Osteoporosis Diagnosis, Treatment and Controversies

June, 2019
Shawn Baca, MD, Hero in Medicine of the Year award
Shawn Baca, M.D., F.A.C.R.

Rheumatology Associates of South Florida RASF
RASF Clinical Research

Osteoporosis Diagnosis and Treatment Center of South Florida

Clinical Faculty, Schmidt
School of Medicine at Florida Atlantic University

Boca Raton, Florida
Disclosures

None regarding this talk
OBJECTIVES

• Define Osteoporosis and its Risk Factors

Discuss Treatment and Prevention of Osteoporosis

• Controversies and Difficulties in Osteoporosis Management
Definition of Osteoporosis

“Osteoporosis is defined as a compromised bone strength predisposing to an increased risk of fracture.”

Bone strength = bone density + bone quality

Bone density: grams of mineral/ volume

Bone quality: architecture, turnover, damage accumulation, and mineralization

Medical and Societal Impact of Osteoporosis
Incidence

• NOF estimates 10 million Americans have osteoporosis and 44 million have osteopenia.

• About 1 in every 3 Caucasian women and 1 of every 5 males will have an osteoporosis-related fracture at some point in their lifetime.

1. NOF Fast Facts 2012

Age and Fracture Rates

- **Vertebral Fracture Incidence**
- **Hip Fracture Incidence**
- **Wrist Fracture Incidence**

**Age (years)**
- 35
- 45
- 55
- 65
- 75
- 85+

**Annual Fracture Incidence, per 100,000**
- 0
- 1000
- 2000
- 3000
- 4000

Estimated Annual Incidence of Osteoporosis-Related Fractures in Women and Men

Values are from 2005 estimates.
Economic Toll of Osteoporosis-related fractures

• 432,000 hospital admissions
• 2.5 million medical office visits
• 180,000 nursing home admissions annually in the US
• The cost of osteoporosis-related fractures has been estimated at $17 billion for 2005 and $25.3 billion in 2025.  

Medical Impact of Osteoporosis

• Hip fractures result in 8 to 36 percent excess mortality within one year. ¹

• Approximately 20 percent of hip fracture patients require long-term nursing home care, and only 40 percent fully regain their pre-fracture level of independence. ¹

• Mortality is also increased following vertebral fractures. ¹

• Mortality higher for a hip fracture than a diagnosis of breast cancer. Hip fracture mortality was 48.1% (n = 386) compared with 25.1% (n = 94) ²

Medical Impact of Osteoporosis
continued

• Vertebral fractures can cause significant chronic complications including chronic back pain, height loss and kyphosis, restrictive lung disease, abdominal pain, distention, reduced appetite and premature satiety.

• Development of arthritis of previously fractured joints such as, hip, shoulder and wrist.
Osteoporosis-Related Fractures in Women Versus Other Diseases

Risk Factors

**Major:**
- Personal history of fracture as adult
- History of fracture in first-degree relative
- Low body weight (<127 lbs)
- Current smoking
- Oral steroid > 3 months

**Additional:**
- Impaired vision, early estrogen deficiency, dementia, frailty, recent falls, lifelong low calcium intake, low physical activity, alcohol (>2 drinks/day)

Secondary Causes of Osteoporosis

Endocrine: Hyperparathyroidism (primary and secondary)  
Hyperthyroid (primary and iatrogenic), Hypogonadism, elevated cortisol levels, androgen insensitivity

Hematologic: myeloma, thalassemia, mastocytosis, hemophilia

Nutritional: Poor dietary calcium intake, poor dietary Vit D intake, excessive Vit D intake, excessive alcohol, excessive caffeine, eating disorders

Renal: renal bone disease, hypophosphatemia, hypercalciuria

Genetic: Osteogenesis imperfecta, Vit D resistance, Turners, Cystic Fibrosis, Glycogen Storage disease, hemochromatosis

Rheumatic: poor weight bearing, chronic inflammation such as rheumatoid arthritis, spondylitis

Gastrointestinal: Celiac, Inflammatory bowel dis, PBC
Medications Associated With Bone Loss

- Anticoagulants (heparin) and to less extent (coumadin)
- Proton pump inhibitors
- Cancer chemotherapeutic drugs
- Gonadotropin releasing hormone agonists
- Anticonvulsants
- Cyclosporine A and tacrolimus
- Lithium and Barbiturates
- Aromatase inhibitors
- Depo-medroxyprogesterone
- Glucocorticoids
- Excessive Thyroid Medication
Fracture Risk and Dose of Glucocorticoids

DXA Testing: Who should we test?

• Women age 65 and older and men age 70 and older

• Postmenopausal women and men over 50, with risk factors

Fracture after age 50

NOF Guide 2018
Measurement of BMD

• T-score: the difference in standard deviation in a patient’s BMD compared with peak bone mass in a young adult

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1.0 and above</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>&lt;-1.0 to &gt;-2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>&lt;-2.5 and below</td>
</tr>
</tbody>
</table>

T Score

• T score compares an individual's bone density to that of a normal young healthy adult population.
• T score is the measure used to describe an individual's diagnosis.
Z scores

- Z scores are used to compare a patient's BMD within the same age group.
- If a patient has a Z score that is substantially lower than 100 percent, consider secondary causes of bone loss.
Diagnosis

• If a patient has a site that shows osteoporosis of any standard site than the diagnosis should be reported as osteoporosis.

• If a patient has had a fragility fracture and DXA osteopenia than the diagnosis is osteoporosis.
Pearls: Hip Densities

• Femoral neck BMD is most predictive of fracture.
• Ward’s triangle should not be used in patient reports to determine fracture risk
• Total hip bmd should be used to compare different scans between the years
Pearls: Lumbar spine densities

• Often have falsely higher results due to scoliosis, osteoarthritis or previous fractures.
• The average of two vertebral levels is acceptable to use for diagnostic purposes.
Follow up Scans

• Generally every two years but may need to be more frequent for certain clinical situations such as hyperparathyroidism or chronic glucocorticosteriod treatment

• Can not directly compare scans of different manufactures

• Patients *should be done on same machine* for comparison
NOF Treatment Guidelines

- Treat if patient had previous hip or vertebral clinical or morphometric fracture
- Treat if t score < -2.5 total of femoral neck, total hip or spine
- Treat postmenopausal females or males with osteopenic who have a positive FRAX analysis
• Designed to determine which patients with osteopenia should be treated with medication

• Treat if the 10 year risk of fracture is greater than 20 percent for non-vertebral fractures, or greater than 3 percent for hip fractures
BMI 24.5
The ten year probability of fracture (%)

with BMD

- Major osteoporotic 18
- Hip fracture 1.8
Clinical Evaluation of Patients With Low Bone Densities
History

• Medications associated with bone loss
• Premature Menopause
• Previous cancer treatment, medications and radiation therapy
• Parental history of hip fractures and osteoporosis
• History of hypercalcemia, and kidney stones
• Fracture history
• Fall history
Discuss Lifestyle Issues

- Alcohol
- Smoking
- Exercise
- Diet
- Fall prevention
Physical

- Height loss
- Kyphosis
- Balance and strength
Tests used in Metabolic Evaluation of OP

• PTH intact
• 25, hydroxy vitamin D
• 24 hour urinary calcium
• SPEP
• Thyroid profile, Cortisol level
• BSAP, NTX or CTX, P1NP
• Calcium, phosphorous, creatinine
Imaging

• Lateral x-ray to see if patient had previous vertebral fracture or significant height loss
• DXA Morphometry
• Fracture on x-ray + Osteopenia = Osteoporosis
Male Patients
Special considerations

• Hormone therapy for prostate cancer produces rapid bone loss and all patients on androgen depravation therapy should be screened regularly
• Consider testosterone deficiency in all male patients with unexplained bone loss
• NOF recommends all males over age 70 should have a bone density test
Osteoporosis Prevention
and Treatment Options
Non Pharmacologic Therapy

- Fall Prevention-assistive devices, walkers, canes, grab bars.
- Weight bearing exercise
- Balance and posture exercise
- Avoidance of sedative hypnotic medications
- Life style modification
<table>
<thead>
<tr>
<th>Gender</th>
<th>Age Range</th>
<th>Calcium Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Age 50 &amp; younger</td>
<td>1,000 mg* daily</td>
</tr>
<tr>
<td></td>
<td>Age 51 &amp; older</td>
<td>1,200 mg* daily</td>
</tr>
<tr>
<td>Men</td>
<td>Age 70 &amp; younger</td>
<td>1,000 mg* daily</td>
</tr>
<tr>
<td></td>
<td>Age 71 &amp; older</td>
<td>1,200 mg* daily</td>
</tr>
</tbody>
</table>

Estimating daily dietary calcium intake

Step 1: Estimate calcium intake from calcium-rich foods a Product $x$ of servings/day

Estimated calcium/serving, in mg

Milk (8 oz.) $_______$  $\times 300 = ________$

Yogurt (6 oz.) $_______$  $\times 300 = ________$

Cheese (1 oz. or 1 cubic in.) $_______$  $\times 200 = ________$

Dark Green Vegetable (1 serving) $_______$  $\times 100 = ________$

Subtotal = ________

Step 2: Add 250 mg for nondairy sources to subtotal above

Total calcium, in mg = _________
Pearl
How Much Vitamin D?

Enough to keep 25 Vitamin D levels between 30 and 60 mcg/dl

Tablets of vitamin are more stable. Capsule forms degrade more quickly so if a patient’s vitamin D level does not increase with therapy and you believe they are taking correct dose consider changing to a tablet.

If vitamin D levels remain low check for Celiac Disease with IgA TTG
Prevention

- Non pharmacologic intervention, fall, lifestyle, and nutrition counseling
- Estrogen, Oral Bisphosphonates and SERMs all have FDA approval for prevention but are under prescribed
- Consider this for patients that you believe have future high risk and look at the FRAX calculation.
Pharmacologic options

**Antiresorptive therapy**

Inhibit osteoclastic activity in excess of osteoblastic activity

HRT, SERMs, Calcitonin, Bisphosphonates, Biologic / currently Rank ligand inhibition

**Anabolic therapy**

Increase osteoblastic activity in excess of osteoclastic activity

PTH analogs
HRT and SERMs

Antiresorptive work via estrogen receptors on bone

Decrease bone turnover

Reduce the incidence of vertebral fractures HRT 34%, and up 30 to 50% Raloxifene. Not proven to reduce non vertebral fractures.

Estrogen approved for prevention but NOT treatment of osteoporosis

SERMs approved for both prevention and treatment
Calcitonin

In the form of Salmon calcitonin
By injection and nasal spray

**Advantages**

- No GERD issues, can help with pain of acute fractures,
- no renal issues

**Disadvantages**

Not indicated for non vertebral fracture prevention
Bisphosphonates

- **Advantages**
- Lower cost
- Available in many forms ie po and IV
- Daily, weekly, monthly dosing
- Do not have certain side effects of hormone medication such as dvt, hot flashes, or risk of malignancy
Bisphosphonates

• **Disadvantages**
• GI upset, esophagitis
• Not recommended in renal patients with GFR <30cc
• Potential risk?? Of ONJ, esophageal malignancies
  Non-compliance rates are high
Bisphosphonates Special Considerations

• Ibandronate not proven to reduce risk of hip and non vert fractures

• For patients with gastrointestinal upset delayed release risedronate may be administered orally after breakfast

• Oral therapy reduces risk of vertebral fracture approx 50 percent for oral therapy and 70 percent for iv zoledronic acid

• Don’t use in patients with intolerance or Barrett’s Esophogus
Refill Compliance and Fracture Protection Over 24 Months for Bisphosphonate-Treated Patients

Antiresorptive Biologics

• Denosumab a monoclonal antibody

AMG 162 inhibition of rank ligand which prevents activation of osteoclast
Reduces risk of both vertebral and hip fracture

Advantages: ease of administration and compliance and no GI or Renal toxicity. Bone density continues to do up with prolonged therapy

Disadvantage: Higher cost and can NOT be stopped. However 10 year data suggests that strong, prolonged remodeling inhibition does not impair bone strength

J Clin Endocrinol Metab. 2018 Jul 1;103(7):2498-2509. doi: 10.1210/jc.2017-02669
Anabolic Therapy

Teraparatide and Abaloparatide: Biologic analogs of PTH. Indications vertebral and non vertebral fractures prevention in patients with osteoporosis. Used with more advanced disease.

Abaloparatide has a longer anabolic window but clinical outcomes between the two drugs have not been compared.

Advantage: Shows rapid onset of effect.

BMD and enzyme changes are seen in months
Disadvantages

- Expensive, daily injections
- Limited to 2 years of treatment
- Patient needs to self inject daily (may be advantage if patient has gi issues with medications)
- Black box warning of osteosarcoma......However to date there have been fewer cases than expected in the general population.

The New Kid On The Block

• Romosozumab (Evinity) - a biologic agent targeted against sclerostin. Has both antiresorptive activity AND anabolic activity.

• ------------------------INDICATIONS AND USAGE----------------------------

• EVENITY is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. (1)

• Limitations of Use: Limit duration of use to 12 monthly doses
BMD Response vs Other Meds

**Lumbar Spine**
- ROMO: 11.4% increase from baseline
- ALN: a, b, c
- TPTD: a, b, c
- Placebo: -0.1%

**Total Hip**
- ROMO: 4.2% increase from baseline
- ALN: a, b, c
- TPTD: a
- Placebo: -0.7%
Romosozumab Key Points

- Rapid bone growth but anabolic effect becomes less potent by a year.
- Expensive 21,900 dollars for a year's treatment.
- New drug so coverage will be poor initially.
- Will need to be followed by antiresorptive agent most likely denosumab or BMD will return to baseline at one year.
- There is substantial fracture reduction vs placebo and alendronate.
- ONJ and Atypical fractures have been reported
Increase cardiac signal noted vs Alendronate noted in the Alendronate arm. Has black box warning on package insert but note the Alendronate event rate was lower than placebo. Other 2 major studies did not see a difference in cardiac events. Label suggests to avoid in patients with stroke or MI in the preceding year.
Current Controversies In Osteoporosis Therapy
Calcium and Cardiovascular Risk

• In October of 2016,
• National Osteoporosis Foundation and American Society of Preventive Cardiology
• Released a joint position statement on the lack of evidence linking calcium with or without vitamin D supplementation to cardiovascular disease in generally healthy adults.
**Fake News:** Calcium and Vitamin D Don’t Reduce Fractures in the Elderly The Problem

- Recent study (JAMA), Dr. Jia-Guo Zhao et al, used data from 33 prior studies found no significant relationship between calcium and vitamin D supplementation and fracture incidence.

- Problems: study looked at healthy, community dwelling individuals and did not address people with osteoporosis. Baseline vitamin D levels were not measured in all study participants Also, Dr. Zhao et al. used data where patients were treated for less than six months, which is likely not long enough to have an effect on fractures.

Jia-Guo Zhao, MD1; Xian-Tie Zeng, MD1; Jia Wang, MD1; et al JAMA. 2017;318(24):2466-2482. doi:10.1001/jama.2017.19344
NOF Response to JAMA Article Published December 26, 2017

• Calcium plus Vitamin D Supplementation and Risk of Fractures: An 2016 NOF study, found a significant risk reduction in fractures with calcium and vitamin D.

• The NOF study excluded those who were taking their own supplements and those who had previous fractures, which increases their risk of future fractures.

• The NOF study also considered adherence to study protocols.

• These results strongly suggested that calcium plus vitamin D supplementation in select populations can significantly reduce the risk of total fractures by 16% and hip fractures by 32%.

Duration of treatment: Drug Holidays

FLEX trial in the general population there was no additional benefit of medication up to 5 years following therapy.

However, the post-hoc analysis of women with low femoral neck BMD T Score < -2.5 in the FLEX and VERT studies suggest that patients who discontinued therapy had a higher non vertebral fracture rate. 15 percent of patients who undergo bisphosphonate drug holiday have a fracture during the holiday.

Since there is no extensive evidence base to guide treatment, therapy should be individualized.

FDA recommends that patients DO NOT stop Denosumab (Prolia) as fracture rates increase after 18 months. If you stop must have an exit strategy and is should NOT be Zolendronic acid (Reclast).

Osteonecrosis of the Jaw

Definition

• Exposed bone in maxillofacial region
• Unhealed for > 8wks
• No history of radiation to craniofacial region

Accepted by ASBMR, AAOMS and ESCEO, 2007
ONJ

- **Not a new diagnosis** 1st described in 1850 it was associated w heavy metals and infections.
- ONJ can also be seen w chemotherapy, radiation and steroids. Majority seen after tooth extraction.
- Mostly associated in cancer patients on IV bisphosphonates 97% of cases in German study.
- There were no cases in any of the bisphosphonate osteoporosis drug studies with the exception of Reclast in the Horizon drug trial in which there was 1 case in the placebo group and 1 case in the treated group. Therefore the incidence is extremely low at worst.
ONJ

• Rare in osteoporosis patients without cancer therapy

• Rate from 1:10,000 to 1:263,000 to none depending on studies in patients without cancer associated therapy

• No evidence based guidelines only various expert opinions

• Risk felt to be higher in patients on IV bisphosphonates or Denosumab it is not seen w HRT or SERMs or PTH analogs.

• Prevention. Good oral hygiene regular dental care
  Hold drug with dental extractions, implants and infections, and don’t restart until bone completely healed.
Atypical Femur Fractures and ONJ

Across all studies, no clear association between overall bisphosphonate exposure and the rate of serious or non-serious atrial fibrillation was observed.
Esophageal Cancer and Alendronate

• Drug Administration (FDA) received reports of 23 patients in the United States receiving a diagnosis of esophageal cancer, with alendronate (Fosamax, Merck) Investigation started 2008.

• 2011: FDA has not concluded that patients taking oral bisphosphonate drugs have an increased risk of esophageal cancer. State benefits outweigh the risk.

• Wysowski of the FDA suggested, doctors should avoid prescribing the drug to people with Barrett’s esophagus and further review is in progress.
Impediments to Prevention and Treatment of Osteoporosis

- Poor reimbursement for DXA scanning threatens OP treatment
- The number of patients with Osteoporosis on treatment was at 15% and now be as low as 3% due to poor reimbursement and patient fear ie overemphasis by media on potential drug side effects
- Drug reimbursement issues
- Non compliance
- **Step therapy** recommends against using anabolic therapies earlier even though there is data to suggest they are more effective when used earlier. Switching from denosumab to teriparatide results in progressive or transient bone loss.


Bisphosphonate Prescribing Rates Are Dropping

Crisis in osteoporosis treatment adapted from Journal of Bone Mineral Research (JBMR), 2015
We Need to Do A Better Job

• Less than one quarter of women 60 and older who were diagnosed with a fracture of the hip, vertebra, or wrist received drug treatment for osteoporosis within the year following the fracture.

• Analysis of primary care physicians found bone density tests to screen for osteoporosis in postmenopausal women varied from 38% to 62%.

• Hip fracture rates declined from 2002 to 2012 and then plateaued at levels higher than projected for years 2013, 2014, and 2015.


Conclusion

• Osteoporosis treatment has come a long way. There are many available treatment options.

• Osteoporosis has significant morbidity and mortality in numbers that dwarf breast cancer and heart disease and we are not reaching the majority of patients who should be treated.

• Every patient that leaves the hospital with an old or new fragility fracture should have their current osteoporosis treatment plan reviewed with a recommendation for follow up treatment.
Conclusion cont

• Lack of government and insurance support and public awareness of exaggerated negative publicity regarding treatment side effects vs benefits is undermining the gains made in treating this serious condition.

• Drug holidays are detrimental for patients considered high risk for fracture.

• Non compliance is a big issue in treating patients with osteoporosis and consistent follow up, education and support is needed.

• There is no compelling evidence to suggest that calcium increases the risk of cardiovascular disease in a normal population.
Questions?