New treatment targets in osteoporosis

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Bone remodeling

- Physiological process < bone tissue continuously renewed
- Bone resorption
  - Osteoclasts
- Bone formation
  - Osteoblasts

Lewiecki EM, Nat. Rev. Rheumatol. 2011
Bone resorption - osteoclasts

Lewiecki EM, Nat. Rev. Rheumatol. 2011
Bone formation - osteoblasts

Roux S, Joint Bone Spine 2010
Osteoporosis

- Skeletal disorder characterized by low bone mass and compromised bone strength, resulting in increased bone fragility and susceptibility to fracture

Normal bone

Osteoporotic bone

Dempster DW et al., ASBMR
Risk factors

- Lifestyle (low Ca intake, VitD insufficiency, thinness, smoking...)
- Genetic (Cystic fibrosis, Homocystinuria, Ehlers-Danlos...) 
- Hypogonal states (androgen insensitivity, premature ovarian failure, anorexia nervosa...)
- Endocrine disorders (adrenal insufficiency, Hyperparathyroidism, Cushing’s syndrome...)
- Gastrointestinal disorders (Celiac disease, IBD, PBC, pancreatic disease...)
- Hematologic disorders (Hemophilia, Multiple myeloma, Leukemia and lymphomas...)
- Rheumatic/ Autoimmune diseases (AS, SLE, RA)
- Miscellaneous conditions/diseases (alcoholism, emphysema, amyloidosis...)
- Medications (glucocorticoids, anticoagulants...)


Osteoporosis by BMD

- Bone Mineral Density (BMD)
  - correlates with bone strength and its ability to bear weight
  - predicts fracture risk

Terms:
- Measured areal density in g/cm\(^2\)
- T-score
  - Normal: ≥ -1
  - Osteopenia: -1 - 2.5
  - Osteoporosis: ≤ -2.5
- Z-score
Bone Densitometry technologies

- **Dual-energy X-ray absorptiometry (DEXA)**
  - Spine & Hip

- **Peripheral DEXA (pDEXA)**
  - Calcaneus, distal tibia, patella

- **Quantitative computed tomography (QCT)**
  - Spine & Hip

- **Peripheral QCT (pQCT)**
  - Forearm, tibia

- **Quantitative ultrasound densitometry (QUS)**
Additional skeletal health assessment techniques

- **Biochemical markers of bone remodeling**
  - **Resorption markers**
    - Serum C-telopeptide (CTx), urinary N-telopeptide (NTx) & Tartrate-resistant acid phosphatase 5b (TRAP-5b)
  - **Formation markers**
    - Serum bone specific alkaline phosphatase (BSAP), osteocalcin & N-terminal propeptide of type 1 procollagen (P1NP)

- **Tools for fracture risks & treatment decisions**
  - FRAX
  - SOF
Who should be considered for treatment?

- Postmenopausal women/men age ≥ 50 presenting with
  - Hip or vertebral fracture
  - T-score ≤ -2.5 at the femoral neck or spine (exclude secondary causes)
  - Low bone mass (T-score between -1.0 and 2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20%
### Table 1 | Conventional drugs for the treatment of postmenopausal osteoporosis*

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Administration</th>
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<tbody>
<tr>
<td><strong>Antiresorptive (anti-catabolic)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>Alendronate(^{70})</td>
<td>Daily or weekly, oral (after overnight fast followed by post-dose fast in upright position)</td>
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<tr>
<td></td>
<td>Risedronate(^{71})</td>
<td>Daily, weekly, or monthly, oral (after overnight fast followed by post-dose fast in upright position)</td>
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<tr>
<td></td>
<td>Risedronate (delayed release formulation)</td>
<td>Weekly, oral (immediately after breakfast)</td>
</tr>
<tr>
<td></td>
<td>Ibandronate(^{72})</td>
<td>Monthly, oral (after overnight fast followed by post-dose fast in upright position) Every 3 months, intravenous</td>
</tr>
<tr>
<td></td>
<td>Zoledronate(^{73})</td>
<td>Every 12 months, intravenous</td>
</tr>
<tr>
<td>SERM (EAA)</td>
<td>Raloxifene(^{74})</td>
<td>Daily, oral</td>
</tr>
<tr>
<td>Biologic</td>
<td>Salmon calcitonin(^{75})</td>
<td>Daily, intranasal</td>
</tr>
<tr>
<td><strong>Osteoanabolic (bone-forming)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td>Teriparatide (PTH(_{1-34}))(^{76})</td>
<td>Daily, subcutaneous</td>
</tr>
<tr>
<td></td>
<td>PTH(_{1-84})(^{77})</td>
<td></td>
</tr>
<tr>
<td><strong>Antiresorptive and osteoanabolic?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline earth metal</td>
<td>Strontium ranelate(^{14})</td>
<td>Daily, oral</td>
</tr>
</tbody>
</table>

*All drugs listed, except for PTH\(_{1-84}\) and strontium ranelate, have received regulatory approval for the treatment of postmenopausal osteoporosis in the USA, and all have been shown to reduce fracture risk in clinical trials. References for the appropriate pivotal fracture trials are provided in the “Drug” column. PTH\(_{1-84}\) and strontium are approved in many countries other than the USA. Abbreviations: EAA, estrogen agonist/antagonist; PTH, parathyroid hormone; SERM, selective estrogen receptor modulator.
Guidelines for management & treatment of osteoporosis

| Obtain a detailed patient history pertaining to clinical risk factors for osteoporosis-related fracture. |
| Perform physical examination to evaluate for signs of osteoporosis and its secondary causes. |
| Modify diet-supplements and other clinical risk factors for fracture. |
| Estimate patient’s 10-year probability of hip and any major osteoporosis-related fracture using the US-adapted WHO algorithm. |
| Decisions on whom to treat and how to treat should be based on clinical judgment using this Guide and all available clinical information. |
| Consider FDA-approved medical therapies based on the following: |
| ■ A vertebral or hip fracture |
| ■ A DXA hip (femoral neck) or spine T-score ≤ -2.5 |
| ■ Low bone mass and a US-adapted WHO 10-year probability of a hip fracture ≥ 3% or 10-year probability of any major osteoporosis-related fracture ≥ 20% |
| ■ Patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels |
| Consider non-medical therapeutic interventions: |
| ■ Modify risk factors related to falling |
| ■ Consider physical and occupational therapy including walking aids and hip pad protectors |
| ■ Weight-bearing activities daily |
| Patients not requiring medical therapies at the time of initial evaluation should be clinically re-evaluated when medically appropriate. |
| Patients taking FDA-approved medications should have laboratory and bone density re-evaluation after two years or more frequently when medically appropriate. |

NOF 2010
New treatment targets

- **Resorption inhibitors**
  - RANKL inhibitors
  - Cathepsin K inhibitors
  - ανβ3 antagonists
  - Glucagon-like peptide 2 (GLP-2)

- **Bone formation inducing agents**
  - Calcilytic agents
  - Blocking Wnt signaling pathway
    - Antibodies to sclerostin
    - Anti-Dkk1 antibody
  - Soluble activin receptor
New treatment targets

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RANKL inhibitor (Denosumab)

- human anti-RANKL antibody
- 60mg SC injection /6 months
- FDA and Europe approved

Studies

- Phase I: single-dose placebo-controlled study
  
  *Bekker PJ et al., J Bone Miner Res 2004*

- Phase II: effects on BMD/ bone turnover in postmenopausal women
  
  - 332 postmenopausal women, 60mg SC/6 months , 2 years
  - Results
    - ↑ BMD(lumbar spine, total hip, distal radius)
    - ↓ serum CTx, P1NP
  
  *Bone HG et al., J Clin Endocrinol Metab 2008*
Denosumab

Studies:

- **Phase III/FREEDOM** *(fracture reduction evaluation of denosumab in osteoporosis every 6 months):*
  - 7868 postmenopausal osteoporosis patients, 60mg SC/6 months, 3 years
  - Results
    - 68% ↓ new vertebral, 20% ↓ non-vertebral, 40% ↓ hip fractures
    - 72% ↓ CTx
    - ↑ BMD
  - Adverse events: no significant differences between groups

*Cummings SR et al., N Engl J Med 2009*
Denosumab

Studies:

- **Phase II: denosumab vs placebo and alendronate**
  - 412 postmenopausal women with low BMD
    - 46 placebo
    - 47 alendronate
    - 319 donosumab (6-30mg/3m, 14-210mg/6m)
      1. Continued denosumab at 60mg/6m
      2. Switched to placebo( 210mg) - **Discontinuation**
      3. Switched to placebo(30mg) for 12m and then denosumab 60mg/6m for 12m – **Retreatment**

- **results**
  - ↑ BMD( lumbar spine, total hip)
  - Continuous therapy: ↓CTx/BSAP  
  - Discontinuation: ↓BMD, ↑ CTx/BSAP  
  - Retreatment: ↑ BMD, ↓CTx/BSAP

Lewiecki EM et al., J Bone Miner Res 2007
Miller PD et al., Bone 2008
Denosumab

Studies:

- **Phase III/ DECIDE: denosumab vs alendronate**
  - 1189 postmenopausal patients with T-score ≤ -2
  - 60mg SC/6m denosumab, 70mg/w alendronate
  - Results
    - Greater effects at denosumab group:
      - ↑ BMD, ↓ CTx/ P1NP
    - Adverse events: similar between groups

- **Phase II/ STAND: alendronate to denosumab**
  - 504 postmenopausal women with T-score ≤ -2 treated with alendronate
  - 60mg SC/6m denosumab, 70mg/w alendronate for 12m
  - Results
    - Higher ↑ BMD(spine, total hip, distal radius) than patients left on alendronate
New treatment targets

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  - Soluble activin receptor
Cathepsin K inhibitor

- Odanacatib → peptide

Studies:

- **Phase I:** odanacatib- selective inhibitor of cathepsin K → (-) bone resorption

  *Cysteine protease*  
  *Expressed by osteoclasts*  
  *Degrades type 1 collagen, osteopontin and osteonectin*

  *Gauthier JY et al., Bioorg Med Chem Lett. 2008*

- **Phase II:**
  
  - 399 postmenopausal women with T-score ≤ -2
  - Oral odanacatib/ week for 2 years
  - Results
    - Dose-dependent ↑ BMD
    - ↓ CTx/ P1NP

  *Bone HG et al., J Bone Miner Res 2009*
New treatment targets

- Resorption inhibitors
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αvβ3 antagonists

- Main integrin on osteoclasts
- Interact with bone matrix proteins
  - anchor osteoclasts
  - form resorptive cavity
  - transmit anti-apoptotic signal → ↑ osteoclast survival

- Mice β3⁻/⁻ → high bone mass  
  McHugh KP et al, J Cell Biochem 2001

- Studies:
  - Phase II/III:
    - 227 postmenopausal women with low BMD values
    - Oral nonpeptide L-000845704
    - Results
      - ↑ BMD (lumbar spine), ↓ urinary NTx
  
Murphy MG et al., J Clin Endocrinol Metab 2005
New treatment targets

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Glucagon-like peptide 2 (GLP-2)

- Hormone
  - intestinal endocrine cells

- Studies:
  - SC administration (14 d)
    - diminish bone resorption, no affect bone formation/osteocalcin levels
  - Phase II:
    - 160 postmenopausal women
    - SC administration for 120 days
    - Results
      - ↑BMD (hip & trochanter)
      - ↓serum CTx
      - No effect on bone formation

Henriksen DB et al., J Bone Miner Res 2007
New treatment targets

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Calcilytic agents

- Diminish calcium surface receptor (CaR) → Intermitten ↑ PTH
  - ↑ bone formation
- Ronacaleret → Oral CaR antagonist

Studies

- Phase I:
  - 65 postmenopausal women
  - Results
    - Dose-dependent ↑ of bone formation markers
    - ↑ osteocalcin, P1NP, BSAP
    - No changes of CTx

- Phase II: stopped / lack of efficacy

Fitzpatrick LA et al., J Bone Miner Res 2008
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Antibodies to sclerostin

**Animal models:**
- Transgenic mice ↑ sclerostin → ↓ bone mass
- Mice *Sost* ^/-^ → ↑ bone density
- Ovariectomized rats with osteopenia
  - SC inj for 5w → ↑ bone formation parameters

**Studies:**
- **Phase I:**
  - 48 postmenopausal women
  - Antisclerostin therapy
    - ↑ P1NP/osteocalcin/BSAP
    - Trend ↓ serum CTx

*Winker DG et al., EMBO J 2003*
*Li X et al., J Bone Miner Res 2008*
*Li X et al., J Bone Miner Res 2009*
*Padhi D et al., J Bone Miner Res 2007*
Anti-Dkk1 antibody

- naturally occurring Wnt-pathway antagonist
- inhibit interactions between co-receptor LRP5/6 –frizzled Wnt-pathway receptor

Animal models (mice):

- Bone mass correlates inversely with Dkk1 expression levels
  
  MacDonald BT et al., Bone 2007

- Anti-Dkk1 antibodies
  - In vitro → blocked Dkk1 function
  - In vivo
    - half-life: 17 days
    - ↑ P1NP
    - Induce bone formation (endocortical surface/ trabecular bone)

  Glantschnig H et al., J Bone Miner Res 2008
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Soluble activin receptor

- Member of TGF-β superfamily
- Activin receptor type A (ACVR1) or activin receptor-like kinase 2 (AKL2) = BMP receptors

Activin antagonist

- Mice: RAP-011 → ↑ bone formation/ BMD
  
  [Pearsall RS et al., Proc Natl Acad Sci USA 2008]

- Human: ACE-011 → binds activin

Studies:

- Phase I:
  - 48 postmenopausal women
  - Inj IV or SC → dose-dependent ↓ BSAP, ↓ CTx/TRAP-5b

  [Ruckle J et al., J Bone Miner Res 2009]

- Pharmacokinetics:
  - Cynomolgous monkeys
    - ↑ BMD in the ACE-011 group
Future prospects

- New bone resorption inhibitors target
  - ATPase proton pump
  - C-Src tyrosine kinase
  - ClC-7 chloride channel

- New bone formation target
  - Serotonin
Take home messages

- New agents that target the molecular mechanisms involved in bone remodeling are developed
  - Anti-catabolic agents
  - Anabolic agents
- Too soon to say whether these agents are therapeutic usefull or safe