Premenopausal Osteoporosis

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Disclosures

Industry research support

- Eli Lilly
- Amgen

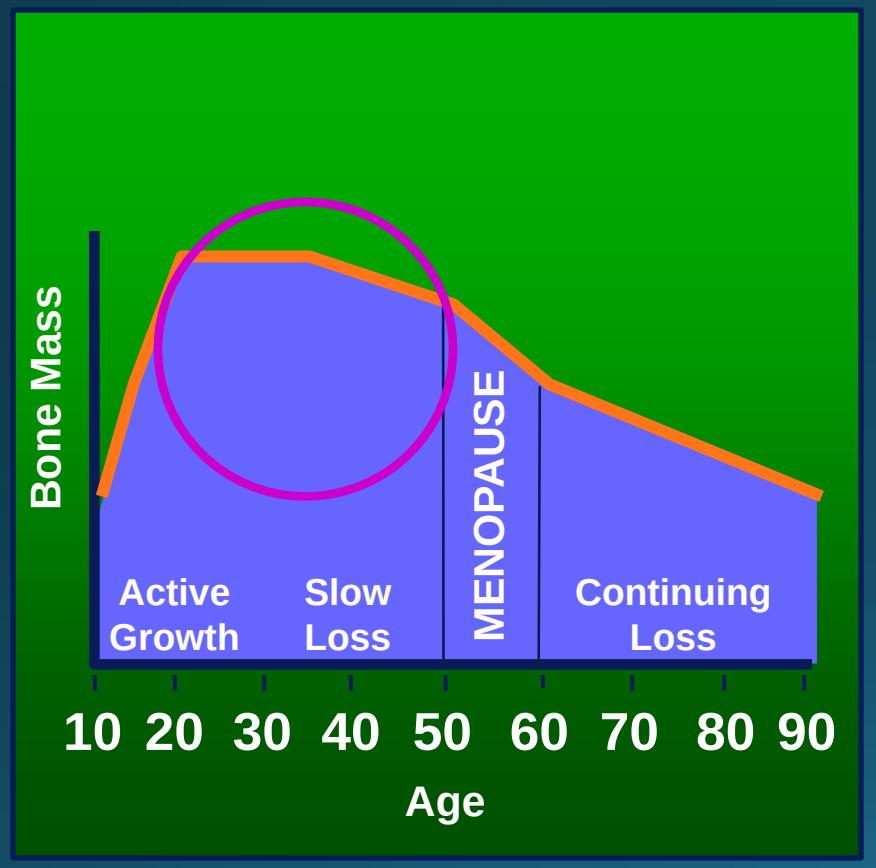
Off-Label uses of medications will be discussed.

Objectives

To review special considerations that apply to premenopausal women in terms of:

- Diagnostic criteria and terminology
- Evaluation
- Management and medical treatment

Bone Mass Changes Over a Woman's Lifetime



Adapted from Wasnich RD, et al. 1989:179-213

Premenopausal years:

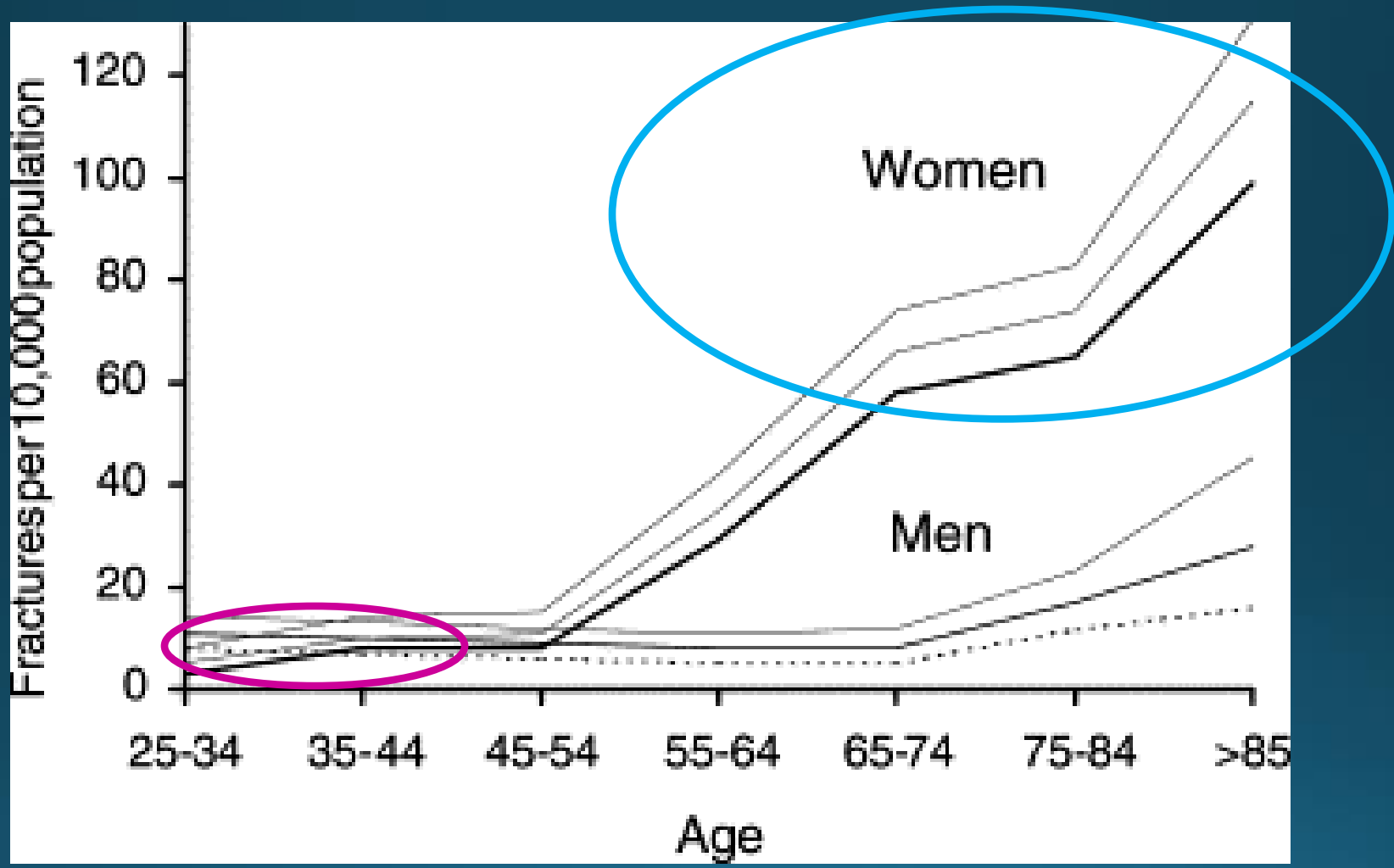
- Correspond with peak bone mass
- Generally considered a time of stable BMD

PREMENOPAUSAL OSTEOPOROSIS IS RARE:

4.1 cases per 100,000 person-yrs[1]
(based on fractures and low BMD)

1.Khosla et al, Bone 1994

Premenopausal Fractures are RARE



The incidence of distal radius fractures in men and women per 10,000 population per year and 95%confidence limits for Dorset residents.

Thompson, Injury 2004.

Osteoporosis before Menopause

- Although rare, bone fragility does present before menopause in some women.

- Diagnostic and management strategies for postmenopausal women cannot be applied uniformly in premenopausal women.

CASES

Case #1:

A 30-year-old healthy woman falls from a seated position on a window seat and sustains a fracture of her greater trochanter. Imaging and surgical pathology show no evidence of malignancy or osteomalacia.

BMD Z scores: LS -2.5
TH -2.8
FN -3.1

Diagnosis: Osteoporosis?

CASES

Case #2:

A 30-year-old healthy woman with no known secondary cause of osteoporosis and no fracture history has a low bone density screening test at a health fair, leading to a DXA scan:

BMD Z scores:

LS -3.0
TH -2.0
FN -3.1

Diagnosis: Osteoporosis?

Diagnostic Criteria
for Osteoporosis in PREmenopausal women

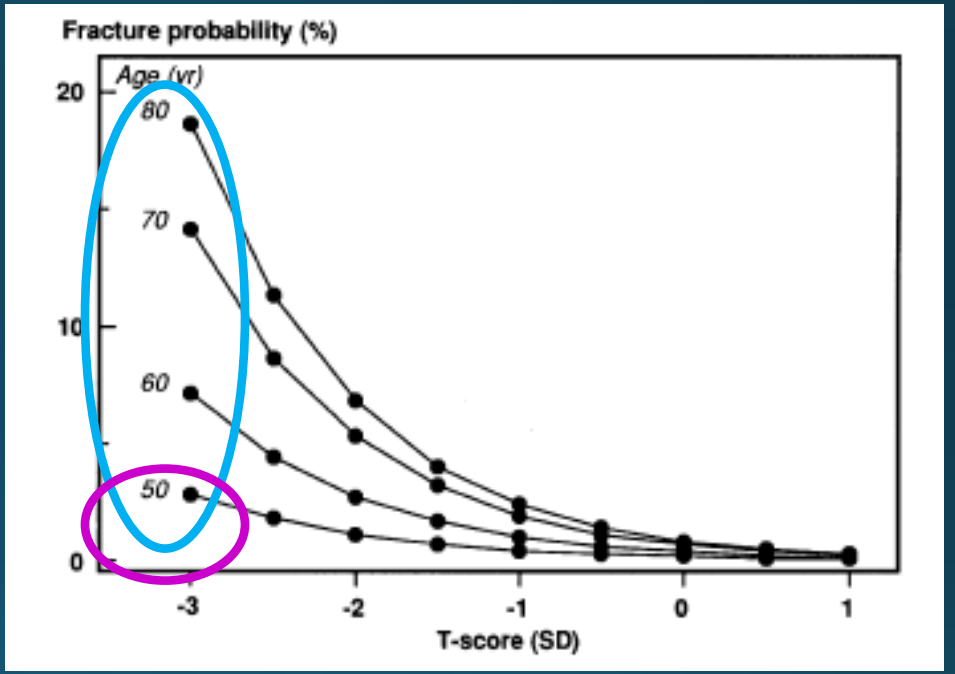
1. The diagnosis of "osteoporosis" is most secure in the context of low trauma fracture. (Case #1)
2. Osteoporosis cannot be diagnosed based on BMD alone. (Case #2)

International Society for Clinical Densitometry, Official Positions, 2015
International Osteoporosis Foundation Committee of Scientific Advisors Working Group, 2012

Relationship between bone density and fracture risk is DIFFERENT in Premenopausal Women

In women ≥ 50:
Fracture risk is related to AGE and T-SCORE

Fracture incidence and prevalence are very low in PREmenopausal women.



Lack of Data: In Premenopausal Women, the relationship between BMD and FRACTURE RISK has not been clearly defined by prospective studies.

Kanis, Osteoporos Int, 2001; Hosmer, Osteoporos Int, 2002; Wu, Arch Intern Med, 2002.

Diagnostic Criteria
for Osteoporosis in PREmenopausal women

1. The diagnosis of "osteoporosis" is most secure in the context of low trauma fracture.
2. Osteoporosis cannot be diagnosed based on BMD alone.

3. Screening BMD is not recommended

   BMD measurement is indicated for those with fracture(s) or a known secondary cause of bone loss.

International Society for Clinical Densitometry, Official Positions, 2015
International Osteoporosis Foundation Committee of Scientific Advisors Working Group, 2012

Diagnostic Criteria
for Osteoporosis in PREmenopausal women

4. Because of a lack of prospective data, DXA BMD (alone or as part of FRAX) cannot be used to:
   - Predict fracture risk
   - Make treatment decisions

5. Thus, to avoid the diagnostic and treatment implications of the T score, ISCD recommends reporting Z scores.

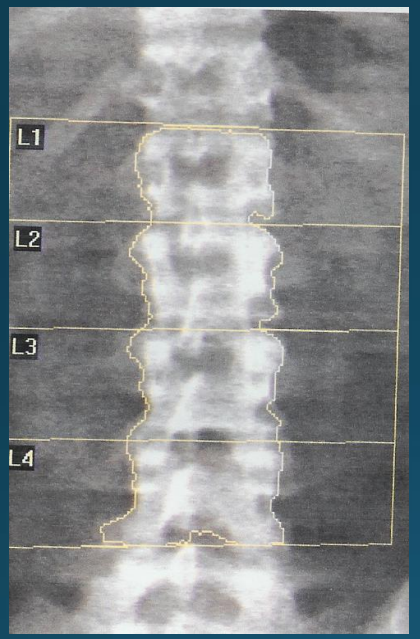
International Society for Clinical Densitometry, Official Positions, 2015
International Osteoporosis Foundation Committee of Scientific Advisors Working Group, 2012

Exceptions

- ISCD: T scores should be used for perimenopausal women.
- IOF: Osteoporosis can be defined based on T score ≤ -2.5 in adult women with a known, ongoing secondary cause of bone loss or fragility.

International Society for Clinical Densitometry, Official Positions, 2015
International Osteoporosis Foundation Committee of Scientific Advisors Working Group, 2012

TERMINOLOGY –
ISCD Recommendations



"Osteoporosis"

- Applies only to those with
  - Low trauma fracture
  - Secondary cause of bone loss
  - NOT based on BMD alone

"Osteopenia"

- Should not be used to describe BMD in premenopausal women

International Society for Clinical Densitometry, Official Positions, 2015
International Osteoporosis Foundation Committee of Scientific Advisors Working Group, 2012

CASES

Case #1: Can be said to have "osteoporosis" based on her fracture history

Case #2: Diagnosis?

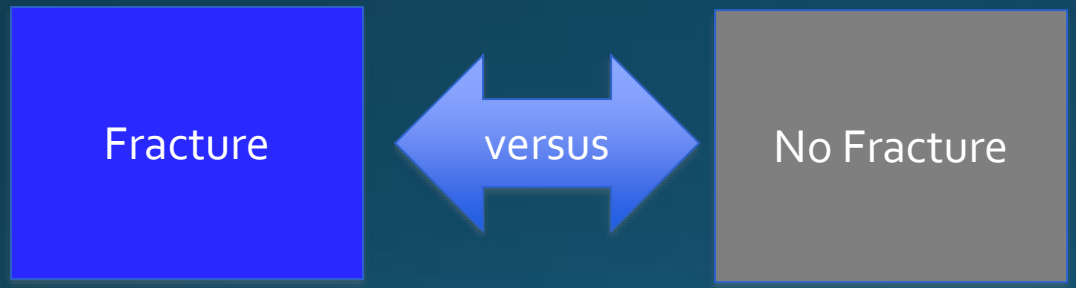
Low BMD – NO fracture, no known predisposing condition

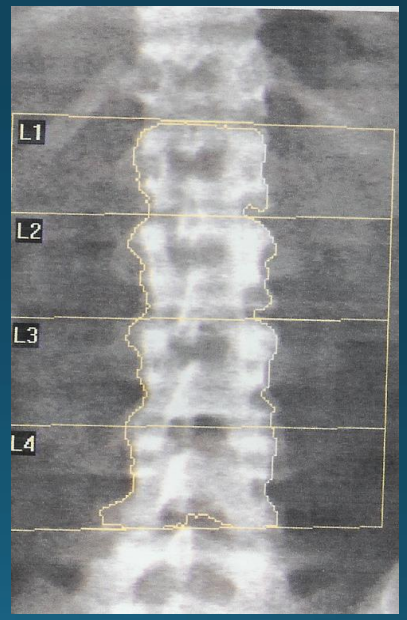
- Cannot be said to have "osteoporosis"
- BMD Z < -2 could be described as "BMD less than expected for age"

Does her BMD give us any information about her bone structure or strength?

Cross Sectional Studies: BMD relates to Bone Strength in Premenopausal Women

- Case-Control studies: young women with fractures have lower BMD





Lauder, Arch Phys Med 2000; Wigderowitz, J Bone Jt Surg 2003; Hung Clin Orthop 2005

Premenopausal Women with Idiopathic Osteoporosis: Bone Structural Studies

40 Healthy Controls

45 with Low Trauma Fracture

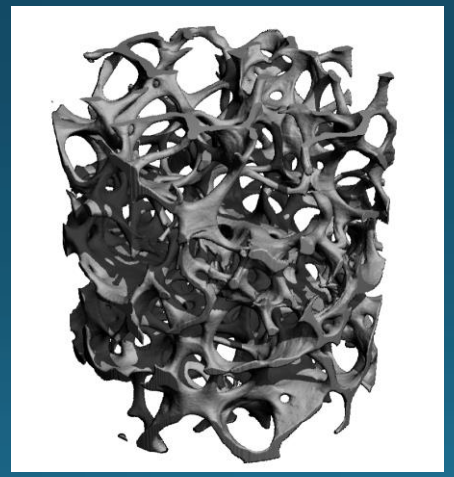
19 with Very Low BMD

At the tissue level (bone biopsies):

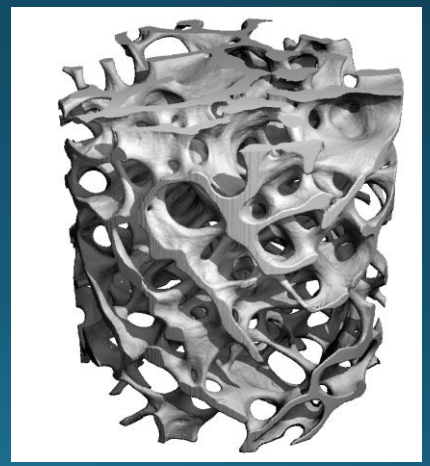
- Young women with fractures have substantial structural deficits
- Young women with very low BMD and no fractures ALSO have substantial microstructural deficits

Trabecular Compartment By MicroCT Müller lab, ETH, Zurich

Control



FRACTURE



LOW BMD

Cohen, et al JCEM 2009, 2011 & 2012

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At the tissue level (bone biopsies):

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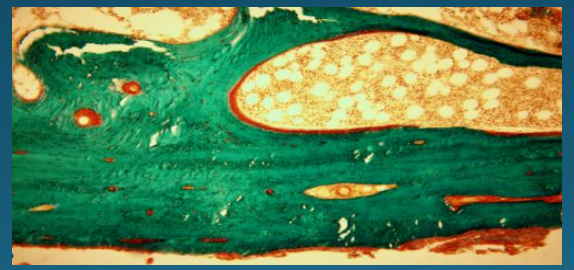
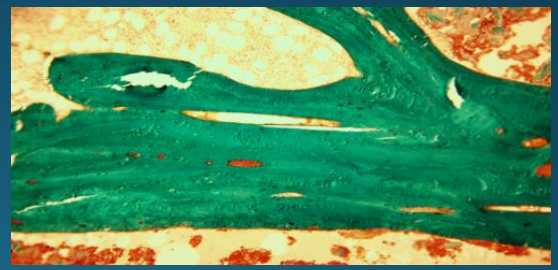
Cortical Thickness Histomorphometry Dempster lab, Helen Hayes Hospital

Control



FRACTURE



LOW BMD

Cohen, et al JCEM 2009, 2011 & 2012

Premenopausal Women with Idiopathic Osteoporosis: Bone Structural Studies

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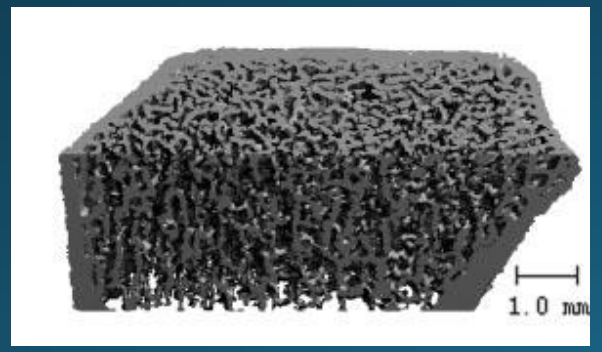
45 with Low Trauma Fracture

19 with Very Low BMD

3D Imaging studies

- Young women with fractures have substantial structural deficits
- Young women with very low BMD and no fractures ALSO have substantial microstructural deficits

High Resolution Peripheral QCT



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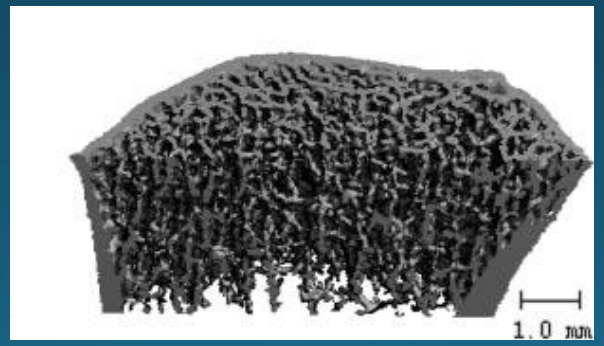
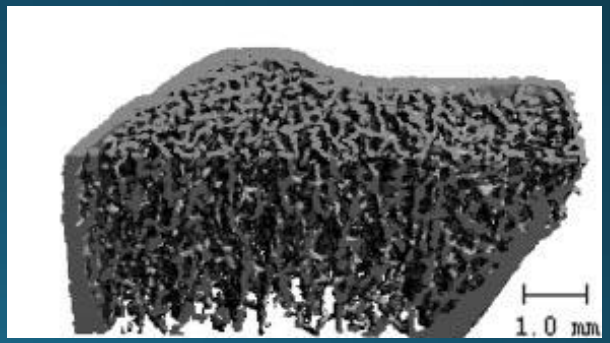


FRACTURE



LOW BMD

Cohen, et al JCEM 2009, 2011 & 2012

Could this be an effect of bone SIZE? 3D CT studies:

19 with Very Low BMD No Adult LT Fx
Unclear osteoporosis status

- Lowest BMI (mean 21.6 ± 3.5 vs mean 23, 26 in the other groups)
- Smaller Radial and Tibial Area by peripheral QCT
- Smaller vertebral cross sectional area by central QCT
- *3D microarchitectural deficiencies vs controls, even after controlling for bone size

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Galusca et al recruited women based on body size:

28 Healthy Controls Mean BMI ~ 21

44 with Anorexia Nervosa

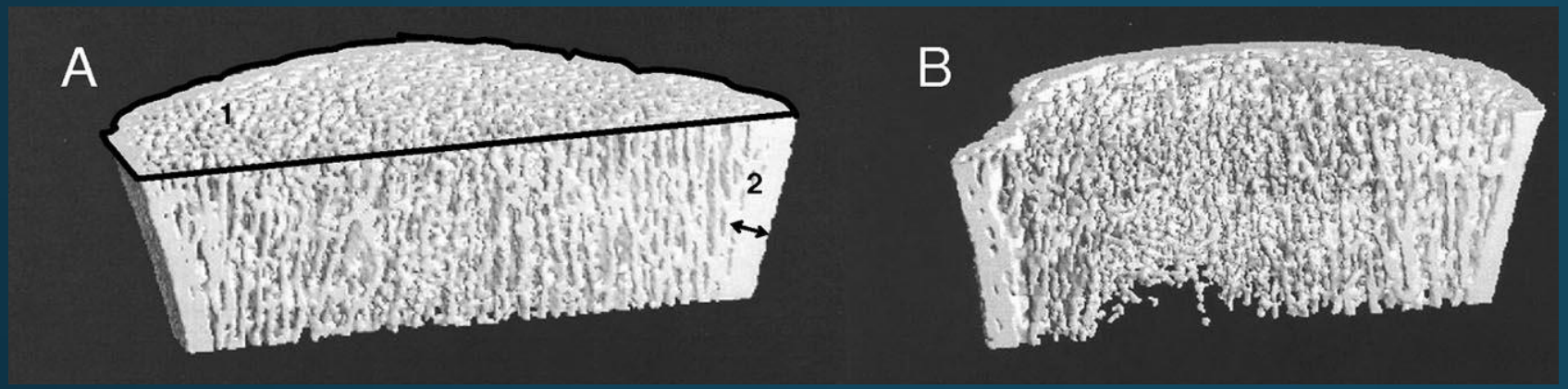
25 with Constitutional Thinness:
BMI<16.5 kg/m^2, normal menses, no 2^o cause
Unclear osteoporosis status

- CT and AN group both had low BMD by DXA vs controls
- CT group had the smallest bone size
- CT and AN groups BOTH had 3D microarchitectural defects

And decreased estimated bone strength

Cohen, et al JCEM 2009, 2011 & 2012; Galusca JCEM 2008

Peripheral QCT (Tibia):



CONTROL

CONSTITUTIONAL THINNESS

Asymptomatic low BMD, even with small bone/body size, is associated with structural abnormalities that lower predicted strength

Galusca et al recruited women based on body size:

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Mean BMI ~ 21

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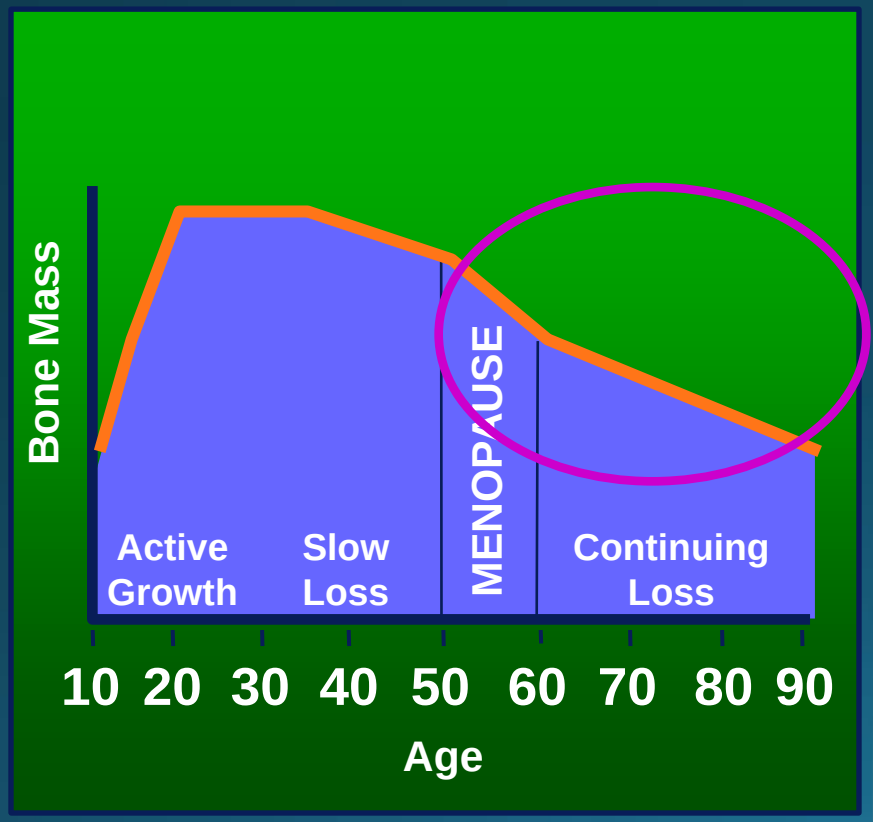
Cohen, et al JCEM 2009, 2011 & 2012; Galusca JCEM 2008

Bone Mass Trajectory: Are Case 1 and 2 actively losing bone?

Postmenopausal Women



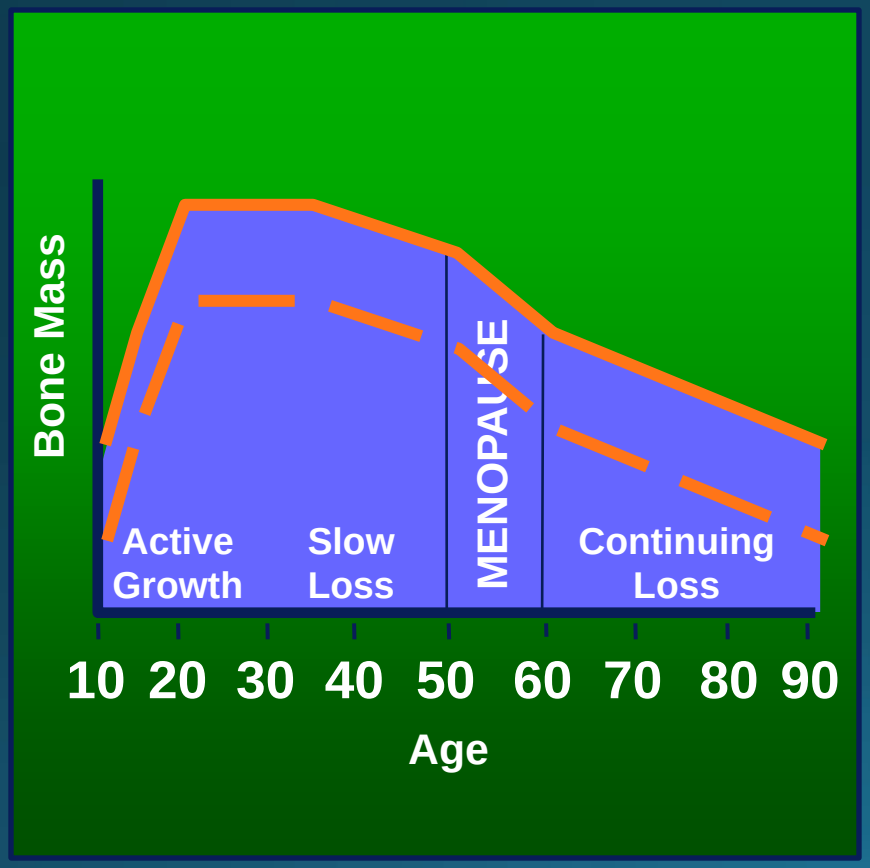
Adapted from Wasnich RD, et al. 1989:179-213

Premenopausal Women

?

Peak Bone Mass VARIES:

Low BMD may not signify an active process of bone loss



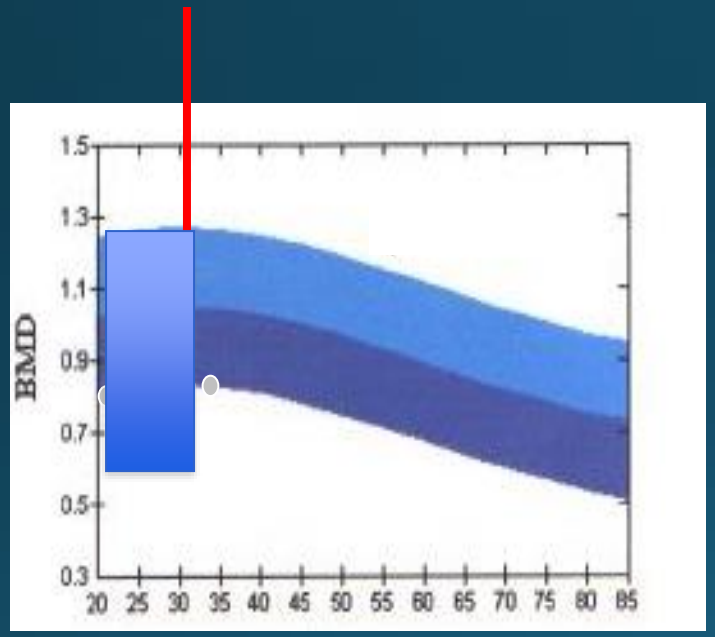
Low Peak Bone Mass

Everyone reaches a peak of bone mass accrual.

Not everyone reaches an OPTIMAL peak of bone mass accrual.

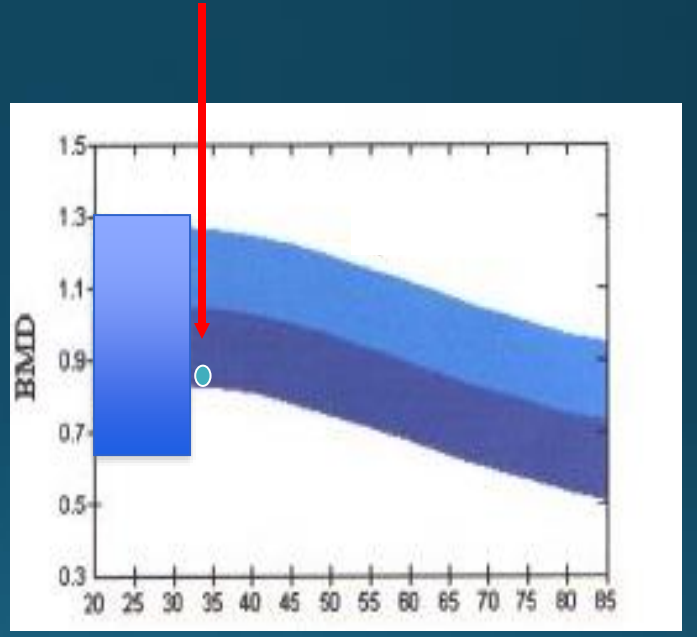
Expectations for Bone Mass Trajectory

Optimal peak bone mass not reached



- Genetic Cause (~50-80% of variability in bone mass is heritable[1,2])
- Illness or Medication exposure, now resolved

Active bone losing state



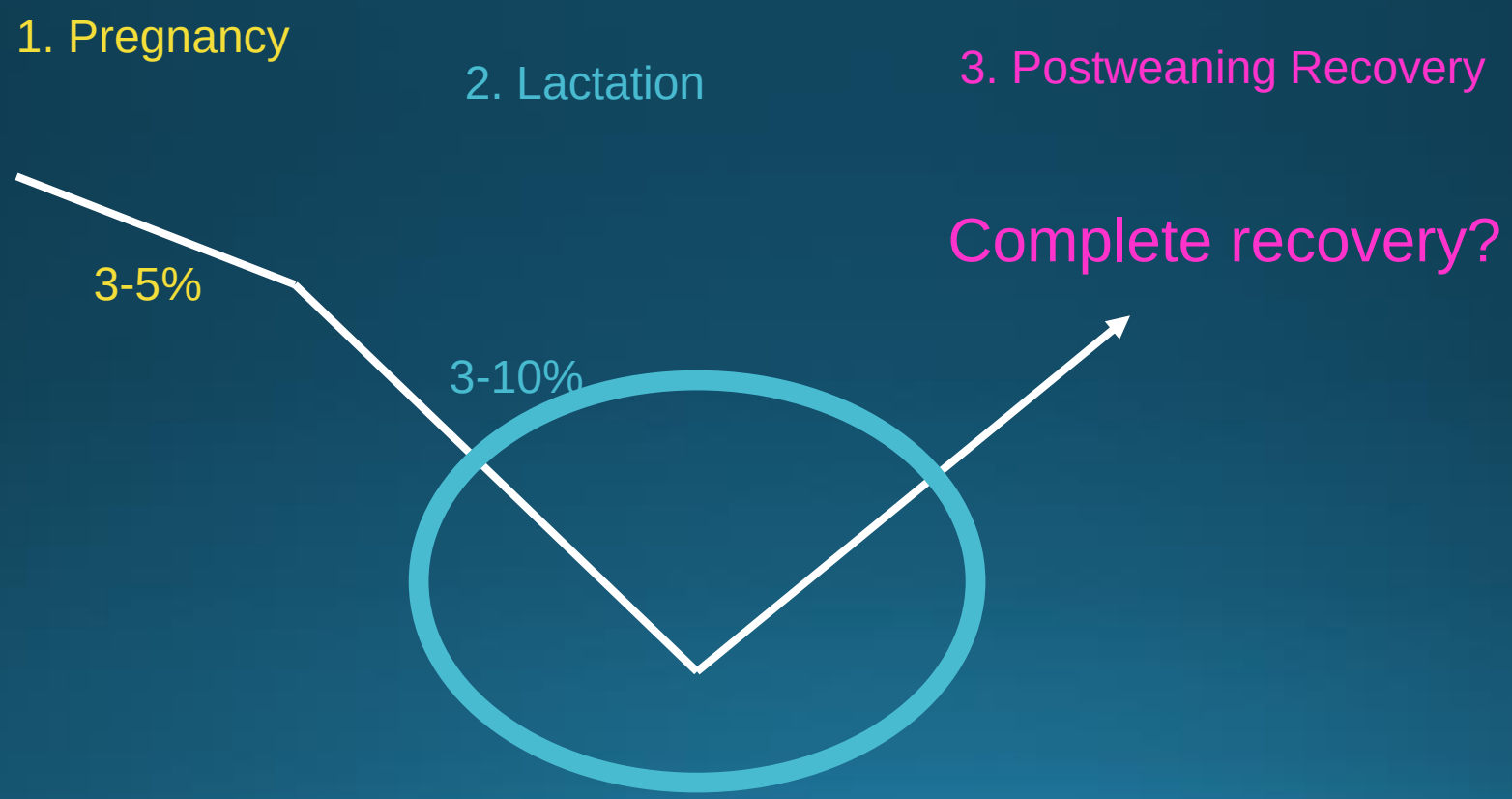
ONGOING Secondary Cause

Bone Mass Trajectory

Pregnancy and Lactation

“Low BMD” in a premenopausal woman may be related to:

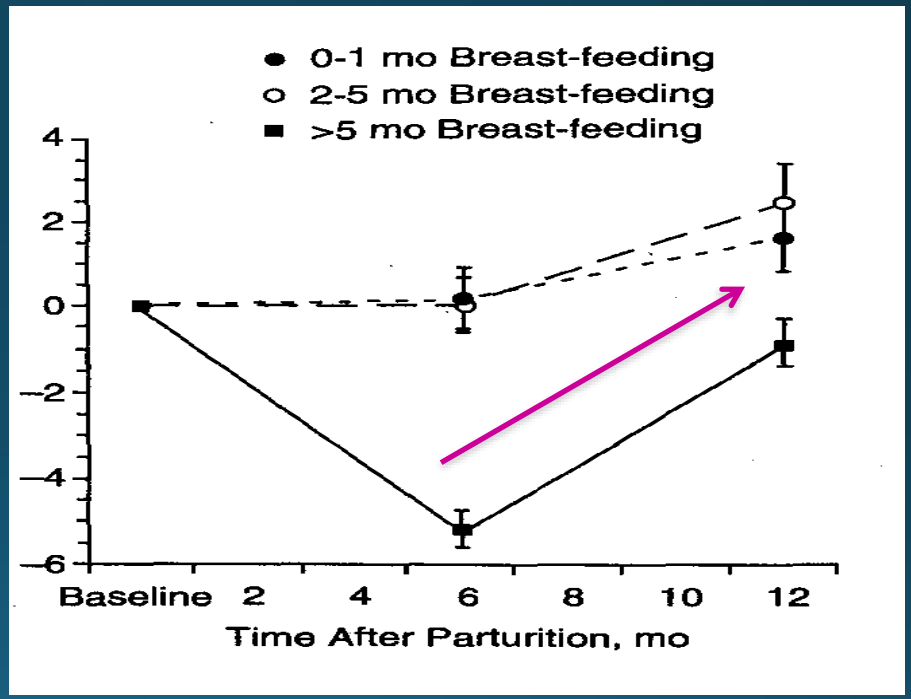
Physiologic BMD Changes of Pregnancy & Lactation



Clinical Implications of the Normal Bone Metabolism Changes Associated with Pregnancy and Lactation

Every bone mass measurement in a premenopausal woman must be placed into the context of these normal and expected changes.

- Low bone mass in a woman who is nursing, 5 months postpartum, can be expected to improve significantly on future measurements.



%Change **LS BMD** ± SE
N=98

Sowers et al, JAMA, 1993

Clinical Implications of the Normal Bone Metabolism Changes Associated with Pregnancy and Lactation

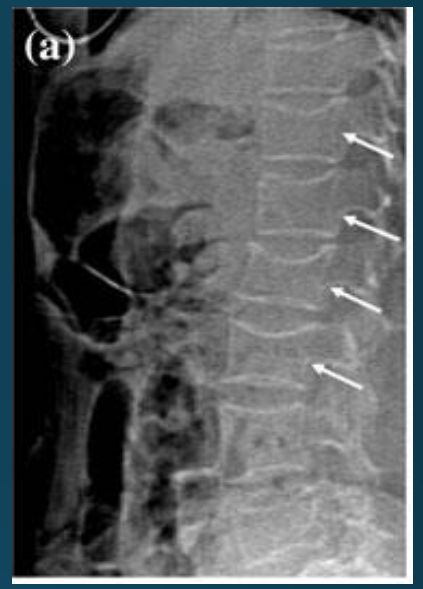
Rarely, fractures occur in the context of these expected bone mass changes

Pregnancy & Lactation Associated Osteoporosis (PLO or PAO):

- Low trauma or spontaneous fractures
- Usually multiple vertebral fractures (in >80%)
- During late pregnancy or lactation
- Majority have no known predisposing condition
- Very rare, described in case reports/case series

- Recent larger cohort study (Kyvernitakis et al, OI 2018)
  - ~100 subjects, median follow up = 6 years
  - Subsequent fractures reported in 24% - suggesting ongoing bone fragility

We are recruiting participants: FDA funded study to investigate etiologies, mechanisms of disease, and genetic characteristics (referrals welcome!)



36 year old woman presenting with back pain while breastfeeding 5 months postpartum

Choe et al JBMM 2012

EVALUATION AND TREATMENT

Who needs an evaluation?

- Low BMD (with or without known secondary cause)
- Low trauma fracture
  - Especially:
    - Major sites (femoral neck, vertebrae)
    - Multiple fractures, including multiple stress fractures

  - What is "low trauma"
    - Acute Injury: Fracture sustained in context of trauma = fall from standing height or less
    - Stress Fracture: fatigue induced fracture from repeated stress over time - can be considered low trauma if consistent with insufficiency fracture

Normal use - Insufficiency Fracture	Overuse - Stress Fracture

Judgement is required to determine how much physical activity is overuse

Evaluation of Premenopausal Women with Low Trauma Fractures (or Low BMD*):

The Search for Primary and Secondary Causes

*Screening BMD is not recommended

General Approach to Evaluation of Early-Onset Osteoporosis in Adults:

1. Does the patient have any findings c/w PRIMARY (genetic or developmental) osteoporosis/bone disorder?
    - Osteogenesis imperfecta
    - Marfan or Ehlers-Danlos Syndromes
    - Hypophosphatasia
    - Other known genetic etiologies

2. Does the patient have any evidence of a SECONDARY CAUSE: underlying conditions or medication exposures that could cause bone fragility

Most premenopausal women with low BMD *or* low-trauma fracture have an underlying disorder or medication exposure

These SECONDARY CAUSES may:

- Interfere with peak BMD acquisition

- or -

- Cause excessive bone loss thereafter

Secondary Causes of Osteoporosis in Young Women

- Endocrine
  - Estrogen deficiency
    - Pituitary diseases
    - Hypothalamic amenorrhea
    - Medications (GnRHa, DMPA)
    - Anorexia Nervosa (multifactorial)
  - Hyperthyroidism
  - Cushing's syndrome
  - Primary hyperparathyroidism
  - Primary Hypercalciuria
- Gastrointestinal/Nutritional
  - Celiac disease
  - Inflammatory bowel disease
  - Postoperative states
  - Cystic Fibrosis
- Inflammatory Conditions
  - Rheumatoid arthritis
  - SLE
- Other
  - Liver disease (esp cholestatic)
  - Renal disease
  - Gaucher disease
  - Mastocytosis
  - Hemochromatosis
  - Thalessemia
  - Diabetes 1 & 2
- Medications
  - Glucocorticoids
  - Some antiepileptic drugs
  - GnRH agonists and DMPA
  - TZDs
  - Heparin
- **Idiopathic**

How often can a secondary cause be found?

In a population-based study →

90% found to have 2° causes

Khosla et al, 1994

In series from tertiary referral populations →

44-53% found to have 2° causes

Kulak et al, 2000, Peris et al, 2003, Cohen et al, 2006

EVALUATION FOR 2° CAUSES

Important Aspects of the Clinical History:

- Fractures
- Kidney stones
- Menstrual history, pregnancy, lactation
- Dieting & exercise behavior
- Current or prior eating disorders
- Family history
- Subtle GI symptoms
- Medications, including OTC supplements

Physical Examination

Some secondary causes may be associated with findings on physical examination:

- Anorexia nervosa
- GI malabsorption
- Cushing syndrome
- Thyroid hormone excess
- Connective tissue disorders
- Cholestatic liver disease

Initial Laboratory Evaluation

- Complete blood count
- Electrolytes, renal function
- Serum calcium, phosphate
- Serum albumin, transaminases, total alkaline phosphatase
- Serum TSH
- PTH
- Serum 25-hydroxyvitamin D
- ESR
- Celiac screen
- 24 hour urine for calcium and creatinine
- 24 hour urine for free cortisol (if indicated)

MANAGEMENT

General Measures – Appropriate for MOST

May lead to small increases in BMD

- Institute of Medicine Recommendations (2010):
  - Calcium: 1000 mg/day
  - Vitamin D: 600 IU/day
- Exercise [1]
- Nutrition
  - Maintain healthy weight [2,3], avoid excess dieting [2,4]
- Lifestyle
  - Smoking cessation
  - Avoid excess alcohol

1. Wallace & Cumming, Calcif Tiss Int, 2000, Mein JBMR 2004
2. Hawker, Osteoporos Int, 2002
3. Bainbridge, Osteoporos Int, 2004
4. Bacon, Eur J Clin Nutr, 2004

Address Underlying Cause, if Possible

Disease	Management
Anorexia Nervosa	Nutritional rehabilitation Miller JCEM 2006
Estrogen Deficiency	Estrogen (unless contraindicated) Sagsveen Cochrane DB 2003, Cundy JCEM 2003
Idiopathic Hypercalciuria	Consider thiazides Adams Annals Int Med 1999 (in men)
1º Hyperparathyroidism	Parathyroidectomy Lumachi Ann NY Acad Sci 2007
Celiac Disease	Gluten-free diet Mautalen Am J Gastroenterol 1997 Newnham J Gastroenterol Hepatol 2016 Zanchetta JBMR 2016

Management

When should medications be used?

1. Idiopathic/Isolated Low BMD: CASE #2
   - Pharmacologic treatment is rarely indicated since fracture risk is unknown
   - Optimize bone health with non-pharmacologic lifestyle measures
   - Follow BMD – decline may indicate undiagnosed secondary causes
   - Consider more aggressive Rx at menopause: LOW premenopausal BMD is associated with an increased risk of postmenopausal fractures (Torgerson JBMR 1996)

2. Low BMD + Ongoing Secondary Cause
   - GIO
   - Other secondary causes

Management: GIO

Low BMD or Fractures in the context of GC use

Specific recommendations for GIO:

Am Col of Rheum 2017 Guidelines for Women < 40:

- RX recommended for those with prior osteoporotic fracture
- In the absence of fracture, guidance is very conservative:
  RX recommended for those
  - on ≥7.5mg/day for ≥ 6 months AND
  - Z score< -3 or bone loss > 10%/yr at spine/hip
- Oral bisphosphonates preferred

Buckley et al, Arthritis & Rheum 2017

Management

When should medications be used?

1. Idiopathic/Isolated Low BMD (Case #2)
   - •Pharmacologic treatment is rarely indicated since fracture risk is unknown
   - •Optimize bone health with non-pharmacologic lifestyle measures
   - •Follow BMD
   - •Consider more aggressive Rx at menopause

2. Low BMD + Ongoing Secondary Cause
   - •As with GIO, Rx may be indicated for those with
     - Very low BMD
     - Large declines in BMD

   (Some might use cutoffs less conservative than T < -3 or bone loss >10%)

3. LOW TRAUMA FRACTURES (Case #1)

   Fractures of the spine or hip
   Multiple fractures
   Clearly low trauma fractures
   Fractures + secondary cause
   Fractures + bone loss

Lead to consideration of treatment options

Treatment Options for Osteoporosis in Premenopausal Women

- **Anti-resorptive agents:**
  - Estrogen
  - Bisphosphonates
  - SERMS (eg Raloxifene)
  - Denosumab

SERMS: Should not be used to treat bone loss in premenopausal women since they block E2 action on bone and lead to further bone loss in menstruating women [1,2]

- **Anabolic agents:**
  - Teriparatide
  - Abaloparatide
  - Romosozumab

Efficacy and safety not defined in premenopausal women

Denosumab: Category X in pregnancy (toxicity in primates)

Abaloparatide and Romosozumab: No pregnancy data

1. Powles, J Clin Oncol, 1996
2. Vehmanen, J Clin Oncol, 2006

Treatment Options for Osteoporosis in Premenopausal Women

Bisphosphonates:

Short term BMD improvement in premenopausal women with

- Lupus and other AI diseases
- GC exposure
- Pregnancy associated osteoporosis

Some are FDA approved for use in premenopausal GIO

- alendronate, risedronate

Treatment not indicated in all:

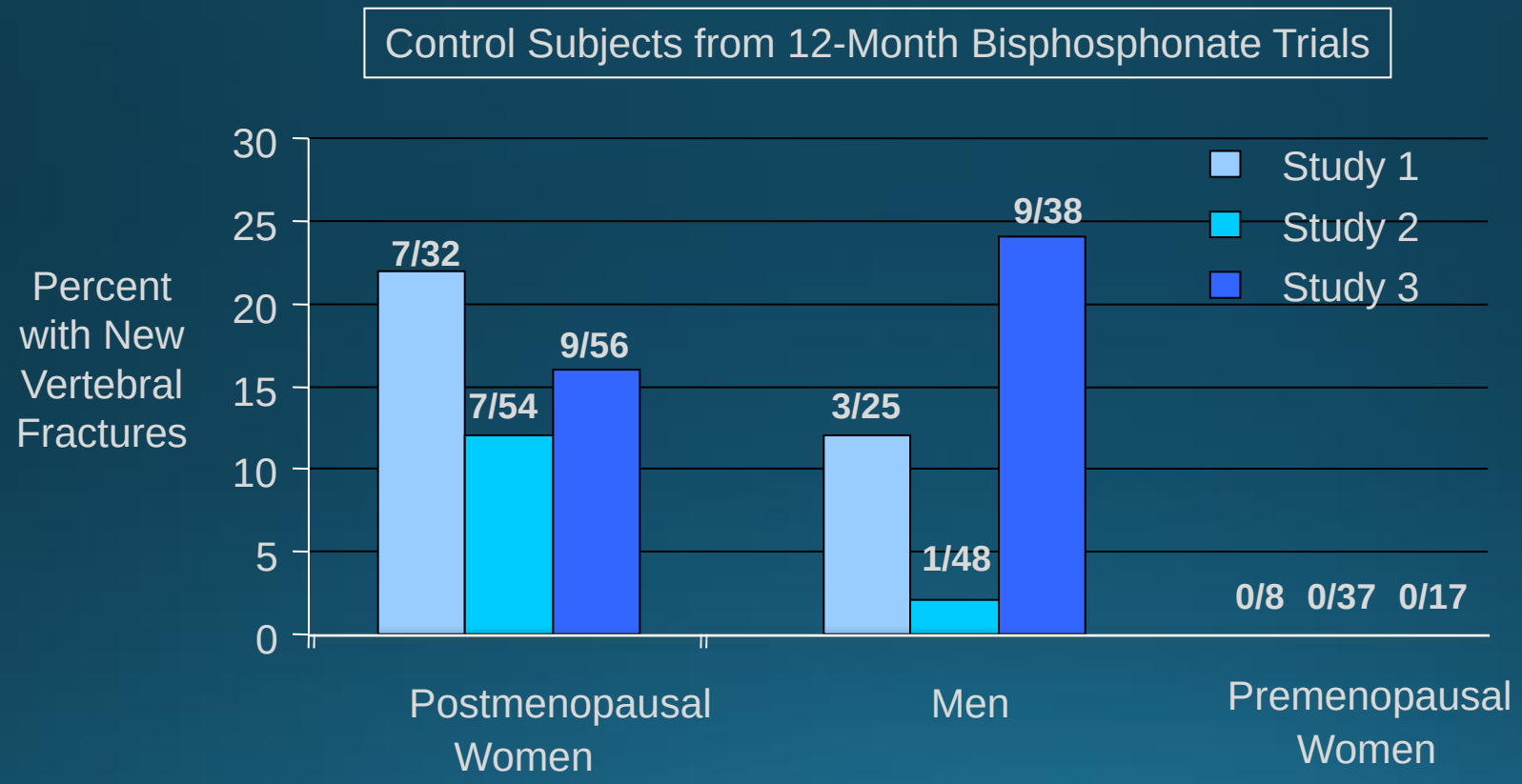
Long term risks are unknown

No fracture data

Nzeusseu Toukap Lupus 2005, Nakayamada J Rheumatol 2004, O'Sullivan OI 2006, Saag NEJM 1998, Wallach CTI 2000, Buckley Arth and Rheum 2017

Premenopausal Women On Glucocorticoid Therapy May Not Be At High Risk Of Fracture

Few premenopausal women in large RCTs of bisphosphonates for GIOP



1. Adachi, *N Engl J Med* 1997
2. Saag, *N Engl J Med* 1998
3. Wallach S, *Calcif Tiss Int* 2000

Bisphosphonates in Premenopausal Women: Special Considerations re RISK

- LONG-TERM EFFECTS
  - Long term effects on bone health are unknown
  - Potential risks of long term use: ONJ, atypical femoral fractures

- RISKS FOR FUTURE PREGNANCY
  - Accumulate in skeleton [1]
  - Category C rating for safety in pregnancy
  - Toxic effects in rats [2]
  - Cross placenta and accumulate in fetal rat bones [3]
  - Unknown effects on the human fetus
  - >50 reported normal pregnancy outcomes [4-10]

Risks and duration of use must be considered in young women

1. Papopoulos, Bone 2006
2. Minsker, Toxicol Appl Pharmcol 1993
3. Patlas, Teratology, 1999
4. Biswas, Osteoporos Int, 2003
5. Illidge, Clin Oncol (R Coll Radio), 1996
6. Chan, J Clin Endocrinol Metab, 2006
7. O' Sullivan, Osteoporos Int, 2006
8. Ornoy, Reproduct Toxicol, 2006
9. Levy, Bone 2009
10. Munns, J Bone Miner Res, 2004

Teriparatide/PTH(1-34) for Premenopausal Women

- Amenorrheic premenopausal women on GnRH agonists for endometriosis[1]: Prevents bone loss.
- Young women on GCs[2]: Increases BMD significantly more than alendronate.
- Premenopausal women with idiopathic osteoporosis[3]: Improves BMD/structure
- Anorexia nervosa: Improves BMD[4]
- Pregnancy associated osteoporosis: Improves BMD[5,6]

1. Finkelstein et al, JAMA 1998
2. Langdahl et al, Osteoporos Int 2009
3. Cohen et al, JCEM 2013
4. Fazeli et al, JCEM 2014
5. Choe et al, JBMM 2012
6. Hong et al Cin Endoc 2018

Teriparatide/PTH(1-34) for Premenopausal Women

- Amenorrheic premenopausal women on GnRH agonists for endometriosis[1]: Prevents bone loss.
- Young women on GCs[2]: Increases BMD significantly more than alendronate.
- Premenopausal women with idiopathic osteoporosis[3]: Improves BMD/structure
- Anorexia nervosa: Improves BMD[4]
- Pregnancy associated osteoporosis: Improves BMD[5,6]

NO FRACTURE DATA

1. Finkelstein et al, JAMA 1998
2. Langdahl et al, Osteoporos Int 2009
3. Cohen et al, JCEM 2013
4. Fazeli et al, JCEM 2014
5. Choe et al, JBMM 2012
6. Hong et al Cin Endoc 2018

Teriparatide for Premenopausal Women: Special Considerations

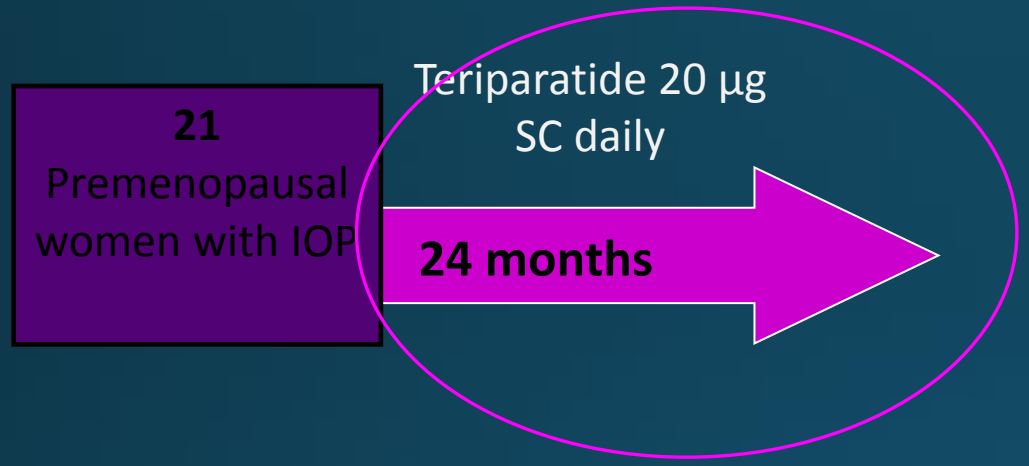
- Only approved in the setting of GIO.
- **Osteosarcoma risk (no longer a black box warning):**

Osteosarcoma: Osteosarcoma has been reported in patients treated with FORTEO in the post marketing setting; however, an increased risk of osteosarcoma has not been observed in observational studies in humans. Avoid use in patients with increased baseline risk of osteosarcoma including patients with open epiphyses (pediatric and young adult patients), metabolic bone diseases including Paget's disease of the bone, bone metastases or history of skeletal malignancies, prior external beam or implant radiation therapy involving the skeleton, and hereditary disorders predisposing to osteosarcoma. There is limited data assessing the risk of osteosarcoma beyond 2 years.

*Document fused epiphyses in very young adults (< 25 years)

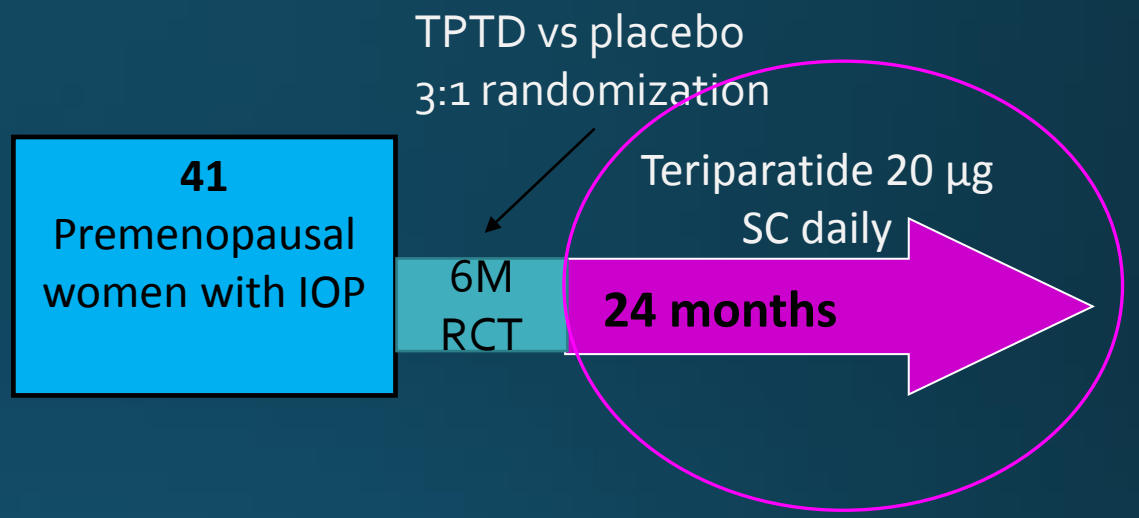
- Treatment plan post-TPTD is unclear

Teriparatide for Premenopausal Idiopathic Osteoporosis (Osteoporosis with no known secondary cause)



- Pilot, open label study
- Investigator Initiated,
  - Funded by Eli Lilly
- Paired bone biopsy
  - BL and 18M

Cohen, Shane et al., JCEM 2013



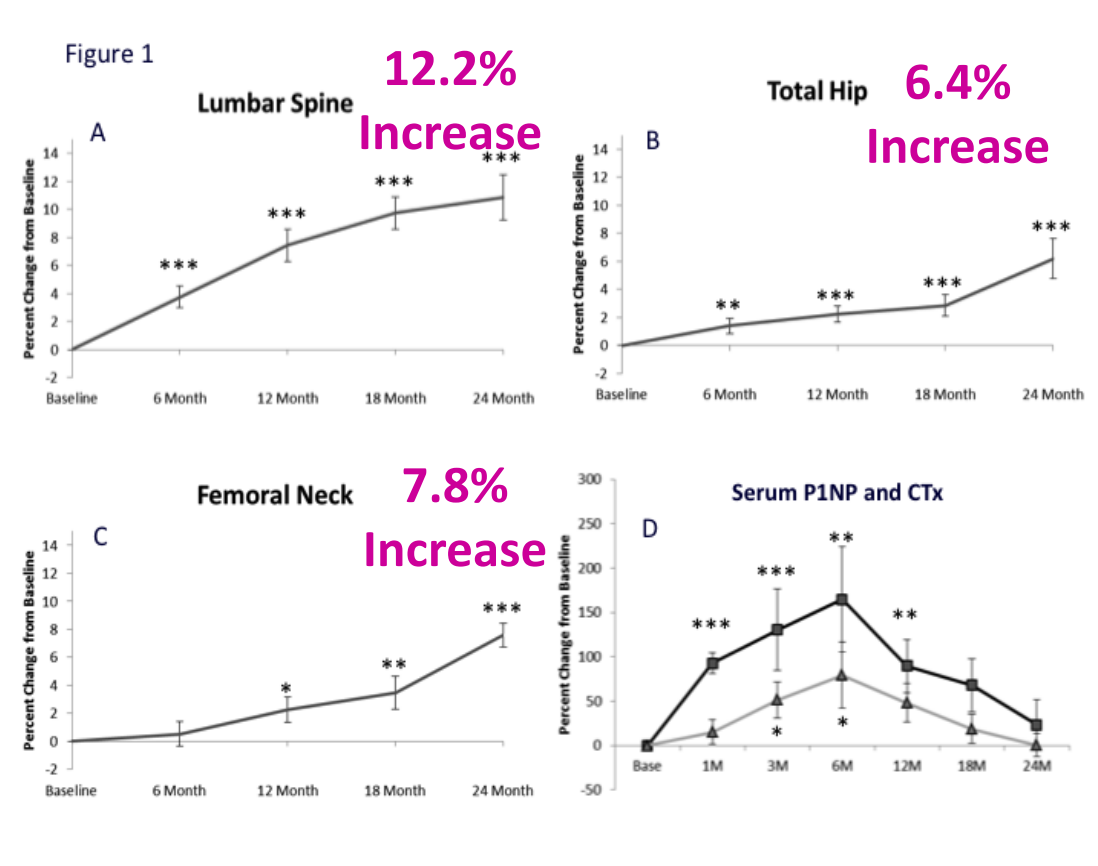
- RCT with switch-over
- FDA funded (OOPD)
- Single quad labeled bone biopsy at 3M

Cohen, Shane et al., JCEM 2020

Teriparatide for Premenopausal Idiopathic Osteoporosis

% Change in BMD over 24 Months

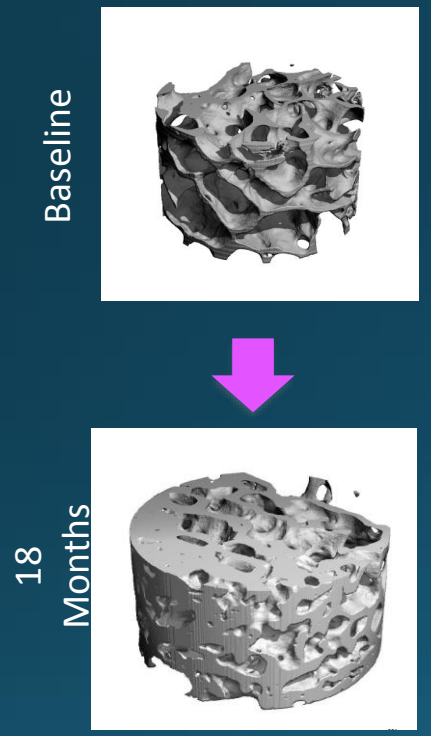
PILOT STUDY (n=21)

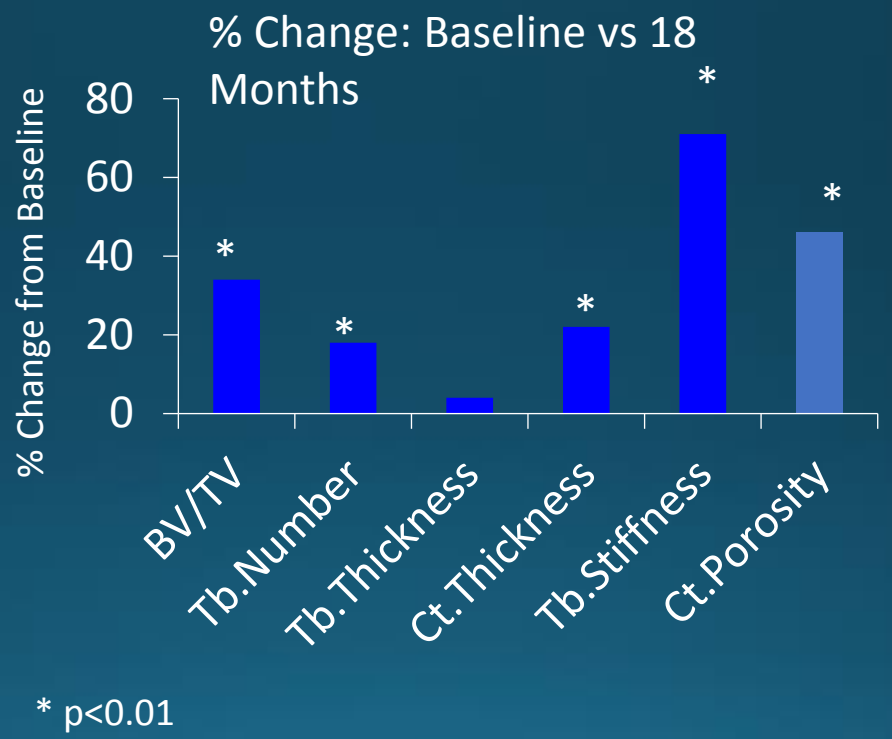


Cohen, Shane et al., JCEM 2013

PILOT STUDY (n=21)
Teriparatide for Premenopausal IOP: Bone Structural Changes on Biopsies

Case #1:





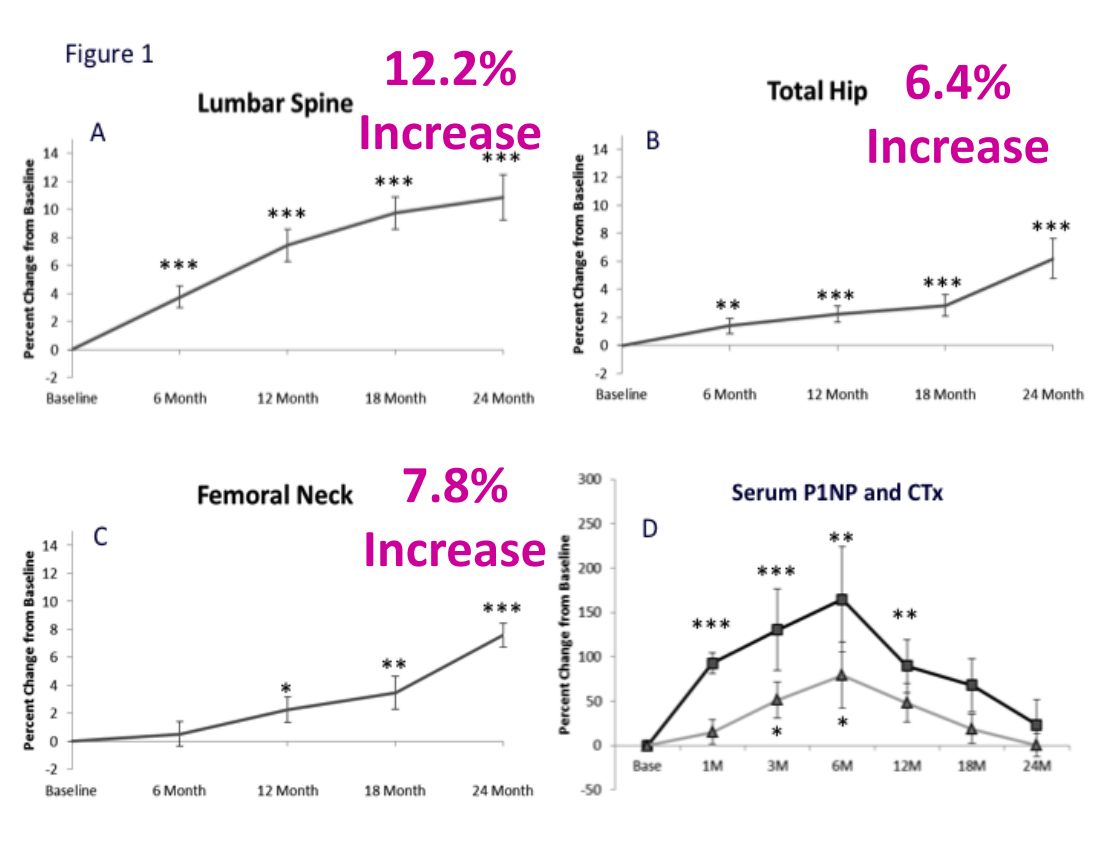
* p<0.01

Cohen, Shane et al., JCEM 2013

Teriparatide for Premenopausal Idiopathic Osteoporosis

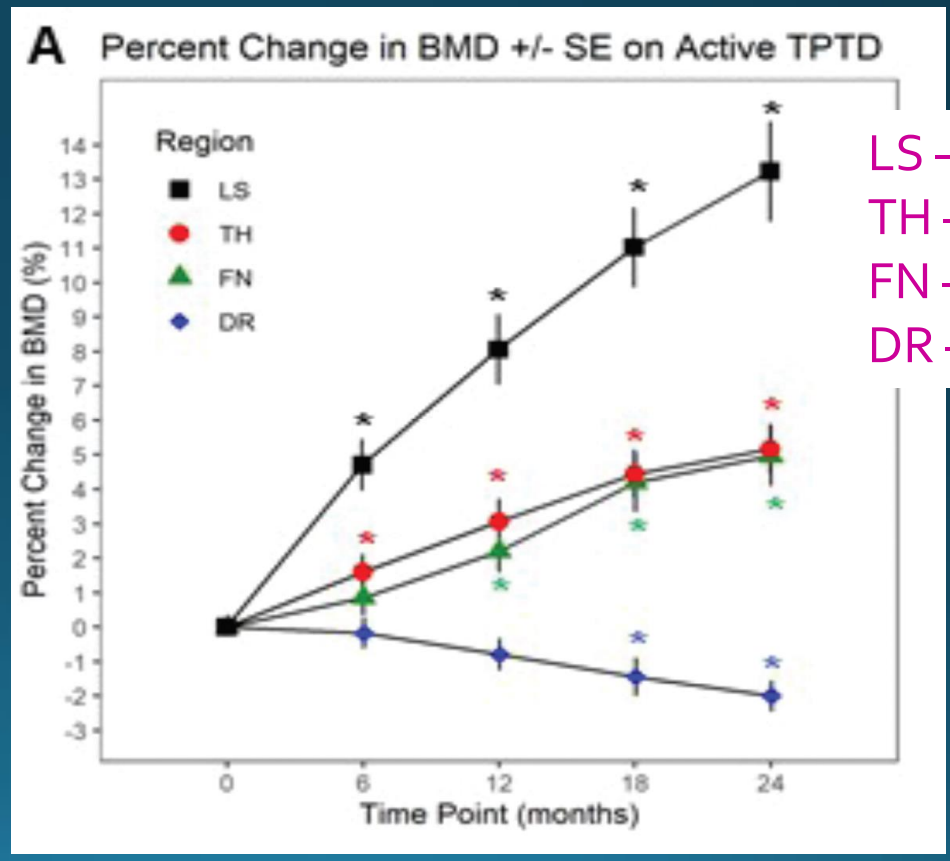
% Change in BMD over 24 Months

PILOT STUDY (n=21)



Cohen, Shane et al., JCEM 2013

FDA STUDY (n=41)



LS – 13% increase
TH – 5% increase
FN – 5% increase
DR – 2% decrease

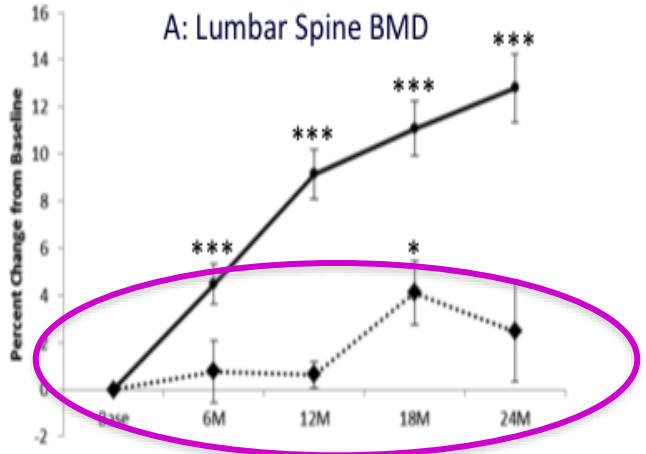
Cohen, Shane et al., JCEM 2020

Teriparatide for Premenopausal Idiopathic Osteoporosis

VARIABLE RESPONSE

PILOT STUDY (n=21)

Figure 3: Percent Change in BMD and Bone Turnover Markers After Teriparatide in Responders and Non-Responders

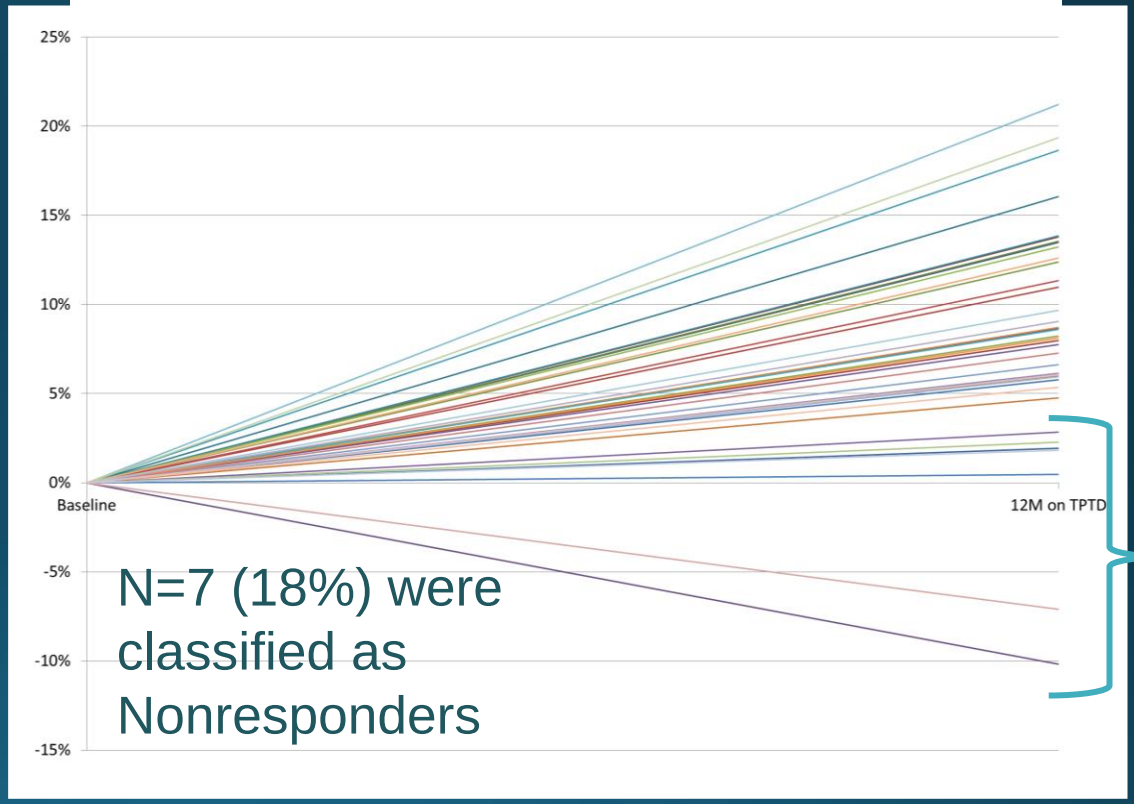


4 women were NonResponders: 19%
At baseline,
Bone formation rate and CTX were significantly lower

Cohen, Shane et al., JCEM 2013

FDA STUDY (n=41)

12M LS BMD %Change in Individual Subjects

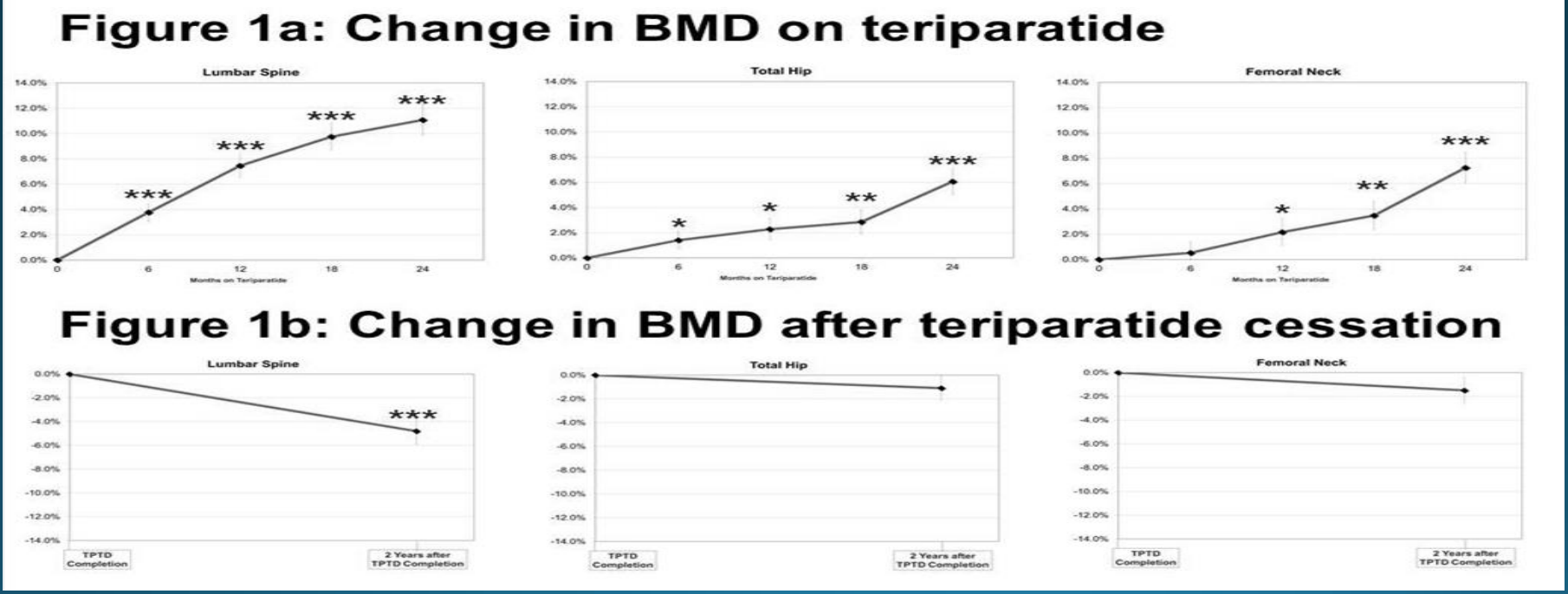


NonResponders:
Baseline bone formation rate 50-60% lower,
but NS (p=0.1)

Cohen, Shane et al., ASBMR 2019 and JCEM 2020

Bone Density after TPTD discontinuation in IOP

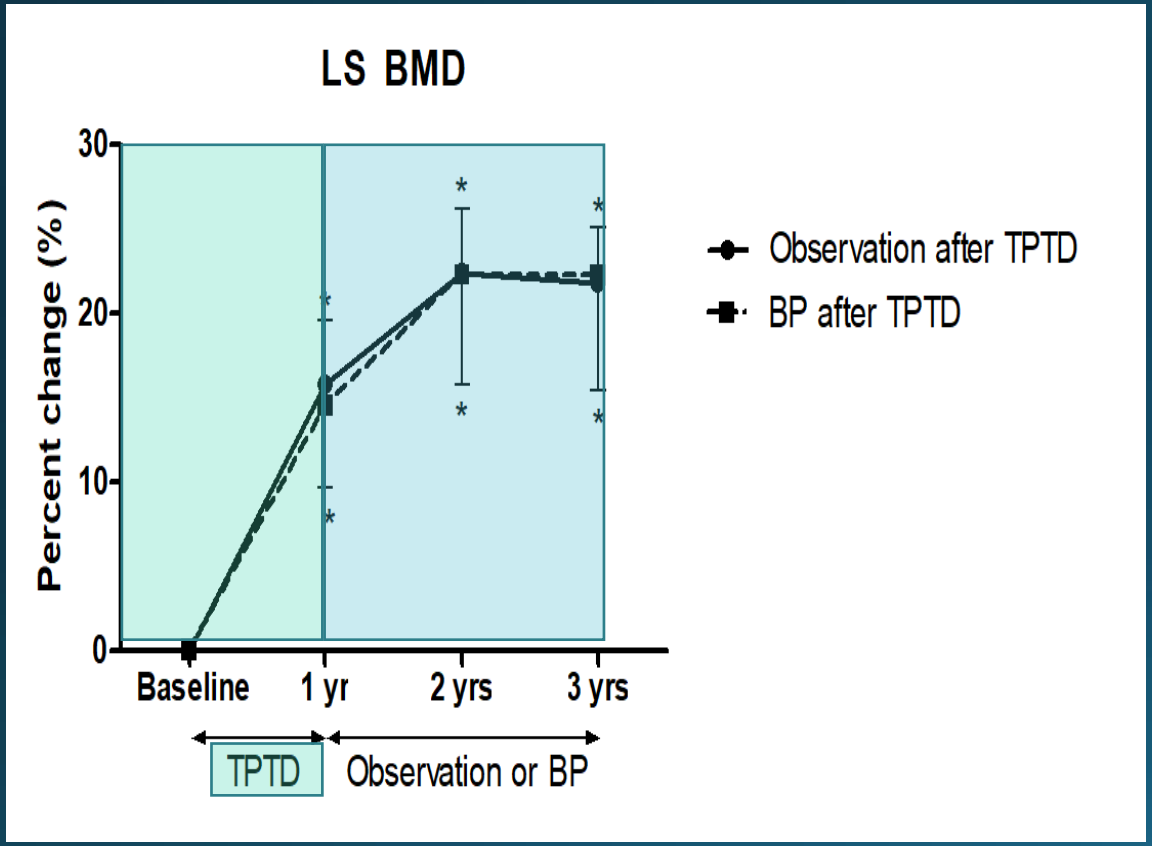
- 15 women followed ~2 yrs after TPTD cessation
- Bone loss at LS, stable at TH and FN
- BMD loss group:
  - Older age (46±3 vs 38±7; p=0.046)
  - More bone gain while on TPTD
  - Faster bone remodeling on Bx only



Cohen, Shane et al JCEM 2015

Bone Density after TPTD Discontinuation: Different Trajectory in PLO

BMD is maintained after teriparatide WITHOUT sequential bisphosphonate rx



37 PLO pts
Rxed TPTD 12M

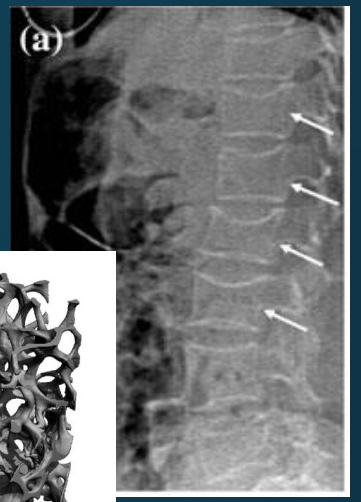
N=17
Sequential Bisphos
Median rx 21M

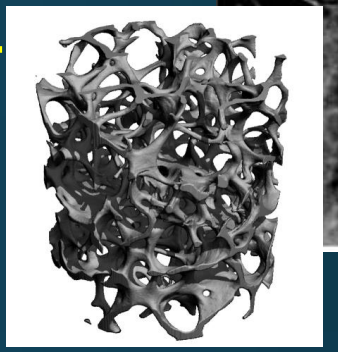
N=20
NO Sequential
Bisphos

All had regular menstrual cycles
Age, BMI, baseline BMD
did not differ between the groups

Lee et al, ASBMR Annual Meeting, 2020

Future Goal: Optimize Therapy for IOP and other Premenopausal Osteoporosis





Bone-anabolic therapies target bone structural deficiencies, BUT…

- Response is very variable with 18-20% nonresponse rate
- Bone loss is documented after teriparatide (?except in PLO)

Ongoing extension studies to the FDA trial: SEQUENTIAL THERAPY WITH TPTD

- Denosumab after TPTD
- Bisphosphonate transition after denosumab

NEW STUDY: Romosozumab/Denosumab Protocol

Now recruiting premenopausal women with:

- Fracture(s)
- No clear secondary cause

*Note: travel funding available

Many Remaining Areas of Uncertainty

- How do we use BMD and BMD trajectory data in this population?

  Should unexplained declining BMD ever be treated?
- Which kinds of fractures represent true evidence of bone fragility?

  Spine and hip fractures

  Foot fractures?

  Stress fractures?
  - What sort of fracture history should lead to a recommendation for medical treatment?
- Which medication(s) should be used?
- How long should a course of treatment last in a premenopausal woman?