Disclosures

• Industry Research Support (To Institution)
  – Eli Lilly, Amgen

• Consultancies, Speakers Bureaus, Financial holdings
  – None

• Discussion of unlabeled use of drugs
  – Teriparatide
Mrs. T.O., 31 yo healthy woman

- 7 vertebral fractures T8, T10, T11, L1-L4, multiple ribs
- 2” height loss
- PMH - unremarkable, no medications
- Menarche age 13, G0P0, normal menses, OCP ages 18-31
- FH - negative for fractures, kidney stones
- PE - 59”, 91 lbs; normal sclerae and dentition
- Z scores: LS -2.0, TH -2.2, FN -1.7
- All routine labs normal; bone turnover markers LOW
- Bone biopsy – VERY LOW bone formation, normal resorption
Outline

• Diagnosis and etiology of osteoporosis in premenopausal women

• Idiopathic osteoporosis in premenopausal women
  – Clinical and biochemical characteristics
  – Bone mass and microstructure
  – Bone remodeling

• Management of osteoporosis in premenopausal women with
  – Secondary osteoporosis
  – Idiopathic osteoporosis
Diagnosis of Osteoporosis in **POST**menopausal Women

- Based on the WHO classification

- Areal BMD by DXA
  - T-Score \( \leq -2.5 \) 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 **POST**menopausal Women

- Low areal BMD (T score $\leq -2.5$)
- Low trauma fractures

**No clear intervention thresholds for PREmenopausal women.**

- By FRAX or other risk assessment tools
Osteoporosis in Premenopausal Women

- Uncommon

- Difficult to diagnose in absence of low trauma fractures

- Most have a secondary cause
Diagnosis of Osteoporosis in PREmenopausal Women is NOT Straightforward
No Clear Definition of Osteoporosis in Premenopausal Women

Low BMD in young women may be due to...

- Low Peak Bone Mass\textsuperscript{1-3}
- Small Stature
- Constitutional Leanness\textsuperscript{4-6}
- Statistical Definition of a Z or T Score

95% of Peak Bone Mass Attained by Age 20

Major determinant of bone strength and fragility throughout life
• Everyone reaches a peak of bone mass accrual

• Not everyone achieves an optimal peak of bone mass accrual
Factors That May Affect Peak Bone Mass Accrual in Premenopausal Women

- **Not modifiable**
  - Genetics
    - approximately 50-80% of variation in bone mass is heritable
  - Race
  - Ethnicity

- Particularly During Adolescence
  - Estrogen deficiency
    - Late menarche, hypothalamic amenorrhea
  - Poor nutrition
    - Calcium, protein, vitamin D
  - Low body weight
  - Weight cycling
  - Physical inactivity
  - Smoking
  - Excess alcohol
  - Medications
    - Glucocorticoids, anticonvulsants, GnRH agonists, Depo-Provera
  - Diseases associated with bone loss
    - Cushing’s, hypogonadism, celiac disease, hyperparathyroidism, cystic fibrosis

1 Pocock, J Clin Invest 1987;80:706
2 Guerguen, J Bone Miner Res 1995;10:2017
Low BMD May Be Related to Small Stature - Artifact of DXA

- Measures **areal** BMD (g/cm\(^2\)) and converts it mathematically to **volumetric** BMD.
- Does not account for bone **thickness**.
- Underestimates BMD in small people (< 63” or 160 cm).
- Low BMD with **normal bone quality**?
  - We often say this but no data to support.
Constitutional Leanness (or Thinness)

- Nonpathological state of underweight
  - Body weight in lower percentile for age, gender, ethnicity
  - Normal menses
  - Normal thyroid and cardiac function
  - Normal insulin sensitivity
  - Often familial

- BMD by DXA, trabecular and cortical microstructure at distal radius, bone breaking strength
  - Lower than normal weight controls
  - Similar to women with anorexia nervosa

References:
2. Fernandez-Garcia et al., Br J Nutr 2009
3. Galusca et al., JCE&M 2008
Peak Bone Mass in Healthy Women Aged 30-40

Bell-shaped Curve Distribution

• In a group of normal young adult women
  – 16% will be 1.0 SD below mean
  – 2.5% will be 2.0 SD below mean
  – 0.5% will be 2.5 SD below mean

• Based on the WHO definition (T ≤-2.5)
  – 0.5% of otherwise healthy young women will have osteoporosis

1. Kanis et al., J Bone Miner Res. 1997;7:390-406
2. Liu et al., J Bone Miner Metab. 2008;26:159-64
3. Diaz Curiel et al., Med Clin (Barc) 2001;116:86-88
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 **PRE**menopausal than **POST**menopausal women. 

1. Thompson, Injury, 2004  
2. Melton, Osteoporos Int, 1998  
3. Hosmer, Osteoporos Int, 2002  
Fracture risk per 1000 person-years

Bone mass (g/cm)

Hui et al., J Clin Invest, 1988
Yet Fractures Are NOT RARE in Premenopausal Women

- Up to 30% of women fracture during childhood or adolescence \(^1\text{–}^4\)
- Fractures often associated with trauma
  - Difficult to assess degree of trauma
- Fractures in youth associated with poor bone microarchitecture and low bone strength \(^5,^6\)

2. Clark et al., JBMR 2006.
3. Ferrari et al., JBMR 2006.
6. Farr et al., JBMR 2014
The 2007 ISCD Guidelines for Reporting BMD Results in PREmenopausal Women

Use the Z SCORE, NOT the T SCORE!

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

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”

Does not apply to perimenopausal women where the T-score is now used
• Use Z score < 2.0 to define Low Bone Mass in growing children & adolescents who have NOT YET ACHIEVED PEAK BONE MASS
• Keep T score definition of osteoporosis (≤-2.5) in young adults who have STOPPED GROWING
• In young adults WITH chronic illness that affects bone metabolism
  – T score ≤-2.5 is diagnostic of osteoporosis
• In young adults WITHOUT chronic illness, consider genetic or idiopathic osteoporosis if
  – Prevalent vertebral fractures without major back trauma
  – >2 low trauma fractures

Ferrari et al., Osteoporos Int. 2012; 23:2735-2748
A premenopausal woman can be considered to have osteoporosis when she has......

- BMD Z-score ≤ -2.0 or T score ≤ -2.5 + secondary cause of osteoporosis
  - e.g., glucocorticoids, hypogonadism, celiac disease, hyperparathyroidism

- 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 very low BMD (T-score $\leq -2.5$, Z score $\leq -2.0$) BUT NO SECONDARY CAUSE AND NO FRACTURES?

- Neither ISCD or IOF would say such a woman has osteoporosis.

- I am not convinced that is true.
Etiology & Evaluation of Premenopausal Osteoporosis
Who Should Be Evaluated?

- Women with low BMD
  - Z score $\leq -2.0$
  - T score $\leq -2.5$

- Women with fragility fracture(s) or prevalent vertebral fracture, regardless of BMD
  - IOF suggests should have $> 1$ fracture to warrant w/u

1. Ferrari et al., Osteoporos Int. 2012; 23:2735-2748
Goals of Evaluation – Assess Whether Low BMD is Related to...

- Failure to attain optimal peak bone mass
- Previous bone loss
- Ongoing bone loss

This doesn’t usually lead to fractures in young women

This is more likely to lead to fractures 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
  - Lactose intolerance
- **Rheumatologic**
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
- **Pulmonary**
  - Cystic fibrosis
  - Emphysema
- **Medications**
  - Prednisone
  - Antiepileptic drugs
  - GnRH agonists
  - Thyroid hormone
  - Depo-Provera
  - Cancer chemotherapy
  - SSRI
  - PPIs
  - HAART
- **Miscellaneous**
  - Major depression
  - Pregnancy-associated
  - HIV
- **Idiopathic**
Secondary Causes of Osteoporosis in Young Women

- What are the most common causes?
- How often will you find a cause?
Most Common Causes of Osteoporosis in Premenopausal Women

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

Khosla et al, Bone 1994
Peris et al, Sem Arthr Rheum, 2003
Kulak et al, Endocr Pract, 2000
Cohen et al, J Women’s Health, 2009
Secondary Causes of Osteoporosis in Young Women

How often will you find a cause?

- In a population-based study of $\text{♂}/\text{♀}$ age 20-44
  - 90% had a secondary cause $^1$

- In series from tertiary referral centers (young $\text{♀}$)
  - Only about 50% had a secondary cause $^{2-4}$

1. Khosla et al, Bone 1994
2. Kulak et al, Endocr Pract, 2000
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
- 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-dihydroxvitamin D
- Iron and Total Iron Binding Capacity, Ferritin
- Carotene
- Celiac screen
- Serum/urine protein electrophoresis
- Erythrocyte sedimentation rate or C-reactive protein
- Serum tryptase and histamine
- COL1A genetic testing for osteogenesis imperfecta
- Whole exome sequencing for mutations in Wnt?
Bone Turnover Markers?

- May be useful
- 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
Transiliac Bone Biopsy?

• Should be performed after tetracycline labeling of active bone-forming sites
• 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
Most Common Causes of Osteoporosis in Premenopausal Women

- Glucocorticoid excess
- Premenopausal estrogen deficiency
- Pregnancy-associated osteoporosis
- GI disease
  - Celiac disease, inflammatory bowel disease, malabsorption
- Medications
  - Antiepileptic drugs, cancer chemotherapy, prednisone
- Alcoholism
- Primary hyperparathyroidism
- Osteogenesis imperfecta
- **Idiopathic**
• Diagnosis and etiology of osteoporosis in premenopausal women

• Idiopathic osteoporosis in premenopausal women
  – Clinical and biochemical characteristics
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  – Bone remodeling

• Management of osteoporosis in premenopausal women with
  – Secondary osteoporosis
  – Idiopathic osteoporosis
Idiopathic Osteoporosis (IOP)

• First described by Fuller Albright in 1944
  – Premenopausal women and men < 50
  – Otherwise healthy
  – Intact gonadal function
  – No secondary cause of bone loss

• Rare, estimated annual incidence
  – 0.4 cases per 100,000 based on fractures and low BMD

1. Albright & Reifenstein, 1944
2. Khosla et al, Bone 1994
Clinical Features of IOP

- Usually Caucasian
- Often present in mid-30s
- One or more low trauma fractures
  - Cluster over 5 to 10 years
- Fractures of sites rich in cancellous bone
  - Hip and long bone fractures also reported
- May be mild or devastating
IOP in Men

• Biochemical features
  – Hypercalciuria common
  – Low free estradiol (E2) and testosterone
  – LOW serum IGF-1

• Bone biopsy
  – Most have low bone formation
  – IGF-1 and free E2 directly related to bone formation
  – Minority have high or normal turnover

• Define abnormalities in bone mass, microstructure, mineralization, collagen and strength
  – High resolution imaging and transiliac bone biopsy

• Elucidate pathogenesis
  – Gonadal & calciotropic hormones, urinary calcium, bone turnover markers, IGF-1

• Improve diagnosis and guide management
IOP Without Fractures?

- Clinical significance of isolated low areal BMD in otherwise healthy young woman uncertain
  - Small bone size?
  - Low peak bone mass?
  - Fracture risk increased?
  - Microarchitecture - normal or abnormal?

Do women with Fractures differ from those with Low BMD?
Cross-sectional Case-Control Study

Control – 40
- No adult fractures
- Normal BMD – Z score > -1.0

Fracture group - 45
- 1-12 adult fractures
- 25 had multiple fractures
- Mean age at 1st fracture – 30
- Fracture type
  - Vertebrae, ribs, hip, pelvis, forearm, humerus, ankle, metatarsal

Low BMD group - 19
- No low trauma adult fractures BUT
  - 16% had high trauma adult fractures
  - 26% had childhood fractures

Cohen et al., Osteoporos 2012, 23:171-82
## Characteristics of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Fracture</th>
<th>Low BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>37 ± 8</td>
<td>37 ± 8</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>165 ± 7</td>
<td>164 ± 7</td>
<td>162 ± 6</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>70.7 ± 14.6</td>
<td>63.0 ± 14.9 *</td>
<td>57.1 ± 10.2 **</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 4.7</td>
<td>23.4 ± 4.9 *</td>
<td>21.6 ± 3.5 **</td>
</tr>
</tbody>
</table>

* *p*<0.05 vs Controls   ** *p*<0.01 vs Controls

Cohen et al., Osteoporos 2012, 23:171-82
IOP Subjects and Controls did **NOT** differ by

- Whole body or trunk fat, caloric intake
- Reproductive history
  - Low BMD group slightly later menarche
- Reproductive hormones, vitamin D metabolites, serum/urine calcium

Cohen et al., Osteoporos 2012, 23:171-82
IOP Subjects and Controls did NOT differ by

- Whole body or trunk fat, caloric intake
- Reproductive history
  - Low BMD group slightly later menarche
- Reproductive hormones, vitamin D metabolites, serum/urine calcium

But DID differ by

- FH of osteoporosis more frequent
- More calcium supplements
- More SSRI use (3% vs 16%; p=0.11)

Cohen et al., Osteoporos 2012, 23:171-82
Serum PTH and TRAP5b Higher in IOP

<table>
<thead>
<tr>
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<th>Control</th>
<th>Fracture</th>
<th>Low BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PTH (nl 10-65)</td>
<td>22 ± 9</td>
<td>29 ± 11 ***</td>
<td>30 ± 16 **</td>
</tr>
<tr>
<td>TRAP5b</td>
<td>1.6 ± 0.9</td>
<td>2.2 ± 1.2 **</td>
<td>2.3 ± 1.0 **</td>
</tr>
</tbody>
</table>

** p<0.05 compared to Controls
*** p<0.01 compared to Controls

- Direct associations between PTH and
  - Bone alkaline phosphatase, osteocalcin
  - C-Telopeptide and TRAP5b

NO Control had PTH > 38 pg/ml
~20% IOP had PTH > 40 pg/ml

Cohen et al., Osteoporos 2012, 23:171-82
Be very suspicious of PTH levels in the upper third of the normal range in a premenopausal woman – could be a clue to a subtle secondary cause such as malabsorption or idiopathic hypercalciuria
In contrast to Men With IOP, Serum IGF-1 Not Lower in Women With IOP

- Control, Fracture and Low BMD did not differ
- No association with age-adjusted bone turnover markers in any group
- No association with BMD at any site
Areal BMD by DXA – Z Score

Figure 1
Areal BMD by DXA – Z Score

Controls
Fracture
Low BMD

* p<0.05
** p<0.01
***p<0.001
vs Controls
High Resolution Peripheral CT (HR-pQCT)

- Volumetric BMD
- Microarchitecture
  - Trabecular number, thickness & separation
  - Heterogeneity of trabecular network
  - Cortical thickness
- Finite element analysis (FEA)
  - Estimate bone stiffness

Region of Interest

Radius

Tibia

Control

Fracture

Low BMD
HR-pQCT in Premenopausal IOP: Distal Radius

Percent Difference from Controls

* p<0.05; ** p<0.01; *** p<0.001 compared to Controls

Cohen et al., J Clin Endocrinol Metab 2009
Volumetric BMD of Spine and Hip by Central QCT in IOP

Measures

- Important fracture sites
- Bone size
- Trabecular vBMD at the spine
- Trabecular and Cortical vBMD at hip
- Cortical thickness at hip

Lang et al JBMR 2004, 2006; Cohen, ASBMR 2010
Central QCT in IOP: % Lower Than Controls

Compared to Controls:
All P<0.05 to <0.001
Except Stiffness of Hip in Fracture Group

Cohen, et al., J Clin Endocrinol Metab 2011
In Premenopausal Women With IOP, Low aBMD by DXA (Z ≤-2.0) Predicts Low vBMD 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

- Positive predictive value of DXA for cQCT Z-score ≤-2.0
  - 95% at the lumbar spine
  - 90% at the total hip
  - 86% at the femoral neck

Cohen, et al., J Clin Endocrinol Metab 2011
Transiliac Bone Biopsy

Trabecular Bone Microstructure by MicroCT
Transiliac Crest Microstructure in IOP by $\mu$CT

Percent Difference from Controls

- Tb BV/TV
- Tb Number
- Tb Separation
- Tb Sp SD
- Connectivity
- Stiffness
- Ct. Thickness

Cohen et al., JCE&M 96:3095-3105, 2011
Remodeling Was Heterogeneous

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

Bone Formation Rate

Cohen et al., JCE&M 96:3095-3105, 2011
Women in **LOWEST** Tertile of BFR

- Lowest trabecular BV/TV & stiffness
- Lowest osteoid width & wall width (thinner completed bone remodeling units)

**Significantly higher serum IGF-1**

- Since IGF-1 is anabolic for osteoblasts this raises the question of IGF-1 Resistance

Cohen et al., JCE&M 96:3095-3105, 2011
Women in **HIGHEST** Tertile of BFR

- Less severe deficits in bone volume
- Higher Urine Calcium and PTH
- Higher $1,25(\text{OH})_2\text{D}$
- Mild idiopathic hypercalciuria?

Cohen et al., JCE&M 96:3095-3105, 2011
Did serum bone turnover markers predict bone formation rate on iliac crest bone biopsies in women with IOP?

NO
Serum C-telopeptide in Premenopausal IOP by Turnover Status
Summary

• Consistent deficits in volumetric BMD, microarchitecture and stiffness at spine, hip, distal radius and tibia, iliac crest

• Heterogeneity of bone turnover c/w 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
Part of a continuum?
Fractures due to happenstance?
Outline

• Diagnosis and etiology of osteoporosis in premenopausal women

• Idiopathic osteoporosis in premenopausal women
  – Clinical and biochemical characteristics
  – Bone mass and microstructure
  – Bone remodeling

• 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 - 1-2%

• **Identify secondary cause(s), treat specifically**

• **Control inflammation in chronic inflammatory states** (RA\(^1\), Inflammatory bowel disease\(^2,3\))

Most Common Causes of Osteoporosis in Premenopausal Women

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

Khosla et al, Bone 1994
Peris et al, Sem Arthr Rheum, 2003
Kulak et al, Endocr Pract, 2000
Cohen et al, J Women’s Health, 2009
12 premenopausal & 36 postmenopausal women

BMD before and 1 year after PTX

10% increase in spine BMD in both groups

BMD After One Year on Gluten-free Diet

% Change From Baseline

- Lumbar Spine
- Femoral Neck

Sategna-Guidetti, Aliment Pharmacol Ther. 2000;14:35-43
Ciacci, Am J Gastroenterol. 1997;92:992-6
McFarlane, Gut, 1996;39:180-4
Mautalen, Am J Gastroenterol. 1997;92:313-8
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)
Center for Treating 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%
  - Fem neck BMD increased by ~6%
- No new fractures

Peris, Clin Rheumatol, epub August, 2006
Management Principles for Premenopausal Osteoporosis

• If drug therapy necessary, **avoid SERMs**
  – Cause bone loss in premenopausal women \(^1,2\)

• Use bisphosphonates with caution in childbearing women \(^3\)
  – Long residence in the skeleton and cross placenta
  – Animal studies - adverse effects on fetus (high doses)
  – Case reports suggest safe in pregnancy & lactation \(^4-9\)

• Teriparatide contraindicated in pregnancy

BPs 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. No data that treatment with BPs or Teriparatide prevent fractures in premenopausal women

   1. Probably never will be!

Ferrari et al., Osteoporos Int. 2012; 23:2735-2748
Glucocorticoids in Premenopausal Women

- Bisphosphonates and teriparatide prevent bone loss and/or increase BMD in premenopausal women on GCs\textsuperscript{1-4}

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. Nzeusseu, Lupus, 2005
4. Roux, Osteoporosis Int, 2011
Teriparatide vs Alendronate for Treatment of GC-Induced Osteoporosis
Saag et al, NEJM, 2007

- 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

Langdahl et al. Osteoporos Int, 2009;20:2095-04
Recommendations For Premenopausal Women on GCs: ACR 2010

• Assess for
  – GC dose
  – Likely duration of GC therapy
  – Prevalent fragility fracture
  – Childbearing potential

• Measure BMD

• Prescribe calcium and vitamin D

• **Estrogen if deficient (oligo- or amenorrhea)**
Recommendations For Premenopausal Women on GCs: ACR 2010

- Women of **NON**childbearing potential, prescribe BPs if
  - Prevalent fragility fracture(s)
  - Prednisone > 5 mg/day for > 1 month

- Women of **childbearing potential**, prescribe BPs if
  - Prevalent fragility fracture(s)
  - Prednisone > 7.5 mg/day for > 3 months

- No consensus if
  - 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 Premenopausal women with IOP | Teriparatide 20 µg SC daily | 24 months |

- Mean age 39 yrs
- 18 Fractures and 3 Low BMD
- BMD by DXA
- Transiliac bone biopsies at baseline and 18 months
- HR-pQCT as baseline and 18 months

Cohen A et al. J Clin Endocrinol Metab 2013
Teriparatide for Premenopausal IOP: % Change in BMD Over 24 Months

Figure 1

A. Lumbar Spine

- Baseline
- 6 Month
- 12 Month
- 18 Month
- 24 Month

B. Total Hip

- Baseline
- 6 Month
- 12 Month
- 18 Month
- 24 Month

C. Femoral Neck

- Baseline
- 6 Month
- 12 Month
- 18 Month
- 24 Month

10.8% Increase
6.4% Increase
7.8% Increase

Cohen A et al. J Clin Endocrinol Metab 2013
Teriparatide for Premenopausal IOP: Bone Structural Changes on Biopsies

Cohen A et al. J Clin Endocrinol Metab 2013

% Change: Baseline vs 18 Months

% Change from Baseline

* p<0.01

Cohen A et al. J Clin Endocrinol Metab 2013
Teriparatide Pilot Study: HR-pQCT at the Radius and Tibia

- **Improved Trabecular Structure**
  - $2-3\% \uparrow (p<0.05)$ in Tb BV/TV
  - $7-8\% \uparrow (p<0.05)$ in Tb PLATE BV/TV
    - Individual Tb Segmentation Analyses

- **Cortical Changes**
  - Increased cortical thickness
  - $16\% \uparrow$ in Ct porosity – radius only

- **Stiffness and Failure Load**
  - Significant $\uparrow$ at radius and tibia

Nishiyama et al, ASBMR Oral Presentation 2013
In 4 Women, BMD Did Not Increase at Any Site During Teriparatide Rx

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

A: Lumbar Spine BMD
Responders versus Non-responders

BMD response correlated DIRECTLY with baseline serum bone turnover markers and INVERSELY with baseline serum IGF-1.
Circulating Osteoblast Progenitor Cells Reflect TPTD Response and Predict BMD in Premenopausal IOP

- Flow cytometry of Peripheral Blood Mononuclear Cells (PBMCs)
- Antibodies to early stem cell markers, osteocalcin, and RUNx2 (osteoblast-specific transcription factor)
- Isolate, identify and characterize circulating osteoblast progenitor (COP) cells among PBMCs
- COPs correlate directly with bone formation on transiliac biopsies \(^1,^2\)
- Used antibodies against COP cell surface IGF-1 receptor and intracellular phosphorylated (p)AKT to assess expression of peptides related to PTH/TPTD action as described for several proteins \(^3\)
- Mean channel fluorescence (MCF) - index of density of peptide expression

In 10 IOP women treated with TPTD, significant and substantial 3 month changes in COP cells and cell surface expression of IGF-1 Receptor

<table>
<thead>
<tr>
<th>COP cells after 3 months of TPTD</th>
<th>% change vs baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>%COP cells</td>
<td>+234% *</td>
</tr>
<tr>
<td>IGF-1 receptor density</td>
<td>+139% *</td>
</tr>
<tr>
<td>pAKT density</td>
<td>+35% *</td>
</tr>
</tbody>
</table>

- Increase in IGF-1 receptor density predicted 6-month rise in
  - LS BMD: \( r=0.7; p=0.02 \)
  - FN BMD: \( r=0.7; p=0.02 \)
- Lower in Nonresponders than Responders
  - Mean 1300 vs 2200; \( p=0.03 \)

Figure 4: IGF-1R MCF (density) on COP cells (lacking hematopoietic precursors (LIN-) and co-expressing OCN and Runx2) at baseline and 3M

RESPONDER: 183% Increase

NONRESPONDER: 30% Increase

More evidence for IGF-1 resistance at the osteoblast level in premenopausal women with IOP and low bone formation

Cohen A et al. ASBMR 2014
Limitations

- Small and uncontrolled
- No fracture outcome
- Baseline and 18 month biopsies on opposite iliac crests
- BMD increases may dissipate after TPTD stopped if not followed by anti-resorptive therapy

In menstruating women, is endogenous estrogen production sufficient to prevent this?
What Happened After Discontinuing TPTD in Premenopausal IOP?

• Follow-up data in 15 women from pilot study

• At 2 years, significant loss at spine (~5%; p<0.001)

• Stable BMD at the total hip, femoral neck and forearm

• Those who lost >3% BMD at spine were older (46 ± 3 vs 38 ± 7; p=0.046)

Cohen A et al. ASBMR 2014
Do premenopausal women need antiresorptive treatment to prevent bone loss after teriparatide?

PROBABLY

Which antiresorptive should be used?
Bisphosphonates?

Denosumab?

Cathepsin K Inhibitors?

DEPENDS ON THE CLINICAL SITUATION
Summary

• IOP is characterized by increased marrow fat and deficits in volumetric BMD, microarchitecture and stiffness at the central and peripheral skeleton
  – Comparable in women with low BMD
• Biochemical abnormalities may be subtle and missed by relying on established normal ranges
• Bone remodeling activity varies and transiliac biopsy may help with diagnosis
  – Low bone turnover – osteoblast dysfunction and IGF-1 resistance
Summary

- Teriparatide improved microarchitecture, increased volumetric BMD and stiffness at the spine, hip, radius, tibia and iliac crest.
- Those with very low bone formation may not respond to Teriparatide.
  - Osteoblast resistance to IGF-1?
- 2 years after stopping Teriparatide.
  - BMD stable at the hip.
  - Partial loss at the spine.
- Ongoing efforts to develop effective treatment strategies for IOP.
Key Points

- Diagnosis of osteoporosis in premenopausal women most secure if there is a secondary cause of bone loss.
- Isolated low BMD measurements in otherwise healthy women should be interpreted with caution.
- Bone turnover markers of limited assistance in assessing bone turnover but bone biopsies may be helpful.
- Crucial to assess for secondary causes of bone loss and treat specifically.
- Most women with low BMD don’t require pharmacotherapy.
- Antiresorptive drugs and teriparatide increase BMD in premenopausal women with various causes of bone loss.
- No fracture data are available for treatment studies in postmenopausal 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
- At completion, observation vs antiresorptive Rx
- Funded by FDA Orphan Products/Disease Branch
- To refer women with IOP:
  - Call 212-305-7225
Proposed Study of DENOSUMAB post-TPTD in Premenopausal IOP:

- To maintain/improve upon benefits to **TRABECULAR** bone structure associated with TPTD

- To improve **CORTICAL** bone architecture as cortical porosity increases on TPTD and Dmab has been beneficial for cortical bone

- To estimate effect sizes for future RCT of Dmab in IOP

- To ensure shortest duration of exposure and potential toxicity:
  - Short duration of action relative to bisphosphonates.
Minimizing Risks in Premenopausal Women

• In the pilot study and the current FDA-funded study, measures have been put into place, as specified by our IRBs, to protect women of childbearing age.

• Participants are counseled re:
  – Risks related to the drug (TPTD) during pregnancy
  – Requirement to use effective contraception while on Rx

• Negative pregnancy test at each imaging and medication dispensation visit.

• SAME MEASURES to be maintained during our proposed Denosumab Extension Study.
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Thank you!
Teriparatide in IOP: effects on trabecular bone

Percent change from baseline

0  5  10

Total vBMD (mgHA/cm³)
Tb vBMD (mgHA/cm³)
BV/TV (%)
Tb Number (1/mm)
Tb Thickness (mm)
Plate BV/TV (%)
Rod BV/TV (%)
Plate Tb Thickness (mm)
Rod Tb Thickness (mm)
Teriparatide in IOP: effects on cortical bone

- Cortical vBMD (mgHA/cm³)
  - Baseline: 0.6%
  - 18 months: 0.7%

- Cortical Thickness (mm)

- Cortical Porosity (%)
  - Baseline: 0.6%
  - 18 months: 0.7%
Teriparatide in IOP: effects on estimated bone strength

Scaled stiffness (N/mm)

Scaled failure load (N)

Percent change from baseline

0 1 2 3 4 5

Radius

Tibia

*
Fat and Bone

- Osteoblasts and adipocytes have common marrow mesenchymal precursor

- **Reciprocal** relationship between adipocytes and osteoblasts
  - Bone loss of aging, menopause, anorexia nervosa, glucocorticoids and thiazolidinediones

- We hypothesized that marrow fat would be higher in women with IOP than Controls

Cortical Parameters by 2D Histomorphometry

Compared to Controls

- Fracture - Cortices were 24% thinner (p<0.0001)
- Low BMD - Cortices were 21% thinner (p=0.07)

Cohen et al., JCE&M 96:3095-3105, 2011
In our case-control bone biopsy study of premenopausal women with idiopathic osteoporosis (IOP)……

- 40 Controls, 45 with Fracture, 19 Low BMD (Z score ≤-2.0)
- Thin cortices, low trabecular volumetric BMD, inferior trabecular microstructure, lower estimated strength
  - Spine & Hip by central QCT
  - Distal Radius & Tibia by HR-pQCT
  - Iliac crest by microCT of bone biopsies
- Subjects with Low BMD
  - Just as severely affected as those with Fractures

Cohen et al, JCEM 2009
Cohen et al, JCEM 2011
Cohen et al, JCEM 2012
Marrow Adipocytes in IOP

Translucent, yellow elliptical cells in marrow
Measured by method of Syed et al, OI 2008

Cohen et al., JCE&M 2012
Adipocyte Parameters:
% Difference from Controls

- Ad Area: 28%
- Ad Pm: 24%
- Ad #: 22%
- Ad Density: 15%
- AdV/MarrowV: 26%

Cohen et al., JCE&M 2012
Marrow Adipocytes in IOP

• Fat and bone relationship abnormal in IOP

• Excess marrow fat may not arise from switch from osteoblast to adipocyte cell lines

• Excess marrow fat: “innocent bystander” or involved in pathogenesis of IOP?

Cohen et al., JCE&M 2012
Summary

• Consistent deficits in volumetric BMD, microarchitecture and stiffness at spine, hip, distal radius and tibia, iliac crest
• Heterogeneity of bone turnover c/w varying pathogeneses
  – Primary osteoblast dysfunction, IGF-1 resistance
  – Idiopathic hypercalciuri
• Increased marrow fat
In our case-control bone biopsy study of 64 premenopausal women with IOP...

Women in **LOWEST** Tertile of BFR

- Lowest trabecular BV/TV & stiffness
- Lowest osteoid width & wall width (thinner completed bone remodeling units)
- Significantly **HIGHER** serum IGF-1

- c/w IGF-1 resistance?

Cohen et al., JCE&M 96:3095-3105, 2011
In our case-control bone biopsy study of 64 premenopausal women with IOP……

Women in **HIGHEST** Tertile of BFR
- Less marked deficits in bone structure
- Higher 1,25(OH)$_2$D
- Higher Urine Calcium and PTH
- *c/w* Idiopathic Hypercalciuria?

Cohen et al., JCE&M 96:3095-3105, 2011