An Update on Osteoporosis Pathogenesis, Diagnosis, and Treatment

Introduction

• In the past 20 years, important advances have occurred in our understanding and management of osteoporosis
  o Much of the pathogenesis of bone loss after menopause in women and with aging in men and women is known
  o We have a clear picture of the epidemiology of low bone density and fragility fractures
  o Bone mineral density can be measured reproducibly with DXA
  o Diagnostic criteria, based on DXA measurements, are available
  o Simple, validated tools for estimating fracture risk in individual patients exist

DXA=dual-energy X-ray absorptiometry.
Introduction (cont’d)

- Current management strategies for osteoporosis
  - Thorough clinical evaluation
  - General measures
    - Adequate intakes of calcium, vitamin D, and protein
    - Regular physical activity
    - Avoidance of harmful lifestyle factors
  - Fall prevention measures
  - Pharmacological therapy for patients at high risk for fracture

The Remodeling Sequence

BMU = basic multicellular unit; LCs = lining cells; OBs = osteoblasts; OCs = osteoclasts; OCYs = osteocytes.

Adapted from Baron R, Hesse E. J Clin Endocrinol Metab. 2012;97(2):311-325.
Bone Remodeling

Drug Therapies for Osteoporosis

*Designed to Modulate Remodeling*

- Anti-remodeling agents – *90% of market*
  - Bisphosphonates
  - Estrogen agonist/antagonist
  - RANK ligand inhibitor (denosumab)

- Remodeling stimulating (anabolic) agent
  - Teriparatide (PTH 1-34)

Pharmacological Therapy for Osteoporosis

- Effective protection from fractures
  - Vertebral fracture by 60%–70%
  - Multiple vertebral fractures by 75%–96%
  - Hip fracture by 40%–50%
  - Non-vertebral fracture by 20%–35%
- Multiple dosing options
- In general are well tolerated
- In clinical trials, have been very safe
  - Serious side effects are rare


Pharmacological Therapy for Osteoporosis

- Fracture protection occurs quickly – within months

HORIZON Study
Zoledronic Acid

FREEDOM Study
Denosumab

Pharmacological Therapy for Osteoporosis

- Fracture protection occurs quickly – within months
- For bisphosphonates and denosumab, effectiveness continues as long as treatment is given—at least to 10 years


The “Crisis” in Osteoporosis

- The number of patients being treated for osteoporosis has declined by more than 40% since 2008
- The proportion of patients with hip fracture who receive osteoporosis therapy in the United States decreased from 40% in 2002 to 20% in 2011
- Patients and physicians are uncertain about or resistant to starting therapy
- Patents do not accept recommendations to start therapy or stop early because of concerns about safety

Atypical Femoral Fracture and Long-term Bisphosphonate Therapy

- 11,466 patients with femoral fracture
  - 7430 typical hip fracture
  - 142 atypical stress-type fractures
  - 10% occurred in untreated patients
- Duration-dependent Risk for AFF:
  - 1.78/100,000 patient-years in first 2 years
  - 113/100,000 patient-years in years 8–9.9

AFF=atypical femoral fracture.


Atypical Femoral Fracture

Clinical Practice. Postmenopausal Osteoporosis.

Black DM, Rosen CJ.
Atypical Femoral Fracture

Possible risk factors

- Genetic predisposition
  - Hypophosphatasia
  - Defects in cholesterol synthesis pathway
  - Femoral geometry - Asian background
- Vitamin D deficiency
- Glucocorticoid
- PPI use

PPI=proton pump inhibitor.

Atypical Femoral Fracture: Management Tips

- Caution patients to report prodromal thigh pain
- Evaluate contralateral femur
- Look for stress reaction on DXA femur scan

Images Courtesy of Michael McClung, MD, FACP
“Drug Holiday”

Stopping Bisphosphonates and Restarting Therapy

• Discontinuation of bisphosphonate therapy may be considered in postmenopausal women with low fracture risk
  - After treatment for 5 years with alendronate and 3 years with zoledronic acid
  - Reassessment at 2 to 3 years


New Directions in Osteoporosis

• New insights into bone metabolism
• New imaging techniques
• New drugs with novel mechanisms of action
• New approaches to patient selection and management

Image Courtesy of Michael McClung, MD, FACP
Trabecular Bone Score (TBS)
(FDA approved in 2012)

TBS Associated With Fractures, Weakly With BMD

- TBS and BMD were assessed in 29,407 postmenopausal women
- 1668 (5.6%) had major osteoporotic fracture
- TBS was weakly correlated to lumbar spine BMD: R=0.32
- Both BMD and TBS predicted fracture risk, but the combination of hip or spine BMD and TBS was superior to either BMD or TBS alone

BMD=bone mineral density.


Meta-analysis of TBS and Fracture

- >17,000 subjects in 14 studies (59% women)
- 298 hip fractures and 1109 major osteoporotic fractures
- TBS associated with fracture independent of age and FRAX (HR ~ 1.28–1.50)

FRAX=Fracture Risk Assessment Tool; HR=hazard ratio.

QCT-based Finite Element Analysis

- 3D Geometry
- Material Properties
- Hip and spine FEA (O.N. Diagnostics)
  Approved by FDA in 2012
  Diagnosis of fragile bone, BMD t-score, monitoring

FEA=finite element analysis; QCT=quantitative computed tomography.
Images Courtesy of Tony Keaveny

Reprinted from Bone, 33(4). Crawford RP, Cann CE, Keaveny TM. "Embryonic mesenchymal progenitors influence body compression strength better than quantitative computed tomography." Copyright 2003, with permission from Elsevier.
CT Procedures Amenable to Bone Strength Evaluation – CT Colonography, CT Enterography

Adapted from Melton LJ 3rd et al. J Bone Miner Res. 2007;22(12):1885-1892.

Image Courtesy of Tony Keaveny

High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT) “Virtual Bone Biopsy”

HR-pQCT=high-resolution peripheral computed tomography.

Bone Turnover Markers for Alendronate or Denosumab

Phase 2: Postmenopausal Women With Low BMD: Anti-Resorptives Decrease Bone Turnover

**ALN**=alendronate; **BSALP**=bone-specific alkaline phosphatase; **DMAb**=denosumab; **sCTX**=serum C-telopeptide.


Decreased Remodeling But Maintained Modeling at the Rib Cortical Bone in Cynomolgus Monkeys Treated With Denosumab

**OVX**=ovariectomized; **MBF**=modeling-based [formation]; **RBF**=remodeling-based [formation].

OVX + Vehicle

**Cathepsin K (CatK) and Bone Resorption**

- CatK is a lysosomal protease highly expressed in osteoclasts, where it is released during bone resorption.
- CatK is the major protease responsible for degradation of type I collagen.

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**Odanacatib**

- A highly selective, reversible CatK inhibitor.
- Decreases bone resorption while sparing bone formation.

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*Serum CTX (resorption) vs Serum P1NP (formation)*

P1NP=procollagen type 1 N-propeptide.

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Odanacatib: Changes in BMD

In the Extension of the Phase 3 Long-Term Odanacatib Fracture Trial (LOFT), treatment with odanacatib 50 mg po once weekly for 5 years led to progressive mean percent increases in BMD, compared to placebo, of 10.9% at the lumbar spine and 10.3% at the total hip.

Odanacatib: Effect on Fracture Risk

- In LOFT study of 16,371 postmenopausal women with osteoporosis, odanacatib 50 mg po once weekly significantly reduced fracture risk in women with osteoporosis
  - Relative risk reduction (%), 95% (confidence interval)
    - Spine 54% (2.3% vs 7.2%)
    - Hip 47% (0.7% vs 1.2%)
    - Non-vertebral* 23% (6.5% vs 8.0%)

*time-dependent decrease in fracture risk

Small but significant increase in risk for stroke

Further clinical development has been halted
**Anabolic:**
A molecule that increases bone formation, as measured by biochemical markers and dynamic histomorphometry and results in an increase in bone mass.

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**Bone Formation Marker**
**Bone Resorption Marker**

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**PTH Is Anabolic, But Bone Resorption Increases**

**Bone Formation – eg, P1NP**
**Bone Resorption – eg, CTX**

**Can we prevent or minimize the increase in bone resorption?**

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### Changes in Bone Turnover Markers: Abaloparatide vs Teriparatide vs Placebo

![Graph showing changes in bone turnover markers](image)

- CTX
- P1NP


### Sclerosteosis and Van Buchem: Bone-Specific Activation of Wnt Signaling

#### Van Buchem Disease
- Sclerosteosis – absence of sclerostin (SOST), a bone formation inhibitor
- Van Buchem disease – decreased expression of SOST
- Both disorders are characterized by:
  - Increased bone mass throughout skeleton
  - Very low fracture risk
- While homozygotes have skull deformities and nerve compression syndromes, heterozygotes have normal phenotype except high bone mass


Sclerostin Is Expressed in Osteocytes and Works in a Paracrine-Autocrine Mode

Expression Is Decreased by Mechanical Loading

Wnt Signaling: Dual Action


Reprinted with permission of the Endocrine Society from "Minireview: Targeting the Wnt/β-catenin pathway to regulate bone formation in the adult skeleton. Baron R, Rawadi G. 148(6);2007. Permission conveyed through Copyright Clearance Center, Inc."
Sclerostin Antibody Increases Bone Mass in Ovariectomized Rats

- Treatment of ovariectomized rats with an anti-sclerostin antibody increased bone formation on trabecular, periosteal, endocortical, and intracortical surfaces.
- This resulted in complete reversal of estrogen deficiency-induced bone loss, and increased bone mass and bone strength to levels greater than those found in non-ovariectomized control rats.


Effect of a Single Sclerostin Antibody Injection on Bone Markers in Humans

Antisclerostin Antibody
Romosozumab

- In clinical studies, romosozumab markedly stimulates bone formation while inhibiting bone resorption
- This anabolic effect is transient, lasting only 6 to 12 months
- Rapid increases in BMD

<percentage change from baseline graph>


Romosozumab Phase 2 Study: Year 3 – BMD
Romosozumab Discontinuation: Transition to Denosumab

- During the second year of therapy with romosozumab 210 mg QM, BMD in the lumbar spine and total hip continued to increase, but at a slower rate than occurred during year 1
- When romosozumab was stopped after 2 years, BMD returned to near baseline values within 12 months
- In the group switched after 2 years of romosozumab to denosumab 60 mg Q 6 months for 12 months, BMD values continued to increase, reaching 19.4% and 7.1% from baseline in the lumbar spine and total hip, respectively

Romosozumab Phase 3 FRAME Study

*Top-line Results*

- Year 1: Romosozumab 210 mg Q month vs placebo
- Year 2: Open-label denosumab 60 mg Q 6 months
  - At 12 months
    - 73% reduction in vertebral fracture risk
    - 36% reduction in clinical fracture risk
  - At 24 months
    - 75% reduction in vertebral fracture risk in romosozumab-denosumab group compared with placebo-denosumab group


New Osteoporosis Treatments

*Summary*

- Abaloparatide: similar to teriparatide with possible improved benefit: risk ratio
- Romosozumab: a powerful anabolic agent as an initial therapy for patients in need of skeletal reconstruction
  - Will be used in sequence with anti-remodeling agents
Negative Impact of Spaceflight on Bone Prevented by SclAb

SclAb=sclerostin antibody. Images Courtesy of Mary Bouxsein, PhD

Relationship Between Total Hip T-score and Non-vertebral Fracture Risk

“Preliminary analysis of annual on-treatment hip BMD values in the FREEDOM extension study demonstrates that these values in patients on long-term denosumab therapy are predictive of current non-vertebral fracture risk.”

—Ferrari S et al

Development of New Treatments Is Challenging

- Hip and/or non-vertebral fracture as primary end point
- Very large trials (10,000 – 20,000 subjects), lasting several years
- Ethical need for active comparator and/or to enroll low-risk subjects
  - Further increases trial size and complexity
- Currently, no alternative to fracture end points

FNIH Bone Quality Project (2012–2017)
(Foundation for the National Institutes of Health)

**Ultimate Goal**
Develop a surrogate biomarker that can be used as end point for fracture in clinical trials

**Immediate Goals**
1) Advance validation of biomarkers for drug development in osteoporosis
2) Develop repository and database of clinical trial data from trials of osteoporosis agents
Status of Individual-level Database as of August 2016 (Placebo-controlled trials)

Patients with clinical data: ~ 125,000

1. DXA BMD: 100,000-110,000
2. BTMs: 20,000 – 25,000
3. QCT/FEA scans: 400 – 800

Hip Fractures: 1200 – 1400

BTMs = bone turnover markers.

Conclusion