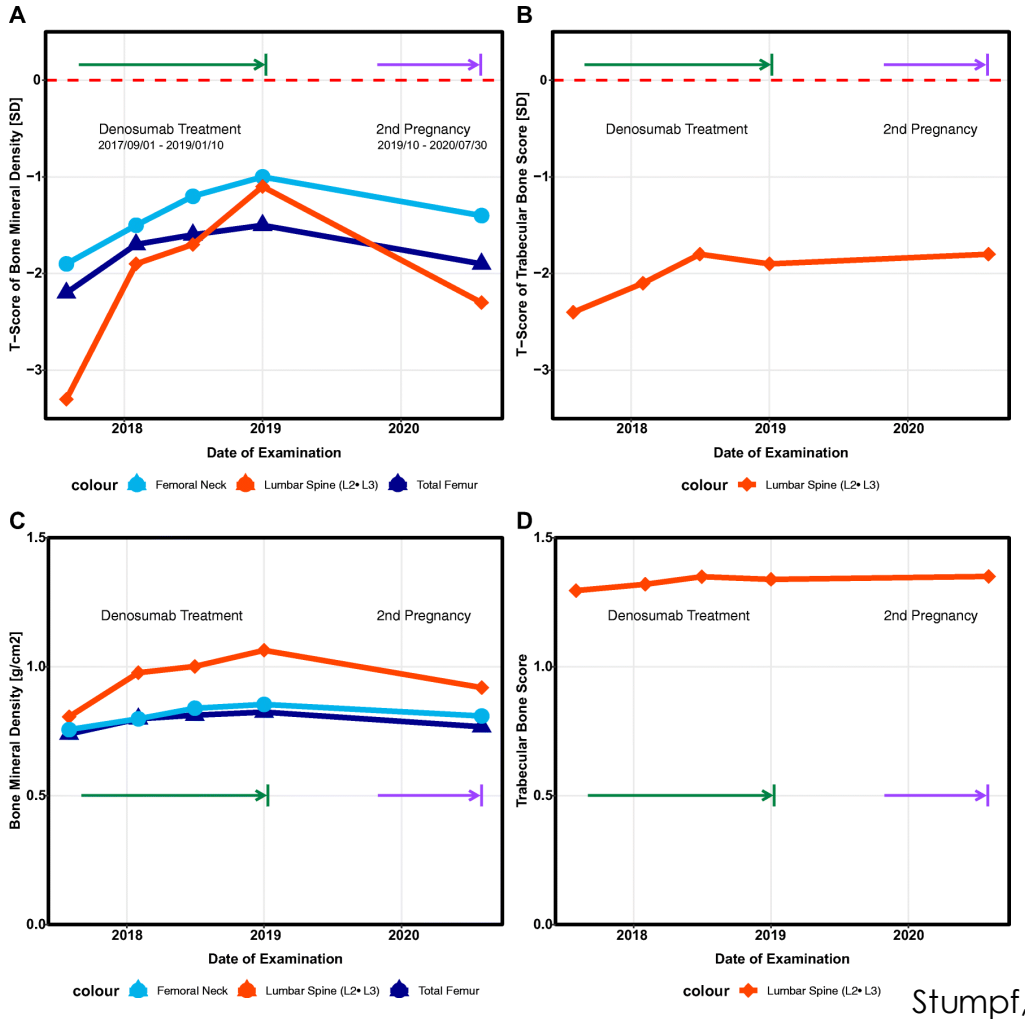
Osteoporosis International (2021) 32:2383–2387
https://doi.org/10.1007/s00198-021-06008-z

CASE REPORT

Influence of denosumab on bone mineral density in a severe case of pregnancy-associated osteoporosis

U. Stumpf[1] · M. Kraus[1] · P. Hadji[2]

- Case report
- 33yo, severe PLO
- Multiple vert #
- Could not afford teriparatide
- Stopped DMAB after 3 doses (pursuing another pregnancy)
  - BTMs stable after



PLO = pregnancy and lactation-associated osteoporosis
DMAB = denosumab
BTMs = bone turnover markers

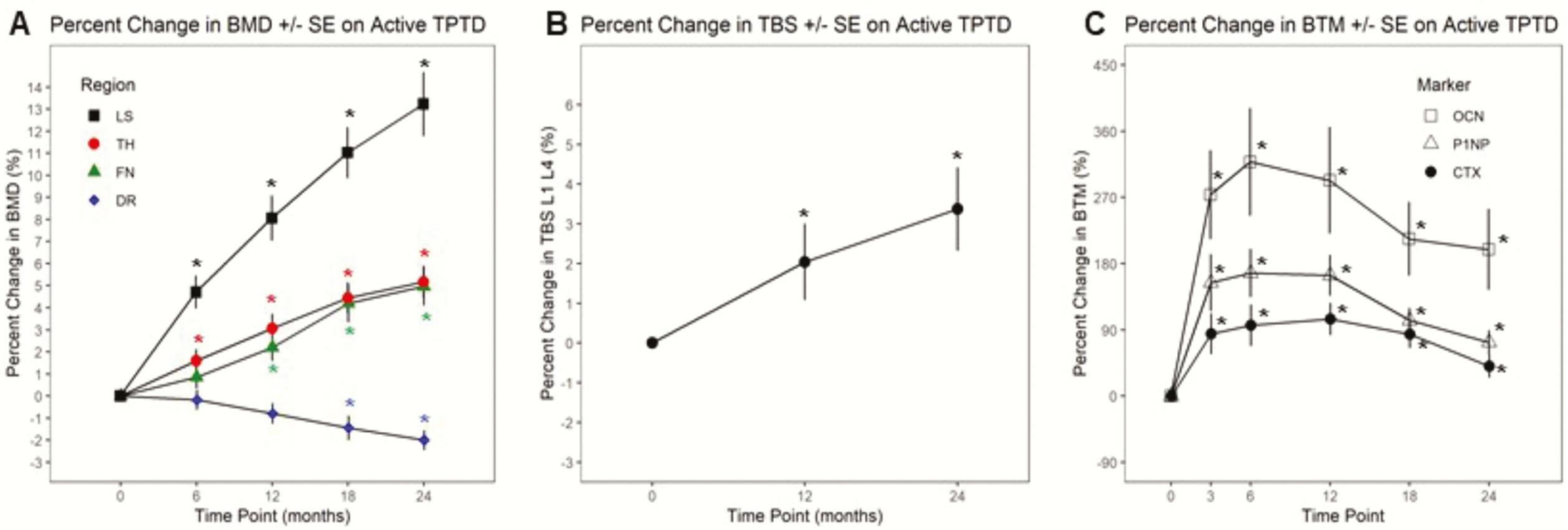
Stumpf, Osteo Int 2021

Premenopausal Osteoporosis: Teriparatide

Effect of Teriparatide on Bone Remodeling and Density in Premenopausal Idiopathic Osteoporosis: A Phase II Trial

Adi Cohen,[1] Stephanie Shiau,[2] Nandini Nair,[1] Robert R. Recker,[3] Joan M. Lappe,[3] David W. Dempster,[4,5] Thomas L. Nickolas,[1] Hua Zhou,[5] Sanchita Agarwal,[1] Mafo Kamanda-Kosseh,[1] Mariana Bucovsky,[1] John M. Williams,[1] Donald J. McMahon,[1] Julie Stubby,[3] and Elizabeth Shane[1]

- Randomized control trial, N = 41
- Teriparatide 20 mcg v placebo (switched to TPTD after 6 months)



Cohen, JCEM 2020

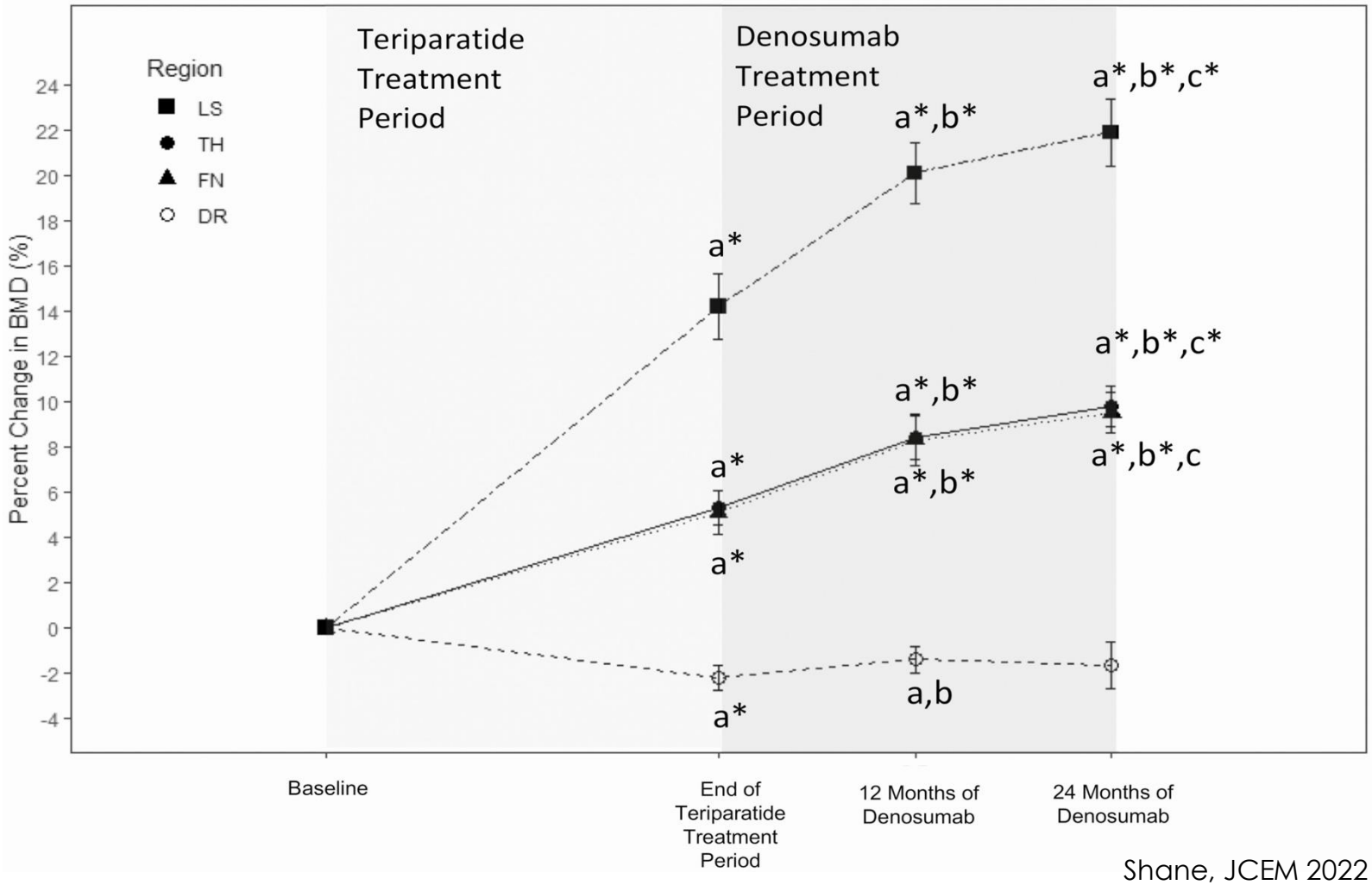
Premenopausal Osteoporosis: Teriparatide → Denosumab

JOURNAL ARTICLE

Denosumab After Teriparatide in Premenopausal Women With Idiopathic Osteoporosis

Elizabeth Shane, Stephanie Shiau, Robert R Recker, Joan M Lappe, Sanchita Agarwal, Mafo Kamanda-Kosseh, Mariana Bucovsky, Julie Stubby, Adi Cohen

- N = 32
- TPTD x 24 months, then DMAB x 12-24 months
- ↑ BMD
- ↑ TBS by 5.8 ± 5.6% ($p < 0.001$)



TPTD = teriparatide
DMAB = denosumab
TBS = trabecular bone score

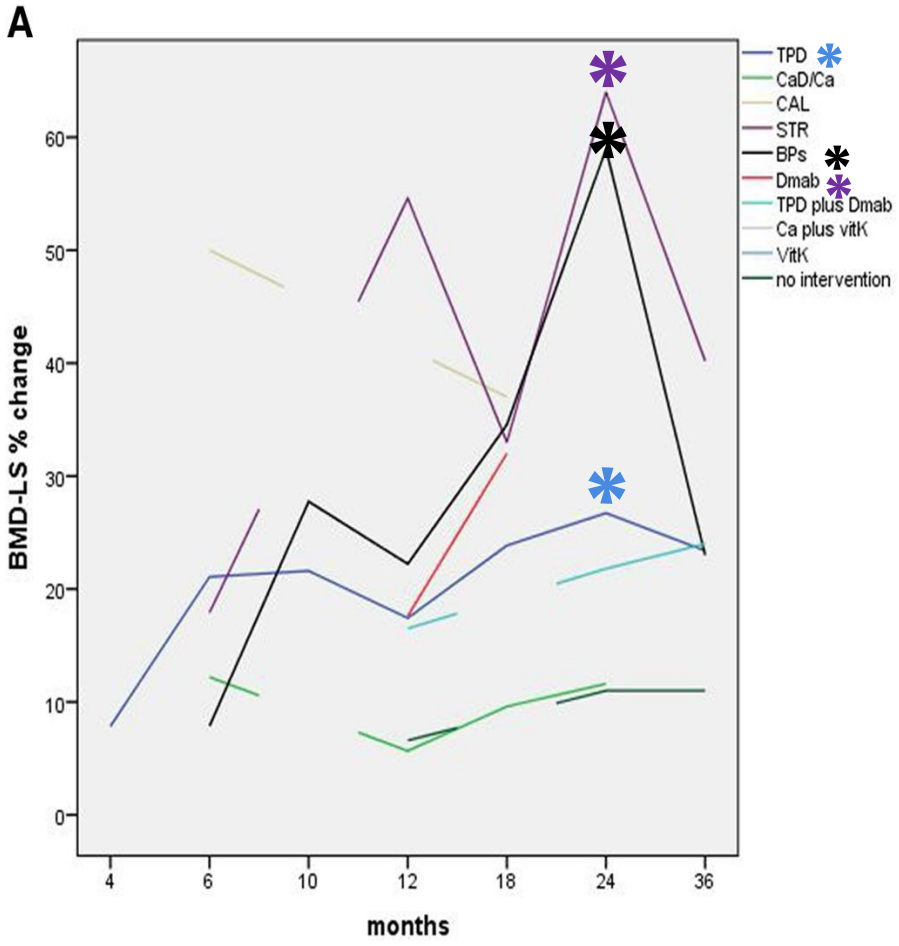
Shane, JCEM 2022

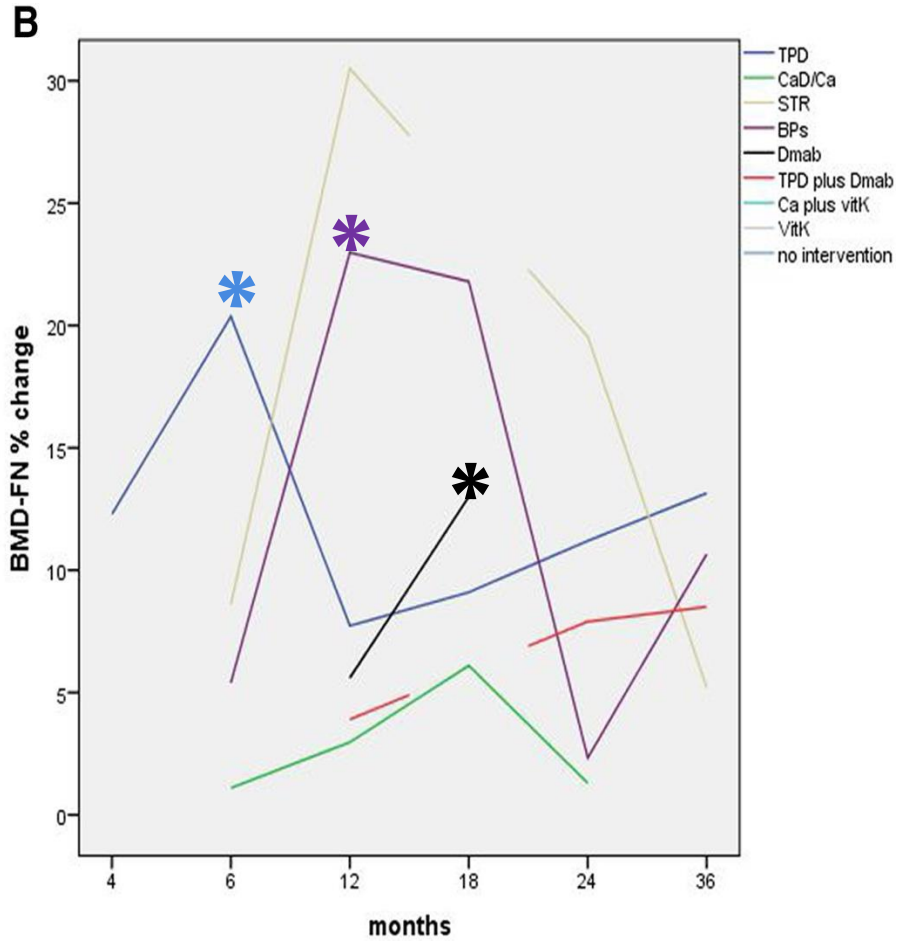
Pregnancy and Lactation-associated Osteoporosis: Effect of therapy on BMD

Comparative Effectiveness of Therapeutic Interventions in Pregnancy and Lactation-Associated Osteoporosis: A Systematic Review and Meta-analysis

Panagiotis Anagnostis,[1] Kalliopi Lampropoulou-Adamidou,[2] Julia K. Bosdou,[3] Georgios Trovas,[2] Petros Galanis,[4] Efstathios Chronopoulos,[2] Dimitrios G. Goulis,[1] and Symeon Tournis[2]

- Meta-analysis, 66 studies
- Rare fractures
- Higher risk of fractures in subsequent pregnancies



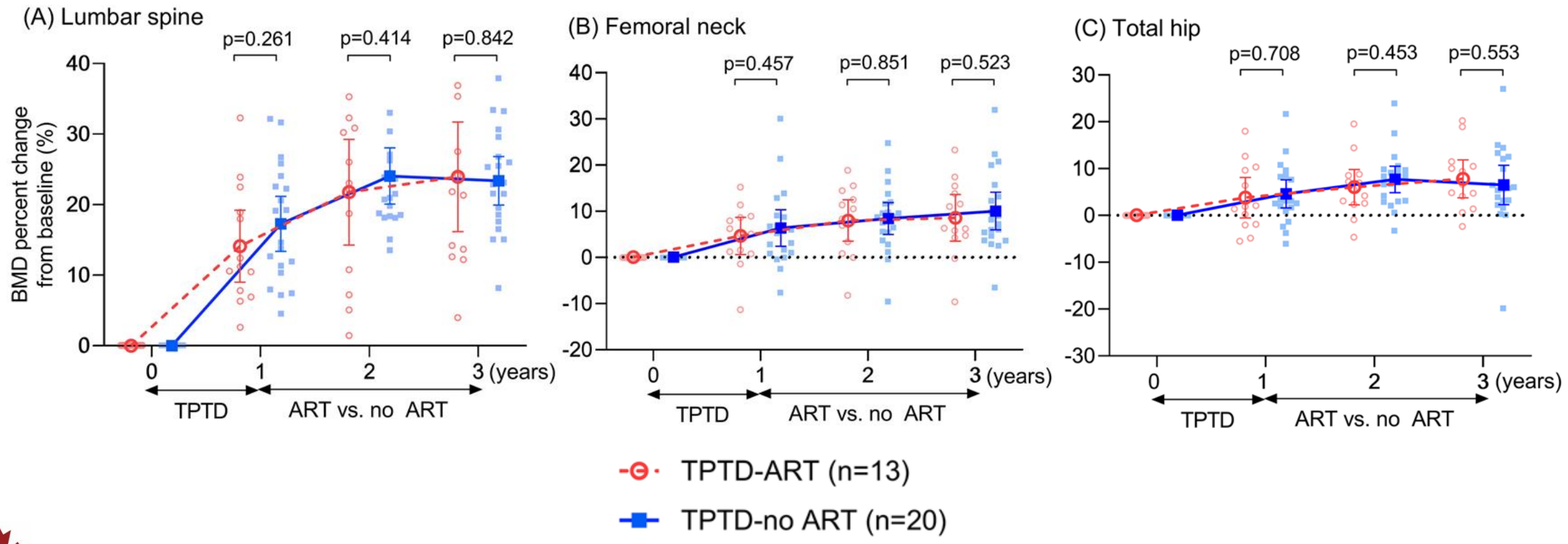


Anagnostis, JCEM 2024

Pregnancy and Lactation-associated Osteoporosis: Maintenance of BMD post-teriparatide cessation

Bone Density After Teriparatide Discontinuation With or Without Antiresorptive Therapy in Pregnancy- and Lactation-Associated Osteoporosis

Seunghyun Lee [1], Namki Hong [1], Kyoung Jin Kim [1 2], Chung Hyun Park [1], Jooyeon Lee [1], Yumie Rhee [3]



Lee, Calcif Tissue Int 2021

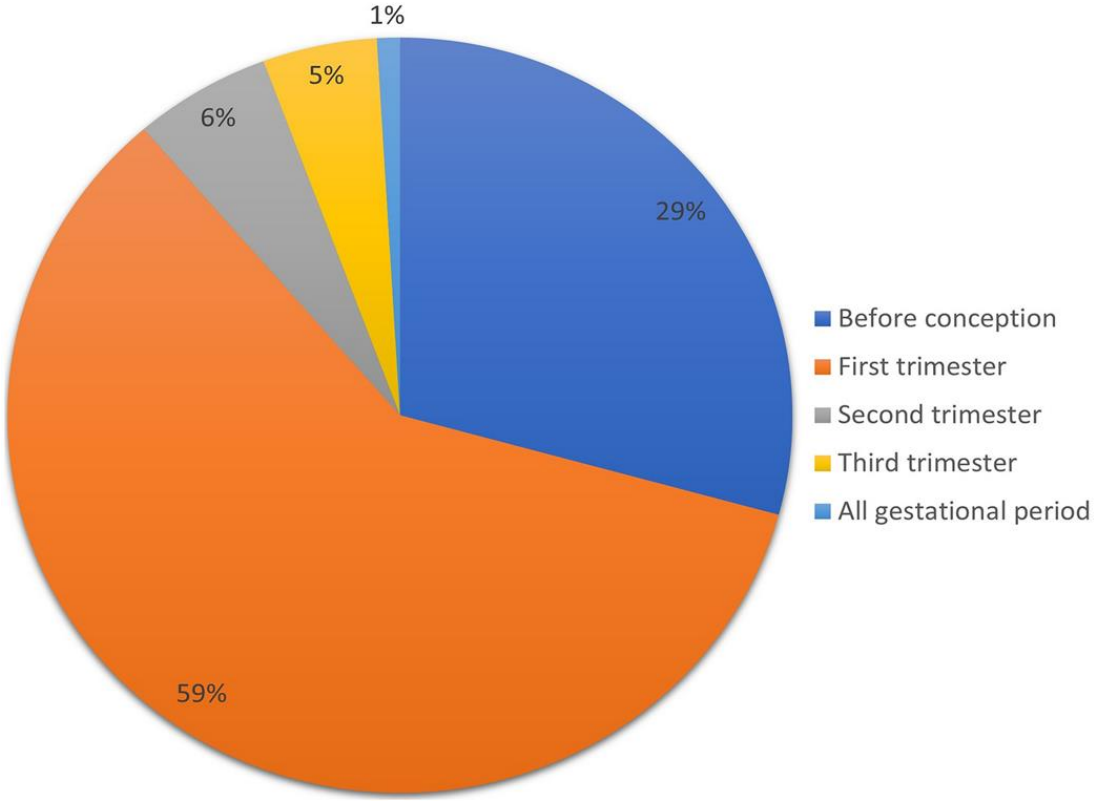
Possible Teratogenic Effects

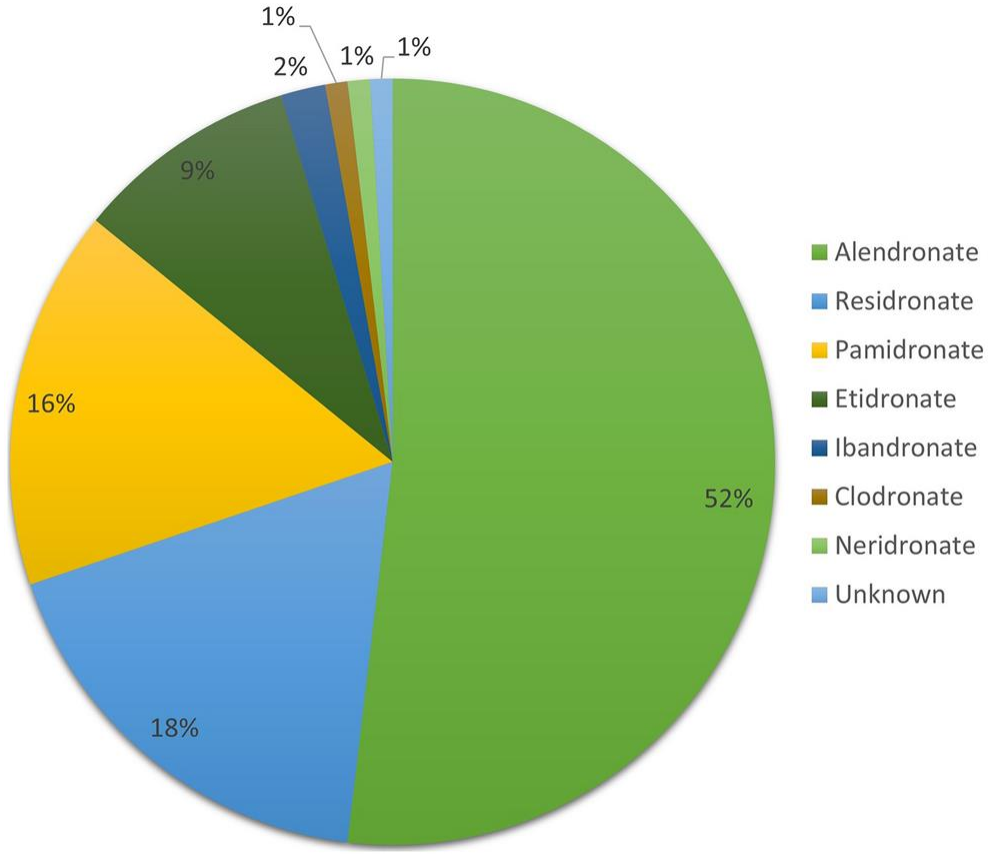
- Limited long-term data
  - No adverse maternal or fetal outcomes
  - Animal models: fetal bone exposure
- Bisphosphonates: long skeletal half-life, cross placenta
- Review of bisphosphonate exposure
  6 weeks prior/during pregnancy with systemic disease:
  - No increased risk of congenital malformations
  - ↑ neonatal complications (25% vs 6%)
    - E.g. arrhythmia, maternal fetal infection, acute fetal distress, polycythemia, thrombocytopenia
  - ↓ live birth rate (90% versus 100%)
  - Transient hypocalcemia with long-acting IV bisphosphonate

Munns; JBMR 2004; Sakal, Osteo Int 2019

Pregnancy: Bisphosphonate Exposure

- 13 studies, 108 pregnancies





Gushiken de Campos, Eur J Clin Pharmacol 2024

Pregnancy: Bisphosphonate Exposure

- Adverse neonatal outcomes did not exceed that of general population
  - Spontaneous abortion (n = 6)
  - Congenital malformations (n = 4)
  - Hypocalcemia (n = 4
  - Preterm birth (n = 3)
  - Low birth weight (n = 3)
  - Distress syndrome (n=2)
  - Jaundice (n=2)


REVIEW

CURRENT OPINION **Osteoporosis in premenopausal women**

Bente L. Langdahl

- Bisphosphonate treatment should not be initiated if a woman planning pregnancy in the next 12 months

Langdahl, Curr Opin Rheumatol 2017; Gushiken de Campos, Eur J Clin Pharmacol 2024

Pregnancy: Denosumab and Anabolic Therapy

- No human studies
- Not recommended for use in pregnancy

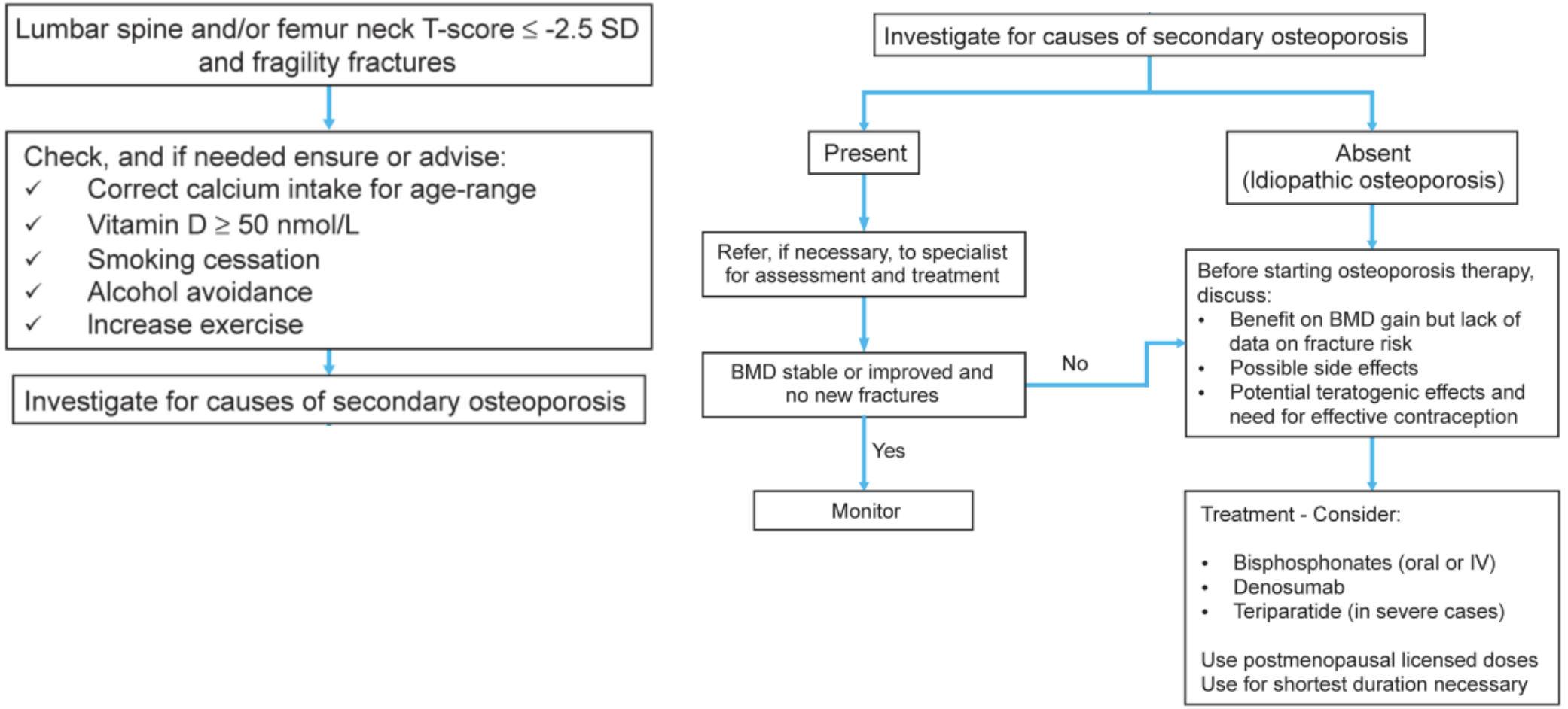
- Denosumab exposure in utero in cynomolgus monkeys:
  - Dental dysplasia
  - ↓ bone length, cortical thickness, femur diaphysis peak load / strength
    - Other bone features resembled an partially reversible osteoporotic phenotype
  - ↑ stillbirth, postnatal mortality
  - ↓ body weight gain, decreased growth/development

Bussiere, Reprod Tox 2013; Boyce, Bone 2014

Premenopausal Osteoporosis: Flowchart

Osteoporosis in Premenopausal Women: A Clinical Narrative Review by the ECTS and the IOF

Jessica Pepe,[1] Jean-Jacques Body,[2] Peyman Hadji,[3] Eugene McCloskey,[4] Christian Meier,[5] Barbara Obermayer-Pietsch,[6] Andrea Palermo,[7] Elena Tsourdi,[8,9] M.Carola Zillikens,[10] Bente Langdahl,[11,*] and Serge Ferrari[12,*]



Pepe, J et al JCEM 2020; 105(8): 2487-2506

Back to the Case

- 37 year old female, postpartum vertebral fractures

Further review:

- Menarche age 12, normal puberty
- PCOS diagnosis with oligomenorrhea, on OCP
- Dentition unremarkable
- Weight stable
- Unremarkable workup for secondary causes

Case

- Did not want to pursue vertebroplasty
- Treatment: calcium, vitamin D, exercise
- Repeat BMD at 1 year:
- Repeat BMD at 3 years:

	Z	Z	Z	
L-spine	–3.4	–2.4	–1.6	+10%
L fem neck	–0.8	–0.7	–0.7	
L total hip	–1.5	–1.1	–0.7	+4%

Post-Test Question #4

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Slido.com with code:
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Post-Test Question #4

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Slido.com with code: **#2041940**

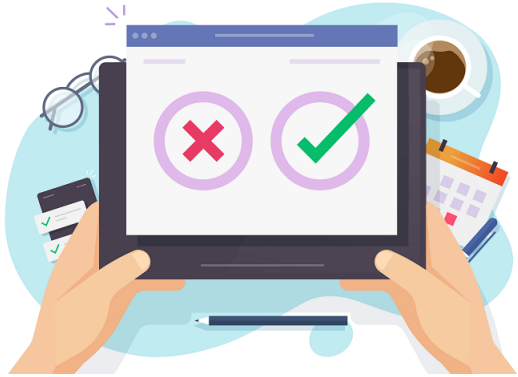
Regarding premenopausal osteoporosis, which of the following is **FALSE?**

A) Bisphosphonates have been shown to increase BMD in premenopausal women.

B) Bisphosphonate exposure in pregnancy has been shown to increase adverse neonatal outcomes above the general population.

C) Teriparatide followed denosumab has been shown to increase BMD in premenopausal women.

D) There is no published data with denosumab and anabolic therapy in pregnancy.



Bhardwaj, Cochrane Database Syst Rev 2016; Shane, JCEM 2022; de Campos, Eur J Clin Pharmacol 2024

Questions and Answers

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Wrap Up

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This activity is an accredited group learning activity under Section 3 as defined by the Royal College of Physicians & Surgeons of Canada for the Maintenance of Certification program.

Approved by CSEM for a maximum of **2.0 hours (credits are automatically calculated)**

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- Complete the evaluation
- 2 weeks post-session, we'll email your results and personal reflection tool
- Review your results
- Reflect using the tool
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Evaluation

- Scan the QR code now to complete the evaluation
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