Update on Osteoporosis

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Osteoporosis

"...a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk"

WHO 1994

Concerns

- Over the past decade, the osteoporosis landscape has changed. Even though more treatment options are available, fewer measurements of bone mass are being performed and fewer prescriptions for antosteoporosis agents are being written... Even among patients with osteoporosis who have had a fracture and are then prescribed bisphosphonates, 70% are nonadherent within a year.

Rosen C. NEJM Oct 12, 2017; 377;15: 1479-80

Osteoporosis

The lifetime risk of an osteoporotic fracture for a 60 yr old woman is 44%.

Fractures are associated with decreased quality of life, including reduced independence, and osteoporotic fractures are associated with increased morbidity and mortality.

Bone is a complex continuously remodeled tissue

Bone remodeling is accomplished within BRUs by a team of cells working in concert

1 million BRUs are actively engaged in bone remodeling at any given time

The adult skeleton is completely regenerated every ten years

Manolagas SC. Endoc Rev 2000, 21(2); 115-137
Primary mineralization occurs within the first few weeks after unmineralized bone matrix (osteoid) is deposited by the osteoblasts.

Secondary mineralization occurs slowly.

The Composite Nature of Bone Provides Strength

Bone is like reinforced concrete:
- Bone mineral (like concrete) provides stiffness to bear loads
- Collagen (like steel) provides toughness, allowing bone to bend under loads without breaking

Ruffoni D, et al. Bone 2007, 40(5); 1308-1319
Ritchie RO, Ann NY Acad Sci 2010, 1192; 72-80

Mineralization of the Bone Matrix

Mineralization occurs in the first few weeks after osteoid is deposited by the osteoblasts.

Osteocytes are the most abundant and longest living cells in bone.
They communicate with each other on the bone surface via cellular processes through canaliculi and also orchestrate bone remodeling by regulating osteoblast and osteoclast activity.
They are mechanosensors that detect damage and mechanical strain.
They play an important role in regulation of bone formation through secretion of osteocalcin and contribute to the endocrine function of bone, involved with the regulation of phosphate and energy metabolism

Bonewald LF. JBMR 2011, 26(2); 229-238
Compton JT, Lee FY. JBJ Surg Am 2014, 96(19); 1659-1668

Vertebral bodies are composed primarily of cancellous bone with interconnected horizontal and vertical trabeculae. Osteoporosis not only reduces bone mass in vertebrae but also decreases interconnectivity in their internal scaffolding. Therefore, minor loads can lead to vertebral compression fractures.

Two thirds of vertebral fractures are painless.

The Importance of Horizontal Trabeculae

Assume: Volume 1 = Volume 2
- Identical material and dimensions for both
- Structure 1 is 16 x stronger than Structure 2
Vertebral Fracture

There may be a decrease in height of 2-3 cm after each vertebral compression fracture and progressive kyphosis.

Vertebral imaging suggested for postmenopausal females and men aged 50 and older with...

- Low trauma fractures
- Height loss of 1.5 inches (4cm) or more since age 20 or 0.8 inches (2 cm) since a previously documented measurement

Osteoporosis affects the entire skeleton

Osteoporosis is responsible for >1.5 million vertebral and non-vertebral fractures annually

- Spine, hip, and wrist fractures are most common

Fracture risk = BMD

and BMD is adequate in identifying at risk patient requiring treatment

... many pts with low BMD never fracture and most fractures occur in those with a ‘normal’ BMD

Predicted Load % of Body Weight on Lumbar Spine during ADLs

- Standing: 51%
- Standing and flexing trunk 30 deg: 146%
- Rising from chair: 173%
- Standing and holding 8 Kg: 230%

Dual Energy X-ray Absorptiometry

Central DEXA:1-5 mrem
Background: 5-8 mrem
Mammogram: 450 mrem

Dexa result interpretation...or mis...

10-Year Fracture Risk: Age and BMD
Fracture Risk Increases with Number of Prevalent Vertebral Fractures

The risk of recurrent fracture is highest during the first 2 years after the first fracture

Osteoporosis Treatment Gap

Many patients with osteoporosis do not receive treatment:

- In 2000, 78% of pts did not receive treatment, 22% did.
- In 2011, 76% of pts did not receive treatment, 24% did.

WHO Diagnostic Categories for Osteoporosis

Bone Density Reports

- T-scores: represent the number of standard deviations (SD) from the mean peak adult bone density values.
- Z-scores: represent the number of SD from the normal mean value for age-matched control subjects. Z-scores of -2.0 or lower may suggest a secondary cause of osteoporosis.

PPIs?

- Though a link between PPIs and fractures has been found many times over, there is a lack of conclusive evidence for causality. (1)
- Increased risk of PPIs and falling, related to low vit B12. (2)
- The increased risk of falling confirmed in an Austrian study of 700 women, where PPI use was associated with an increased of falling and fractures. (3)
BMD and Fracture Risk

- > 50% of women with hip fractures have T scores > -2.5
- Fracture risk doubles for each 1 S.D. decrease in BMD (T score from 0 to -1 or -1.0 to -2.0)
- Fracture risk increases ~1.5X for each incremental decade
- Patients with elevated bone turnover (top quartile)
  - increased risk for fracture
  - increased response to treatment
  - greatest decrease in fracture risk when treated
- Fracture protection can occur before detection of increases in BMD in response to treatment

Importance of Bone Health

Public health threat
- 10 million are estimated to have osteoporosis
- 8 million women
- 2 million men
- 34 million are estimated to be at risk for osteoporosis

All fractures are associated with morbidity

<table>
<thead>
<tr>
<th>One year after a hip fracture (%)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within one year</td>
<td>20%</td>
</tr>
<tr>
<td>Permanent disability</td>
<td>30%</td>
</tr>
<tr>
<td>Unable to carry out at least one independent activity of daily living</td>
<td>40%</td>
</tr>
<tr>
<td>Unable to carry out at least one independent activity of daily living</td>
<td>80%</td>
</tr>
</tbody>
</table>

Risk Factors for Osteoporotic Fracture

<table>
<thead>
<tr>
<th>With Relative Risk ≥ 2 (Major)</th>
<th>With Relative Risk 1 - 2 (Moderate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70</td>
<td>Estrogen Deficiency</td>
</tr>
<tr>
<td>Menopause &lt; 45</td>
<td>Calcium Intake &lt; 500 mg/d</td>
</tr>
<tr>
<td>Fracture Fracture</td>
<td>Primary Hyperparathyroidism</td>
</tr>
<tr>
<td>Hip Fracture in Parent</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Bechterew Disease</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Anticonvulsivants</td>
</tr>
<tr>
<td>High Bone Turnover</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Anemia Neovascular</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>0.36 &lt; T</td>
<td>Smoking</td>
</tr>
<tr>
<td>Immobilization</td>
<td>Alcohol Excess</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>Transplantation</td>
</tr>
</tbody>
</table>

After the third decade of life, bone resorption exceeds bone formation. Women lose 30-40% of their cortical bone and 50% of their trabecular bone over their lifetime. Men lose about 15-20% of their cortical bone and 25-30% of their trabecular bone.

The NOF revealed that 86% of women with osteoporosis had never discussed its prevention with their physicians.*


Hip Fracture

Worldwide, 4.5 million people are disabled from hip fractures each year. Globally, hip fracture ranks among the top 10 causes of disability. It is estimated that by 2050, more than 50% of all osteoporotic fractures will occur in Asia.
Clinical Risk Factors

- Age
- Gender
- BMI
- BMD i.e. femoral neck
- Prior fragility fracture
- Corticosteroid use
- Family history of hip fracture
- Current smoker
- Alcohol intake > 3 units/day
- Secondary causes i.e. RA

Glucocorticoid - Induced Osteoporosis

- Risk factors...
  - high daily dose (e.g. > 7.5 mg daily)
  - cumulative dose > 5 g
  - current or recent use (<3mos)
  - glucocorticoid – associated myopathy
  - glucocorticoid – induced hypogonadism

Buckley L, Humphrey M. Glucocorticoid – Induced Osteoporosis. NEJM 2018;379:2547-2556

Vertebral fractures are the most common associated with osteoporosis.

The risk increases within 3 mos of initiating treatment and peaks at 12 mos.

Pts who receive between 2.5 and 7.5 mg of prednisolone daily have a relative risk of vertebral fx that doubles and hip fx increases by approx 50%

...if high doses (30 mg prednisolone daily or cumulative of at least 5 g) the risk of vertebral fx is increased by a factor of 14 and hip fx by a factor of 3

cumulative doses of 1 g or less and even high dose of inhaled glucocorticoids pose far less a risk

Buckley L, Humphrey M. Glucocorticoid – Induced Osteoporosis. NEJM 2018;379:2547-2556

Fracture risk rapidly decreases after discontinuation of glucocorticoids

...if treatment needed in a woman of child bearing age ...consider risedronate or teriparatide...shorter half lives and less retention in bone

Buckley L, Humphrey M. Glucocorticoid – Induced Osteoporosis. NEJM 2018;379:2547-2556

FRAX – World Health Organization Fracture Risk Assessment Tool

- The FRAX Tool:
  Developed by the WHO to help determine when to consider initiating treatment in treatment-naïve patients
  Designed to estimate the 10-year absolute fracture risk for treatment-naïve patients
  Uses a combination of BMD and accepted risk factors
  Online FRAX calculator is available at: http://www.shef.ac.uk/FRAX/

- Limitations:
  Only applicable to previously untreated patients (...maybe)
  Does not take into account either the number or severity of previous osteoporotic fractures, dose or duration of glucocorticoid use and duration and quantity of smoking ... as examples

http://www.shef.ac.uk/FRAX/

Enter 12 items
Hit calculate
Get 10 yr probability of any significant osteoporotic and hip fracture

http://www.shef.ac.uk/FRAX/
Initiate therapy if 10-yr risk
- Major fracture ≥ 20%
- Hip fracture ≥ 3%

Candidates for Treatment
The following patients can benefit from pharmacologic treatment of osteoporosis:

- Patients with established osteoporosis (T ≤ -2.5)
- Patients with low-trauma fractures and low BMD
- Patients with borderline-low BMD (e.g., T-scores of -1.5 and below) if risk factors are present (increased bone turnover, hormone deficiency, older, diseases that increase bone loss, family history of fractures)
- Patients in whom non-pharmacologic preventive measures are ineffective (bone loss continues or low-trauma fractures occur)
When in Company, put not your hands to any Part of the Body not usually Discovered

Prevention and Treatment
- Assess and modify risk factors and secondary causes for bone loss and fracture
- Maintain Calcium and Vitamin D
- Encourage exercise

World Health Organization
National Osteoporosis Foundation

<table>
<thead>
<tr>
<th>T-score</th>
<th>Postmenopausal women</th>
<th>Men &gt; 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.5 or below</td>
<td>Frailty fracture</td>
<td>Pharmacological therapy</td>
</tr>
<tr>
<td>-1.0 to -2.5</td>
<td></td>
<td>Pharmacological therapy or 10-year risk</td>
</tr>
<tr>
<td>Above -1.0</td>
<td></td>
<td>Prevention of osteoporosis</td>
</tr>
</tbody>
</table>

Calcium Intake
(seems to depend on which week you ask the question)

Recommendations
- 1000 mg in premenopausal women and men < 50 yrs
- 1200-1500 mg in postmenopausal women and men > 50 yrs

Dietary sources of calcium
- Estimating dietary calcium intake:
  - Multiplying the number of dairy servings by 300 mg

Supplemental Source of Calcium

<table>
<thead>
<tr>
<th>Calcium Source</th>
<th>Elemental calcium per gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate</td>
<td>250 mg</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>400 mg</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>392 mg</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>211 mg</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>64 mg</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>139 mg</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>395 mg</td>
</tr>
</tbody>
</table>

Example: 1000 mg of calcium carbonate has 400 mg of elemental calcium

Nutrition: Reference intake for calcium

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Calcium intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>500</td>
</tr>
<tr>
<td>4-8</td>
<td>800</td>
</tr>
<tr>
<td>9-18</td>
<td>1300</td>
</tr>
<tr>
<td>19-50</td>
<td>1000</td>
</tr>
<tr>
<td>&gt;51</td>
<td>1200</td>
</tr>
</tbody>
</table>

National Institutes of Health, 1994
Vitamin D Deficiency

Cutaneous production
Declines with age
Varies with latitude, time of year and skin pigmentation

Insufficient dietary Vitamin D
50% consume <137 IU/d
25% consume <65 IU/d

Holick MF, JCEM 2005

Biochemical criteria
- Reference normal values of 10 to 50 ng/mL
- Serum 25-hydroxyvitamin D concentration of <30 ng/mL suggestive of deficiency

Recommendation
Check 25OHD Vitamin D level
Postmenopausal women
Men or premenopausal women if Z score < -2.0 or risk factors

Less than 20-30ng/ml
Treat with Vitamin D 50,000 IU per week for 8 weeks
Repeat level and retreat if necessary

Greater than 30ng/ml
Recommend Vitamin D 800IU/day
Supplements: MVI or calcium+D
Dietary vitamin D
Vitamin D-fortified dairy products, egg yolks, saltwater fish and liver
Milk 100 IU/100ml
Sun exposure
10-15 minutes exposure of hands, arms and face two to three times a week

Osteoporosis Treatment
NonPharmacologic
- Physical activity
- Calcium (>1200 mg/d)
- Vitamin D (400-800 IU/d)

Pharmacologic
- Anti-resorptives
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronic acid
- Calcitriol
- HRT/ERMs
- Prolia
- Anabolics
- Teriparatide
- Abaloparatide

Exercise
Young women (mean 21yrs)
Gymnastics for 8 mo
Gained 2% lumbar spine and 1.6% femoral neck

Premenopausal women (35-45yrs)
High impact aerobics 3 times week for 18 mo
Increase in BMD at femoral neck versus controls
Exercise

Postmenopausal women (50-70yrs)
Strength training for one year
Gain in lumbar spine 1.0% and femoral neck 0.9%

8600 women (mean 73yrs)
Active exercise for 1 hr per day vs. <0.5hrs per day
Decrease risk of hip fracture (RR 0.6)

Exercise is important for building and maintaining bone mass

Weight-bearing
Bones/muscles work against gravity
Jogging, walking, stair climbing, dancing and soccer
Swimming and bicycling are not weight-bearing

Preventing Falls

One third of individuals 65 years of age or older will fall each year
90% of hip fractures result from falls

Measures to help prevent falls plays an important role in decreasing the frequency of fractures
- Remove rugs and cords that could lead to falls
- Ensure adequate lighting and encourage eye exam
- Review and alter drug regimens to minimize falls

Therapies on Vertebral and Nonvertebral Fractures

<table>
<thead>
<tr>
<th>Agent</th>
<th>Vertebral</th>
<th>Nonvert</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alendronate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zoledronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>+</td>
<td>*</td>
<td>-</td>
</tr>
<tr>
<td>Abaloparatide</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Anabolics and antiresorptives

All antiresorptives work by inhibiting osteoclasts; very effective at preserving bone mass and microarchitecture.

Anabolics work on osteoblasts by directly stimulating new bone formation.

The ACP’s updated clinical practice guideline for treating osteoporosis strongly advocates bisphosphonates and strongly advises against estrogens or raloxifene.

Bisphosphonates

- Increases bone mass
- Reduces vertebral and nonvertebral fractures*

Oral Preparations
- Alendronate (Fosamax)*
- Risedronate (Actonel)*
- Ibandronate (Boniva)

Bisphosphonates

- Potent inhibitors of osteoclast-mediated bone resorption
- They bind to hydroxyapatite and approximately 60% of the absorbed oral dose is deposited into the bone.

Intravenous Preparations
- Ibandronate (Boniva)
- Zolendronate (Reclast)
- Other options: Pamidronate, Etidronate and Tiludronate

Other concerns: GI discomfort, muscular aches, osteonecrosis of the jaw, subtrochanteric fracture.

Reasons for Intravenous Bisphosphonates

- Diagnosis of esophageal stricture, achalasia, or severe esophageal dysmotility
- History of severe malabsorption making use of oral bisphosphonates ineffective
- Inability to stand or sit upright for 60 minutes
- Intolerance to two or more oral bisphosphonates
**Zoledronic Acid (Reclast)**

Parenteral 5 mg over > 15 min once yearly
- Decreased hip fracture incidence 30-50%
- Decreased vertebral fracture incidence 50-80%
- Greater efficacy in preventing vertebral fractures in younger women

**OSTEONECROSIS OF THE JAW**

Clinical presentation:
- Infection and necrotic bone in the mandible
- One-third of the lesions are painless

**Osteonecrosis**

- Occurs at sites of thin or easily traumatized mucosa
- Lingual aspect of the mandible is most common
- Must have exposed bone > 8 wks and no hx radiotherapy
  - 95% patients have cancer and most (89%) were treated with a potent IV bisphosphonate
  - CT more sensitive than x-ray
  - X-ray shows sclerosis, sequestration and fragmentation
- Risk factors: dental extraction, obesity, smoking and periodontal disease
- Increases with increasing dose and potency

**ONJ**

Bisphosphonates are directly toxic to epithelial cells and may add to mucosal breakdown allowing bacterial ingress

Clinical studies have shown impaired wound healing after dental extractions

Bisphosphonates are associated with ONJ in both pts on Cancer therapy (1-7%), and osteoporosis (0.02%). Denosumab in cancer pts (0.7-1.9) and OSP (0.04)

**ONJ and Comparative Risks**

Very rare reports
- Mostly in cancer patients
- Different than our typical osteoporosis patients, doses
- Mostly (not solely) with IV bisphosphonates
- Estimated incidence is 1/10,000 – 1/100,000


(1) Women aged 65-69 from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.)
Recommendations

- Identify and rectify dental problems prior to treatment
- Oral hygiene status should be monitored during treatment

Diagnosis of ONJ:
- Management: Surgical resection of necrotic bone and antibiotic therapy
- Discontinuing bisphosphonate therapy is debated

Frozen Bone

- There is theoretical concern that prolonged bisphosphonate therapy leads to oversuppression of bone turnover and increased skeletal fragility
- High-dose bisphosphonate accumulation results in microscopic damage in animal studies

Frozen Bone

- Case reports of atypical fracture (particularly subtrochanteric fractures) and severely suppressed bone turnover have been reported in the setting of prolonged bisphosphonate therapy
- Observed association do not prove causality

Atypical fractures

- Absolute risk of ~ 5 per 10,000 pt-yrs
- Younger patients, frequently bilateral, prodromal symptoms
- Duration of use dependent (controversial)
- Bisphosphonates appear to prevent at least 100 typical osteoporotic fractures for every 1 associated atypical fracture


- NNT with BP: 91 to prevent 1 Hip Fx
- NNT 14 “ 1 Spine Fx
- NNH (# Needed to Harm): given 3 yrs α=667
- Benefit>Risk

Femoral Fractures

- No warning sign
- Caused by a fall
- Unilateral
- Proximal
- Acute angle femoral neck, intertrochanteric
- May be comminuted
Femoral Fractures

- Atypical
  - Proximal thigh or groin pain
  - Little or no trauma
  - 30% bilateral
  - Subtrochanteric
  - Transverse/oblique
  - Little or no comminution
  - Begin as localized periosteal reaction of the lateral cortex
  - Thick cortices
  - Delayed healing

Atypical fractures & ONJ

"Widespread coverage in the news media, which can be alarming to patients and their physicians, may not present a balanced view of the proven benefits, the uncertain risks of therapy and the relative magnitude of these events. There may be confusion about the risks associated with bisphosphonate use for the treatment of osteoporosis"

Benefits and Risks of Bisphosphonate Therapy for Osteoporosis

"deciding not to treat a patient with osteoporosis with a bisphosphonate because of the concern for rare associated events such as ONJ and atypical fractures places that individual at risk for fracture, with it’s own dire consequences"

KhoslaS et al  J Clin Endocrinol Metab 2012;97:2272-2282

Long term treatment with Bisphosphonates- How long is too long?

10 year follow up with Alendronate documents continued stability or gain in BMD and suppression of bone turnover markers

Upon discontinuation, after 1 year, markers increase and BMD declines

Length of Treatment for OP

Decide based on patient’s fracture risk

- If high risk (history of vertebral fracture or T< -3) consider continuing
  - If with lower dose

- With moderate risk (1.2 to -2.5), consider a drug holiday and check BMD when stopping treatment and 2 years later

- If or when BMD decreases >3%, restart treatment

ACR Meeting 2017

Medicare data 2006-2014: 156,236 women who were ‘highly adherent’ to therapy, long term users of bisphosphonates. [BP]

During follow-up, 3,745 hip fractures occurred; current BP users had the lowest rate of fracture (9.6 per 1,000 pt yrs). The longer the drug holiday, the higher the rate of fx. If a 2 yr drug holiday- 13.3% incidence, if 2-4 yr holiday- a 15.7% incidence"
Recommendations prior to initiating bisphosphonate

- Undergo a comprehensive dental exam before starting and IV bisphosphonate
- Maintain good oral hygiene
- Avoid invasive dental procedures
- Dental consensus panels: no EBM that stopping bisphosphonate prior to procedure alters incidence

...recent data

- Patients newly diagnosed with hip fx from 2005-2013 (Hong Kong Hosp Auth). 494 patients treated with alendronate matched with 13,568 nontreated. Alendronate associated with a significantly decreased cardiovascular mortality, and incident MI. Marginally decreased incidence of stroke noted at 5 and 10 yrs.

Denosumab (Prolia)

Anti-resorptive agent

Approved June 1, 2010
A fully human monoclonal antibody that binds with high affinity to, and inhibits the activity of, human RANK ligand, a key mediator of osteoclast activity.

RANKL is implicated in bone loss across a broad range of conditions

- Postmenopausal osteoporosis
- Male osteoporosis
- Disease-related osteoporosis
- Transplantation osteoporosis
- Inflammatory arthritis
- Periprosthetic osteolysis
- Hyperparathyroidism
- Cancer-related bone loss
- Bone metastases, multiple myeloma
- Treatment-induced bone loss
- Glucocorticoids, aromatase inhibitors, androgen deprivation therapy

RANKL Stimulates Bone Resorption

Growth Factors
Hormones
Cytokines

RANK Ligand is Essential for Osteoclast Formation, Function, and Survival

CFU-M
Pre-Fusion Osteoclast
Multinucleated Osteoclast
Activated Osteoclast

Denosumab Mechanism of Action

Growth Factors
Hormones
Cytokines

RANKL
Dmab
OPG

Bone
CFU-M
Pre-Fusion Osteoclast
Multinucleated Osteoclast
Activated Osteoclast

Cytokines
Hormones
Growth Factors
Dmab-FREEDOM Results

- 68% decrease in vertebral fractures
  - 2.3% vs 7.2%, P<0.0001
- 40% decrease in hip fractures
  - 0.7% vs 1.2%, P<0.0001
- 20% decrease in non-vertebral fracture
  - 1.5% vs 8.0%, P=0.001

Dmab increased BMD and reduced BTMs compared to placebo.

AEs and SAEs generally similar to placebo.

No increased risk of cancer, infection, CV disease, delayed fracture healing, hypocalcemia, no ONJ.

Increased risk of cellulitis, eczema, flatulence.

Decreased risk of falls, concussion.


Combination Therapy

- Alendronate and Raloxifene
- Risedronate and Estrogen
- Raloxifene and teriparatide
- Estrogen and teriparatide

There are small differences (increments) in BMD with combined therapy.

To date, no combination of current agents appears better than monotherapy for fracture reduction.

Falls in the older population

- One third of individuals 65 years of age or older will fall each year.
- 90% of hip fractures result from falls.

- ...remove scatter rugs, obvious impediments to ambulation, use night lights... review use of opioids, narcotics, sedatives...

Anabolic agents

- Administration and dose determine PTH effects on bone.
- Continuous (High Dose)
  - Catabolic
- Daily (Low Dose)
  - Anabolic

Mode

Effect

PTH effects on risk of new vertebral fractures over 18 months

- 64% vs 22% reduction in risk.
- N patients with 1 or more fractures
- Placebo vs PTH 20 µg.
Treatment with PTH

(Dempster DW et al, J Bone Miner Res, 2001;16:1846-1853)

Before CtTh: 0.32 mm
CD: 2.9 mm³

After CtTh: 0.42 mm
CD: 4.6 mm³

Abaloparatide (Tymlos)

Activator of PTH type 1 receptor

Ability to produce anabolic effects with modest stimulation of bone resorption

Net greater anabolic effect than TPTD

Rapid BMD increments in the LS, hip, and other cortical skeletal sites significantly higher than produced by TPTD

Postmenopausal women treated with abaloparatide for 18 mos followed by 2 yrs of alendronate had a significant reduction in both vertebral and non-vertebral fractures through 3.5 yrs. (comp to placebo plus alendronate)

Correct order of treatment: Teraparatide for 2 yrs followed by Dmb,.not via-versa

Parathyroidectomy improves and bisphosphonates worsen fracture risk in primary hyperparathyroidism

Teriparatide vs abaloparatide..any major differences noted so far?

Hypercalcemia a bit lower

Modestly higher BMD especially at sites of cortical bone

Bone formation a bit lower

Hypercalcemia a bit lower

Osteoporosis in men

Prevention and treatment of osteoporosis in men

- Androgens
- Limit corticosteroid therapy, alcoholism or smoking
- Use thiazides for hypercalciuria

In "IDIOPATHIC" osteoporosis
- Exercise and prevention of falls
- Calcium and vitamin D supplements
- Bisphosphonates (alendronate)
- PTH (teriparatide)

Teriparatide vs abaloparatide supplements an earlier study from the Kaiser-Permanente system, 6000 pts with primary hyperparathy.)


Prevention and treatment of osteoporosis in men

In "IDIOPATHIC" osteoporosis
- Exercise and prevention of falls
- Calcium and vitamin D supplements
- Bisphosphonates (alendronate)
- PTH (teriparatide)


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Testosterone treatment for 1 year of older men (65 yrs and over) with low testosterone significantly increased vBMD and estimated bone strength, more in trabecular than peripheral bone and more in the spine than hip (1). …transdermal testosterone replacement to achieve levels similar to those in young men resulted in clear increases in BMD that were quite similar to those previously reported in men treated with approved osteoporosis therapies like bisphosphonates, teriparatide, and denosumab (2).

(2) Orwell E. JAMA Intern Med. 2017; 177 (4): 459-460

Sclerostin Inhibitors

Sclerostin is produced by osteocytes and inhibits bone formation. In a phase 2 trial in postmenopausal women a monoclonal anti-sclerostin antibody (romosozumab) increased bone density at the LS, total hip and femoral neck. Other studies done with positive results vs placebo and alendronate, not as good vs teriparatide with some patients dosed Q 3 months. Of interest there was a transient increase in bone formation markers and a more sustained decrease in bone resorption markers. This pattern has not been seen in our current therapies.

McClung M et al. Romosozumab in postmenopausal women with low bone density. NEJM 2014;370:412

Amgen and UCB were awaiting approval – after a higher rate of serious heart-related side effects were observed in a single late-stage clinical trial. Recent, strong recommendation, from the FDA’s Bone, Reproductive, and Urologic Drugs Advisory Committee (18-1) for approval to treat postmenopausal women at high risk of fracture. Will be marketed by Amgen as Evenity.

Rheumatology News. Feb 2019

….a few final thoughts

- The lifetime risk of hip fracture > risk for breast, endometrial and ovarian cancer combined
- If we can retard bone loss by 10 yrs-risk of fracture decreases by approx 50%

Case Presentation

55 year old postmenopausal woman with a family history of hip fracture is referred for evaluation of her bone health.

What next?
Case 4: T-score of -2.3 FN and -1.9 spine

Prevention of Osteoporosis
- Assess and modify risk factors and secondary causes for bone loss and fracture
- Maintain Calcium and Vitamin D
- Encourage exercise

Case Presentation
81 year old male with no prior history of fractures is referred for evaluation of osteopenia. A T-score of -1.4 at hip and -1.2 at the spine is noted.

What next?
Case

81 year old male with no prior history of fractures and a T-score of -1.4 at femoral neck and -1.2 at spine.

Case presentation

- Ensure that secondary causes of bone loss are thoroughly evaluated
  - For males make sure a history of hypogonadism and ETOH use is reviewed. Check for steroid use
  - Would consider bisphosphonate therapy after review of side effects, etc

Case

- Of course!
- 25OH VitD was 15
- Supplement given
- Lab repeated in 6 wks
- PTH 56 pg/ml
- FRAX WNL

Case presentation

- PE and Hx otherwise unrevealing
- Secondary causes of bone loss reviewed in detail and PTH elevated to 122 pg/ml (14-72)
- Should we check our lab closer?

Case

- Lady Astor: If you were my husband, Winston, I’d put poison in your tea.

- Winston Churchill: If I were your husband, Nancy, I’d drink it.