Evaluation and Management of Low Bone Density in Premenopausal Women

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• Speakers Bureaus, Financial holdings
  — None
• Discussion of unlabeled use of drugs
  — Teriparatide, denosumab

Key References

Ms. A.A., 29 yo healthy woman
• Fractured left hip after minor fall
• BMD below expected range for age
  — -2.5 at spine, -2.8 at total hip, -3.1 at femoral neck
• Menarche age 15, regular menses, no amenorrhea, GOP0
• PMH unremarkable, no medications, tobacco, ETOH
• + FH osteoporosis - maternal aunt & grandmother
• Physically active, 2 servings dairy/day
• Slim but not undernourished
  — 5’3” (160cm) 100lb (45.4 kg) BMI 17.7 kg/m²
• No blue sclerae, kyphosis, bone tenderness
• Routine and special labs normal
• Bone turnover markers in normal premenopausal range

Osteoporosis in Premenopausal Women
• Uncommon
• Most have a secondary cause
• Difficult to diagnose in absence of low trauma fractures

Outline
• Osteoporosis in premenopausal women
  — Diagnosis
  — Etiology
  — Evaluation
• Management of osteoporosis in premenopausal women with
  — Secondary osteoporosis
  — Idiopathic osteoporosis
### World Health Organization T Scores

T scores correlate with lifetime fracture risk for postmenopausal Caucasian women.

#### Diagnosis of Osteoporosis in POSTmenopausal Women

- Based on the WHO classification
- Areal BMD by DXA
  - T-Score < -2.5 SD below young adult mean at spine, hip or forearm

No comparable data are available for PREmenopausal women.

1. WHO Tech Rep Ser 1994;843:1-129
3. Cooper, Bone. 1993;14 Suppl 1:S89-97

### Indications for Treatment of Osteoporosis in POSTmenopausal Women

- Low areal BMD by DXA (T score < -2.5)
- Low trauma fractures

No clear intervention thresholds for PREmenopausal women.

- By FRAX

### In young women, low areal BMD by DXA may be due to...

- Low Peak Bone Mass
  - Genetics
  - Suboptimal bone mass accrual during adolescence due to lifestyle choices, medical conditions or drug exposures
- Statistical Definition of Z or T Score – in population of normal women
  - 2.5% will have Z score < -2.0
  - 0.5% will have T score < -2.5
- Small Stature
  - DXA underestimates BMD in small individuals
- Constitutional Leanness
  - Non-pathological state of underweight, normal menses, often familial
  - Low BMD by DXA
  - Abnormal microarchitecture, low strength by HR-pQCT

2. Chevalley et al., JCE&M 1998
3. Ferrari et al., JCE&M 1998
5. Fernandez-Garcia et al., Br J Nutr 2009
6. Galusca et al., JCE&M 2008

### Low BMD in YOUNG women is not associated with the same risk of fracture as low BMD in OLDER women.

- Premenopausal women are estrogen replete and have more muscle, lower bone turnover, thicker cortices, better trabecular connectivity and fewer falls
- Incidence and prevalence of fractures much lower in PREmenopausal than POSTmenopausal women
- Even when BMD is very low

1. Thompson, Injury, 2004
2. Melton, Osteoporos Int, 1998
3. Hosmer, Osteoporos Int, 2002
A premenopausal woman can be considered to have osteoporosis when she has......

- Low BMD - Z-score ≤ -2.0 or T score ≤ -2.5
  
  + Secondary cause of osteoporosis
  
  - e.g., glucocorticoids, hypogonadism, celiac disease, hyperparathyroidism, rheumatoid arthritis
  
  OR

- History of vertebral or non-vertebral low-trauma fracture(s) at major site
  
  - Whether or not BMD is frankly low

What about premenopausal women with low BMD (T-score ≤ -2.5, Z score ≤ -2.0) BUT NO SECONDARY CAUSE AND NO FRACTURES?

- Neither ISCD nor IOF would say such a woman has osteoporosis.
  
  - I am not convinced that is true.

Who Should Be Evaluated?

- Women with fragility fracture(s) or prevalent vertebral fracture(s), regardless of BMD
  
  - Z score ≤ -2.0
  
  - T score ≤ -2.5

The 2007 ISCD Guidelines for Reporting BMD Results in PREmenopausal Women

Use the Z SCORE, NOT the T SCORE!

Z scores compare people to age-matched controls instead of peak bone mass (age 30)

In premenopausal women and men < age 50

- Z scores above -2.0 should be reported as “within the expected range for age”
  
- Z scores below -2.0 should be reported as “below the expected range for age”

Goal: Avoid terms like “osteoporosis” and “osteopenia” as their predictive meaning less clear in young women

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Goal: Avoid terms like “osteoporosis” and “osteopenia” as their predictive meaning less clear in young women
Goals of Evaluation

- Identify secondary causes of osteoporosis
- Especially treatable causes

Secondary Causes of Osteoporosis in Young Women

- Genetic
  - Idiopathic hypercalciuria
  - Osteogenesis imperfecta
  - Thalassemia
- Endocrine
  - Estrogen deficiency
  - Amenorrhea (except pregnancy)
  - Eating disorders - anorexia, bulimia
  - Prolactinoma, Sheehan’s
  - Hyperthyroidism
  - Cushing’s syndrome
  - Primary hyperparathyroidism
- Gastrointestinal
  - Celiac disease
  - Malabsorption
  - Inflammatory bowel disease
  - Lactase intolerance
- Rheumatologic
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
- Pulmonary
  - Cystic fibrosis
  - Emphysema
- Medications
  - Prednisone
  - Antiepileptic drugs
  - GnRH agonists
  - Thyroid hormone
  - Depo-Provera
  - Cancer chemotherapy
  - SSRIs
  - PPIs
  - HAART
- Miscellaneous
  - Major depression
  - Pregnancy-associated
  - HIV
  - Idiopathic

Most Common Causes of Osteoporosis in Premenopausal Women

- Glucocorticoid excess
- Premenopausal estrogen deficiency
- Eating disorders
- GI disease
  - Celiac disease, inflammatory bowel disease, malabsorption
- Medications
  - Antiepileptic drugs, cancer chemotherapy, prednisone
- Alcoholism
- Primary hyperparathyroidism
- Osteogenesis imperfecta
- Idiopathic

Evaluation of Low BMD in a Premenopausal Woman

A careful history and physical exam are KEY

Ask about
- Fractures
- Family history of fractures
- Kidney stones
- Menstrual history
- Dieting & exercise behavior
- Eating disorders
- Subtle GI symptoms
- Medications, including OTC supplements

Look for signs of
- Cushing Syndrome
- Thyroid hormone excess
- Systemic mastocytosis – urticaria, dermatographia
- Inflammatory disease
- Connective tissue disorders
  - Osteogenesis imperfecta
  - Ehlers-Danlos

Initial Laboratory Evaluation

- Complete blood count
- Serum calcium, phosphate
- Electrolytes, renal function
- Serum albumin, transaminases, total alk phosphatase
- Serum TSH
- Serum 25-hydroxyvitamin D
- 24 hour urine for calcium, creatinine, free cortisol
**Additional Laboratory Tests As Indicated**

- Estradiol, LH, FSH, prolactin
- PTH
- 1,25-dihydroxyvitamin D
- Iron studies
- Vitamin A (retinol)
- Celiac screen
- Serum/urine protein electrophoresis
- Erythrocyte sedimentation rate or C-reactive protein
- Serum tryptase and histamine
- Genetic testing for OI, EDS
- Whole exome sequencing for mutations in Wnt, LRP5/6, other genes?

**Bone Turnover Markers??**

- If low or normal
  - Suggests prior bone loss or low peak bone mass
- If above premenopausal range
  - Suggests ongoing bone loss
- Cautionary notes:
  - Wide normal range
  - Highly variable
  - Must be interpreted according to age
  - Physiologically high in growing children
  - High after fractures

**Tetracyline-labeled Transiliac Bone Biopsy?**

- Not widely available
- Primarily a research tool
- May be indicated in patients with idiopathic low-trauma fractures
- May identify other sources of bone fragility and guide therapy
- May be more accurate reflection of bone turnover at the tissue level than bone turnover markers

**Idiopathic Osteoporosis (IOP) 1,2**

- Operational definition
  - Premenopausal women and men < 50
  - Otherwise healthy
  - Normal gonadal function
  - No secondary cause of bone loss
- Usually Caucasian
- Often present in mid-30s
  - May present during pregnancy or lactation
- One or more low trauma fractures
  - Cluster over 5-10 yrs
- May be mild or devastating

1. Albright & Reifenstein, 1944
2. Khosla et al, Bone 1994

**IOP Without Fractures?**

- Clinical significance of isolated low areal BMD in otherwise healthy young woman uncertain
  - Short-term fracture risk increased?
  - Microarchitecture - normal or abnormal?

**Cross-sectional Case-Control Study**

**Control – 40**

- No adult fractures
- Normal BMD – Z score ≥ -1.0

**Low BMD group - 19**

- No low trauma adult fractures

**Fracture group - 45**

- 1-12 adult fractures
- Mean age at 1st fracture – 30
- Fracture type
  - Vertebrae, ribs, hip, pelvis, forearm, humerus, ankle, metatarsal

Cohen et al., Osteoporos 2012, 23:171-82
Central QCT of Spine and Hip in IOP

Avoids problem of apparent low areal BMD by DXA in small people
Measures
• Important fracture sites
• Bone size
• Volumetric BMD at the spine and hip
• Cortical thickness at hip

In Premenopausal IOP, Low Areal BMD by DXA (Z < -2.0) Predicts Low Volumetric BMD by cQCT

Used cQCT results from Controls to calculate Z-scores for IOP Subjects

• At the spine, 18 of 19 Subjects with Z ≤ -2.0 by DXA also had central QCT Z scores ≤ -2.0
  – 95% at the lumbar spine
  – 90% at the total hip
  – 86% at the femoral neck

Bone Micro-architectural Deficits

Bone Micro-architectural Deficits in IOP

Comparable deficits in women with fractures and those with only Low BMD
Remodeling Was Heterogeneous

- No significant group differences between Controls and Fracture or Low BMD
- High, normal and low turnover (BFR/BS)

Women in **LOWEST** Tertile of BFR

- Lowest serum bone turnover markers
- Lowest volumetric BMD & strength
- Significantly **HIGHER** serum IGF-1
- **c/w** IGF-1 resistance at the osteoblast level?

Women in **HIGHEST** Tertile of BFR

- Highest serum bone turnover markers
- Higher 1,25(OH)₂D
- Higher Urine Calcium and PTH
- **c/w** Idiopathic Hypercalciuria?

Did serum bone turnover markers predict bone formation rate on iliac crest bone biopsies in women with IOP?

**NO**

Serum Osteocalcin in Premenopausal IOP by Turnover Status

- Thin, porous cortices
- Thin, disconnected trabeculae
- Normal eroded surface
- Normal mineralization rate, no osteomalacia
- Low bone formation rate, DESPITE normal bone turnover markers

Ms. A.A.

Tetracycline-Labeled Transiliac Biopsy

- Bone Volume Fraction 19.8%
- Cortical Width 661 microns
- Bone Formation Rate 0.006 mm²/mm/year
IOP in Premenopausal Women

- Consistent deficits in volumetric BMD, microarchitecture, stiffness at spine & hip, distal radius & tibia, iliac crest.
- Heterogeneous turnover - varying pathogeneses
  - Primary osteoblast dysfunction, IGF-1 resistance
  - Idiopathic hypercalciuria

Conclusions

- Assessment of bone turnover by bone biopsy may provide clues to pathogenesis of IOP in individual patient

Fracture and Low BMD subjects:
- Differed comparably from Controls
- Did NOT differ from each other
- Selection bias?
- Part of a continuum?
- Fractures due to happenstance?

Outline

- Osteoporosis in premenopausal women
  - Diagnosis
  - Etiology
  - Evaluation
- Management of osteoporosis in premenopausal women with
  - Secondary osteoporosis
  - Idiopathic osteoporosis

The challenge for physicians caring for premenopausal women with osteoporosis

1. To decide WHETHER to treat
2. To decide HOW to treat

Management of Premenopausal Osteoporosis

- General Measures
  - Adequate nutrition, calcium, vitamin D, exercise
  - Avoid tobacco, excess alcohol
  - Makes sense but minimal effects on BMD
- Specific therapy of secondary cause(s) often yields large increases in BMD
  - Celiac Disease
  - Primary hyperparathyroidism
  - Control inflammation in chronic inflammatory states (RA, inflammatory bowel disease)

Conservative Treatment in Premenopausal Women With Unexplained Fractures

- 16 women
- Calcium, vitamin D and exercise
- BMD followed annually for average of 3 yrs
  - Spine BMD increased by ~2%
  - Femoral neck BMD increased by ~6%
- NO new fractures

1. Cohen et al., JCE&M 97;4244–4252, 2012
2. Cohen et al., JCE&M 94;4351–4360, 2009
3. Cohen et al., JCE&M 96;3095–3105, 2011
5. Cohen et al., Osteoporos Int 21;1487–90, 2010
7. Cohen et al., JCE&M 94;4351–4360, 2009
8. Cohen et al., JCE&M 96;3095–3105, 2011
9. Cohen et al., Osteoporos Int 21;1487–90, 2010
11. Cohen et al., JCE&M 94;4351–4360, 2009
12. Cohen et al., JCE&M 96;3095–3105, 2011
13. Cohen et al., Osteoporos Int 21;1487–90, 2010
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32. Cohen et al., JCE&M 96;3095–3105, 2011
33. Cohen et al., Osteoporos Int 21;1487–90, 2010
Ms. A.A.
Conservative Management

- Calcium intake 1200 mg day from food and supplements
- Vitamin D ~1000 IU daily
- OCP for birth control
- Over next 10 years
  - BMD remained very low but quite stable
  - 2 pregnancies with expected bone loss
  - No new fractures
- Subsequent evaluations for osteoporosis
  - No new medical diagnoses or medications

Management of Premenopausal Osteoporosis

- Pharmacologic therapy rarely justified unless
  - Fractures
  - Ongoing bone loss with conservative Rx
  - Extremely low BMD (T or Z score < -3.0)

Management of Premenopausal Osteoporosis

- If drug therapy necessary, avoid SERMs (e.g., raloxifene)
  - Cause bone loss in premenopausal women
- Use bisphosphonates with caution in childbearing women
  - Long residence in the skeleton and cross placenta
  - Animal studies - adverse effects on fetus (high doses)
  - Case reports suggest safe in pregnancy & lactation
- Teriparatide & Denosumab contraindicated in pregnancy

BP or Teriparatide Improve BMD in Premenopausal Women With Secondary Osteoporosis

- Anorexia nervosa
- Chemotherapy induced amenorrhea
- GnRH therapy for endometriosis
- Crohn's disease (+ infliximab)
- Cystic fibrosis
- Thalassemia major
- HIV-associated osteopenia
- Glucocorticoid-induced osteoporosis

Caveats

1. BPs and TPTD are only FDA-approved in premenopausal women taking Glucocorticoids.
2. No data that treatment with BPs or TPTD prevent fractures in premenopausal women.

Teriparatide vs Alendronate for Treatment of GC-Induced Osteoporosis

- Randomized active comparator trial of 528 patients with GIOP
- Sub-analysis of BMD changes and fractures in 51 premenopausal women
- No fractures in either group

Glucocorticoids in Premenopausal Women

- Bisphosphonates and teriparatide prevent bone loss and/or increase BMD in premenopausal women on GCs

However

- Premenopausal women on GCs may not lose bone
- Bone loss more likely if oligomenorrhea or amenorrhea
- Less likely to fracture on GCs than postmenopausal women

1. Nakayamada, J Rheumatol, 2004
2. Sato, J Rheumatol, 2003
3. Neou, Lupus, 2005
4. Roux, Osteoporosis Int, 2011

1. Powles, J Clin Oncol, 1996
2. Vehmanen, J Clin Oncol, 2006
3. Stathopoulos, Hormones (Athens) 2011
5. Chan, JCE&M 2006
7. Illidge, Clin Oncol (R Coll Radiol) 1996
8. Munns J Bone Miner Res 2004
10. Ferrari et al., Osteoporos Int. 2012, 23:2735-2748
Recommendations for Premenopausal Women on GCs: ACR 2010

- Assess for
  - prevalent fragility fractures
  - childbearing potential
  - dose and likely duration of GC therapy
- Measure BMD
- Prescribe calcium and vitamin D
- Prescribe estrogen if deficient

American College of Rheumatology. Arthritis Care and Research 62:1515-26, 2010

Recommendations for Premenopausal Women on GCs: ACR 2010

- In women of NONchildbearing potential, prescribe BPs if
  - Prevalent fragility fracture(s)
  - Prednisone > 5 mg/day for ≥ 1 month
- In women of childbearing potential, prescribe BPs if
  - Prevalent fragility fracture(s)
  - Prednisone > 7.5 mg/day for ≥ 3 months
- No consensus about
  - Those with no prevalent fragility fracture
  - Women of childbearing potential with prevalent fracture on GCs for < 3 months

American College of Rheumatology. Arthritis Care and Research 62:1515-26, 2010

Teriparatide for Premenopausal IOP: Open-Label Observational Study

- 21 women
- Mean age 39
- TPTD 20 mcg x 2 yrs
- BMD every 6M
  - % change from baseline
- Transiliac biopsies
  - Baseline and 18M
- HR-pQCT
  - Baseline and 18M

Cohen A et al. J Clin Endocrinol Metab 2013

Ms. A.A.
Spine BMD Changes on Teriparatide

Scan Information:
Scan Date: September 18, 2013
Data: 128/6800000
Scan Type: 4 Lumbar Spine
HR-pQCT: Discovery + Dual (4.5.12)
Lumbar Spine
Operator: KM
Model: Discovery + DEXA225

Began Teriparatide
T Score Change: -2.6 to -1.4

Teriparatide for Premenopausal IOP: Bone Structural Changes on Biopsies

Ms. A.A.

% Change: Baseline vs 18 Months

Cohen A et al. J Clin Endocrinol Metab 2013

What about after TPTD?

- In postmenopausal women and men, BMD declines after TPTD stopped if not followed by anti-resorptive therapy.

In menstruating women, is endogenous estrogen production sufficient to prevent this?
Partial Loss at Lumbar Spine 2 Years after Stopping TPTD

- 15 women from pilot study rescanned at ~ 2 yrs
- ~5% loss at spine (p<0.001)
- Stable BMD at total hip and femoral neck
- Those who lost >3% BMD at spine were older – 46 vs 38; p=0.046

Cohen A et al. ASBMR 2014; Poster SUO0373

Do premenopausal women need antiresorptive treatment to prevent bone loss after teriparatide?

PROBABLY

Which antiresorptive should be used?

DEPENDS ON THE CLINICAL SITUATION

- Estrogen?
- Bisphosphonates?
- Denosumab?
- Possible future choices – more anabolic therapy?
  - Anti-Sclerostin Antibodies?
  - PTHrP analogues?

Key Diagnostic Points

- Diagnosis of osteoporosis in premenopausal women most secure if secondary cause or low trauma fractures
- Low areal BMD by DXA in otherwise healthy women should be interpreted with caution – But may reflect low volumetric BMD and strength
- Bone turnover markers of limited assistance in assessing bone turnover – Bone biopsies may be helpful

Key Management Points

- Crucial to assess for secondary causes of bone loss and treat specifically
- No fracture data are available for treatment studies of premenopausal women...
- Given relatively low fracture rates in premenopausal women, there probably never will be...

FDA-Funded RCT of TPTD in Premenopausal IOP

- New study enrolling
- Randomized, placebo-controlled, single switch-over
- Quadruple tetracycline-labeled transiliac biopsy at 3 months
- Funded by FDA Orphan Products/Disease Branch
- At completion, observation vs antiresorptive Rx with denosumab funded by Amgen and hopefully FDA
- To refer women with IOP: – Call 212-305-7225

premenopausal women with various causes of bone loss
Thank you!