

Osteoporosis Diagnosis, Treatment and Controversies

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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

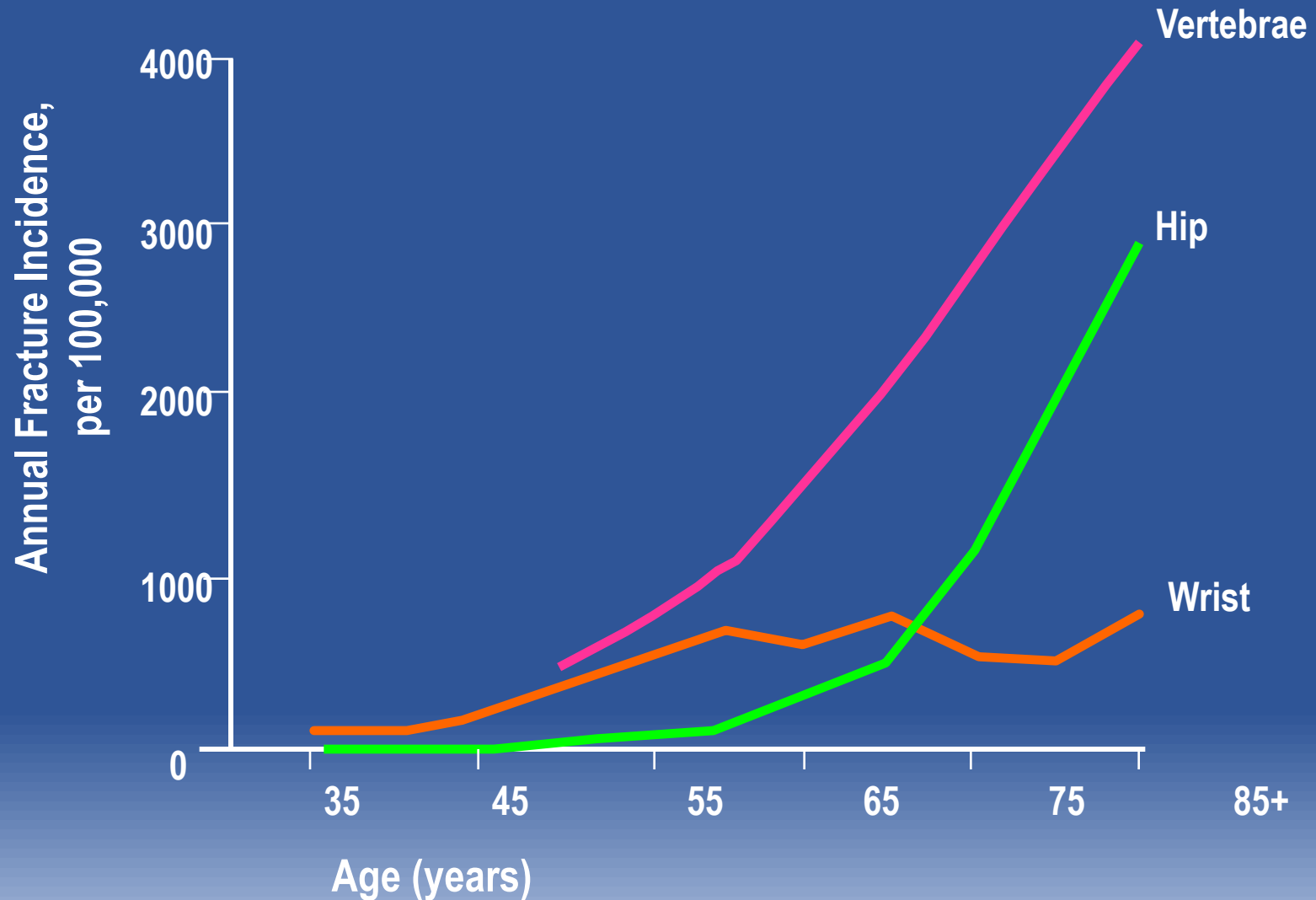
Medical and Societal Impact of Osteoporosis

Incidence

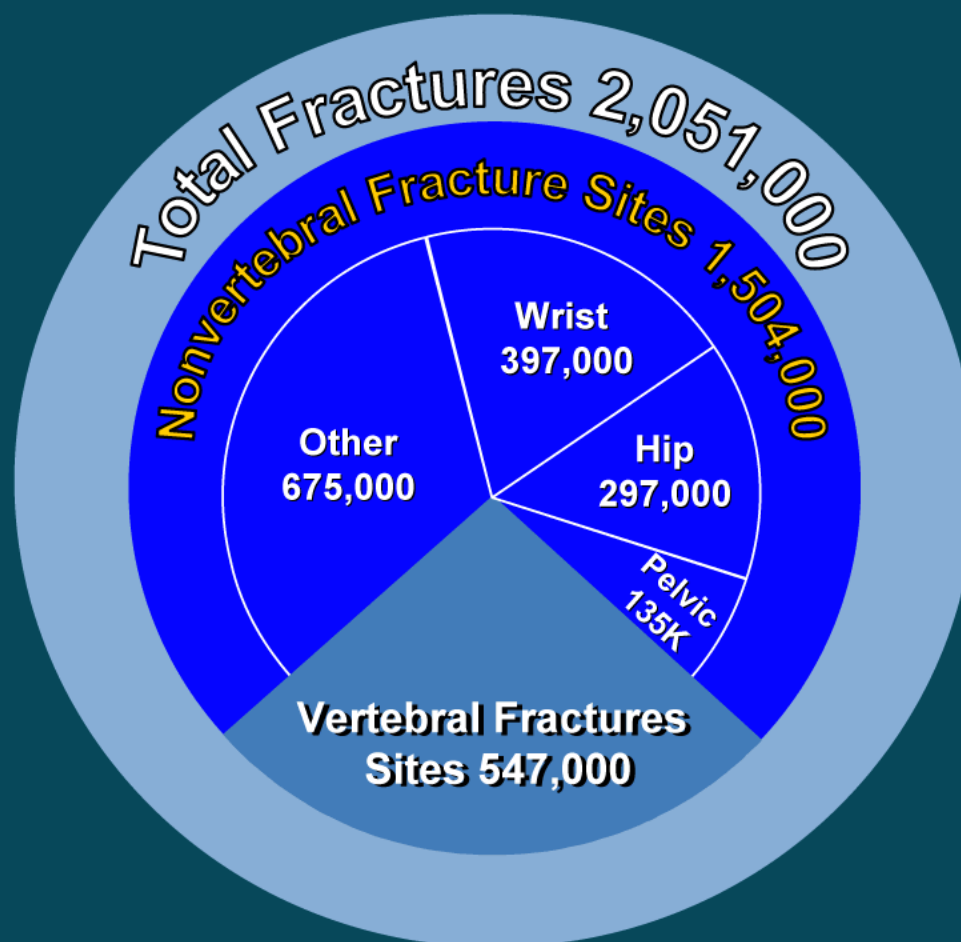
- NOF estimates 10 million Americans have osteoporosis and 34 million have osteopenia
- About 1 in every 3 Caucasian women and 1 of every 5 males will have an osteoporosis-related fracture at some point in their lifetime.

US Department of Health and Human Services. Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004

Age and Fracture Rates



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



Values are from 2005 estimates.

Fast Facts on Osteoporosis. NOF Website. At: www.nof.org/osteoporosis/diseasefacts.htm.

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 osteoporosis-related fractures has been estimated at \$17 billion for 2005 and 25.3 billion in 2025. ¹

1. *J Bone Min Res.* 2007;22(3):465-475.

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

Osteoporos Int. 2003;(14):879-883.

Laurie Barclay. Mortality Greater for Hip Fracture Than Breast Cancer in Elderly Women - Medscape - May 18, 2007.

Medical Impact of Osteoporosis

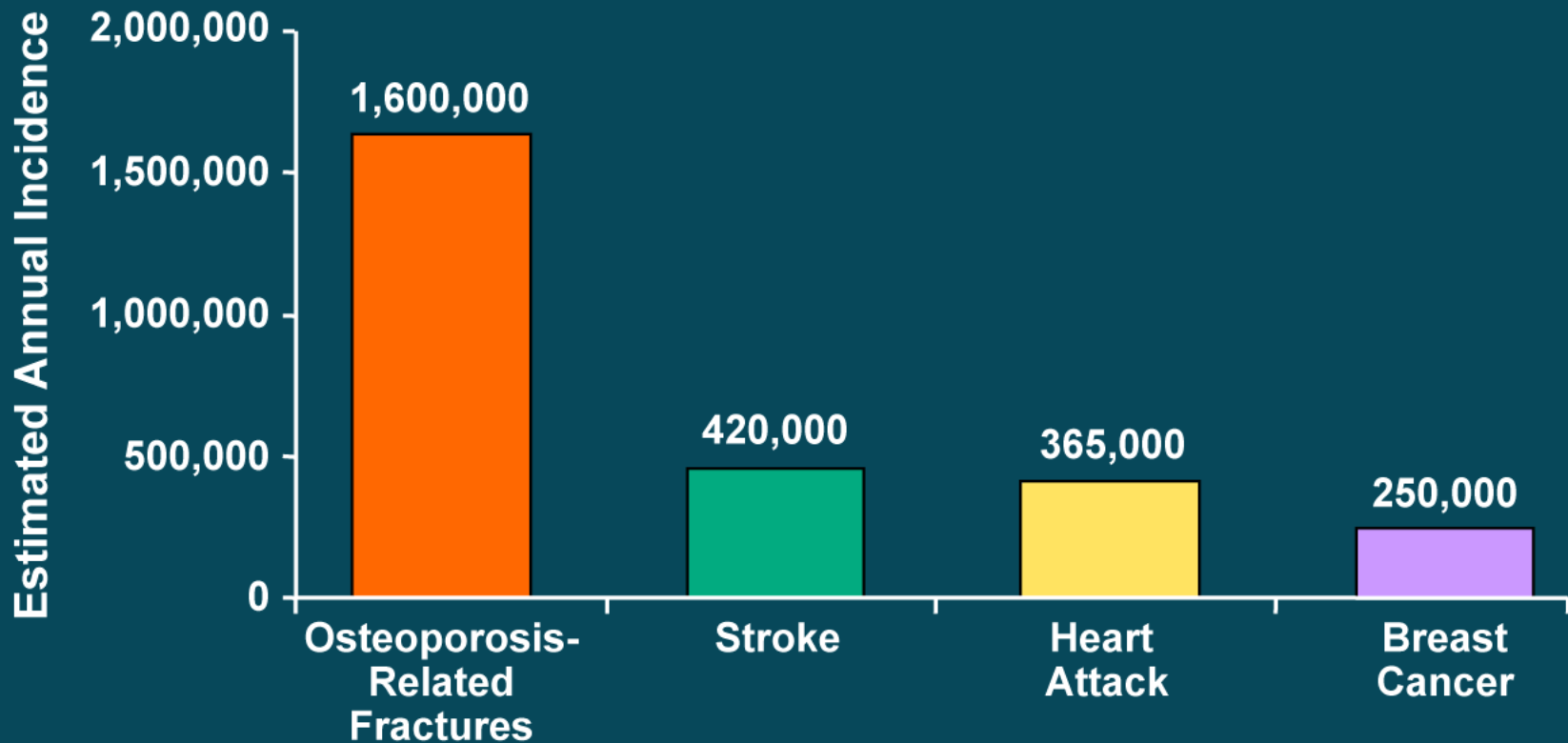
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- Vertebral fractures can cause significant chronic complications including chronic back pain, height loss and kyphosis, restrictive lung disease, abdominal pain, distention, reduced appetite and premature satiety.
- Development of arthritis of previously fractured joints such as, hip, shoulder and wrist.

We Are Loosing The Battle

- Fracture rates and death rates due to osteoporosis are going back up after substantial improvement in the past.
- Due to patients incorrect perception of risks of taking medications for osteoporosis. Poor reimbursement for DXA
- We lost 5000 bone density centers across the US in the past few years due to reimbursement below the cost of providing the service.

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

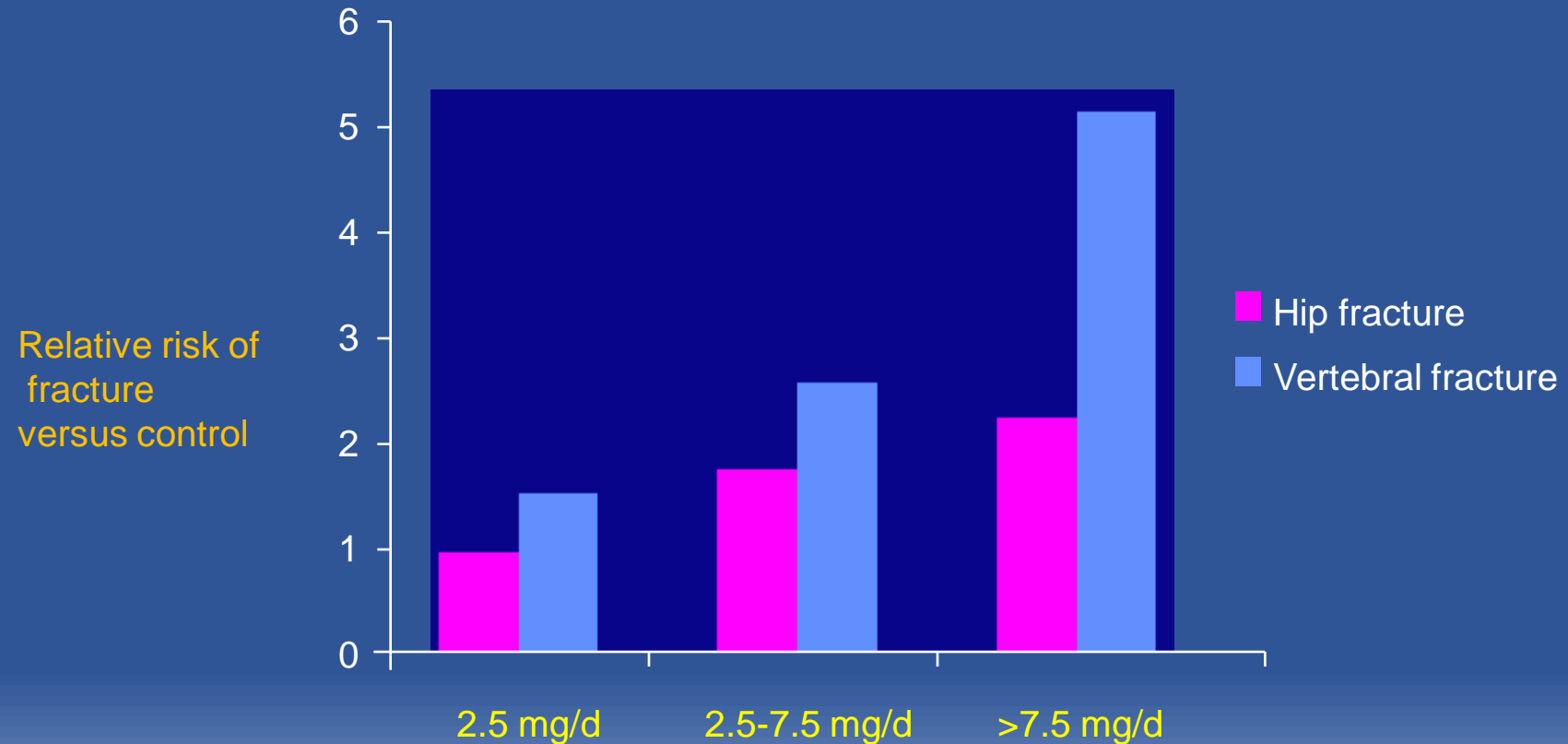
Rheumatic: poor weight bearing, chronic inflammation such as
rheumatoid arthritis, spondylitis

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



Relative risk of fracture by dosages of glucocorticoids of prednisolone. van Staa TP, et al, 1998.

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

National Osteoporosis Foundation & World Health Organization* (T-score)

Normal	-1.0 and above
Osteopenia	< -1.0 to > -2.5
Osteoporosis	-2.5 and below

* Physician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation, 1998

T Score

- T score compares an individuals bone density to that of a normal young healthy adult population
- T score is the measure used to describe an individuals 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 then the diagnosis should be reported as osteoporosis.
- If a patient has had a fragility fracture and DXA osteopenia then 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 glucocorticosteroid 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

FRAX

- **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**

Questionnaire:

1. Age (between 40-90 years) or Date of birth

Age:

55

Date of birth:

Y:

M:

D:

2. Sex

☐ Male☒ Female

3. Weight (kg)

65

4. Height (cm)

163

5. Previous fracture

☒ No☐ Yes

6. Parent fractured hip

☒ No☐ Yes

7. Current smoking

☒ No☐ Yes

8. Glucocorticoids

☒ No☐ Yes

9. Rheumatoid arthritis

☒ No☐ Yes

10. Secondary osteoporosis

☒ No☐ Yes

11. Alcohol 3 more units per day

☒ No☐ Yes

12. Femoral neck BMD

T-score



-2.1

Clear

Calculate

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 deprivation 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

Calcium Recommendations

Women

Age 50 & younger 1,000 mg* daily

Age 51 & older 1,200 mg* daily

Men

Age 70 & younger 1,000 mg* daily

Age 71 & older 1,200 mg* daily

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 to 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

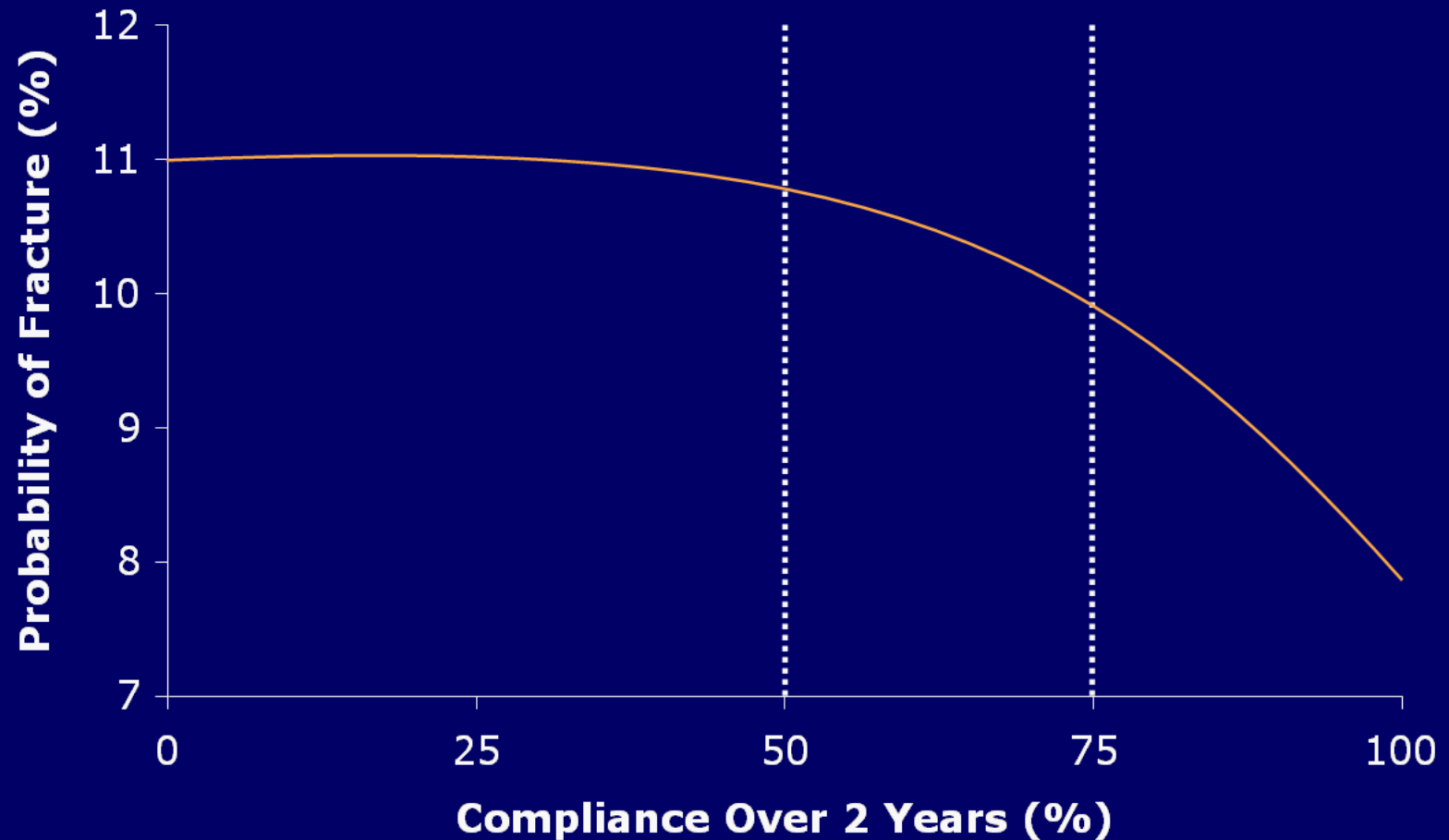
Bisphosphonates

- 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 Esophagus

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

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

PTH Analogs continued

- 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.

Acting on black box warnings requires a GRADE evidence table and an implementation guide: the case of teriparatide. Elraiyah T, Gionfriddo MR, Murad MH. J Clin Epidemiol. 2015 Jun;68(6):698-702. doi: 10.1016/j.jclinepi.2015.01.025. Epub 2015 Feb 11

Future Therapies?

- Sclerostin inhibitors currently in review
- Cathepsin K inhibitorsRIP

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%.

C. M. Weaver, D. D. Alexander, C. J. Boushey, B. Dawson-Hughes, J. M. Lappe, M. S. LeBoff, S. Liu, A. C. Looker, T. C. Wallace, and D. D. Wang. *Osteoporos Int.* 2016; 27: 367–376.

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.

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

FDA recommends that patients **DO NOT stop Denosumab** as fracture rates increase after 18 months. If you stop must have an exit strategy and is should NOT be zoledronic 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

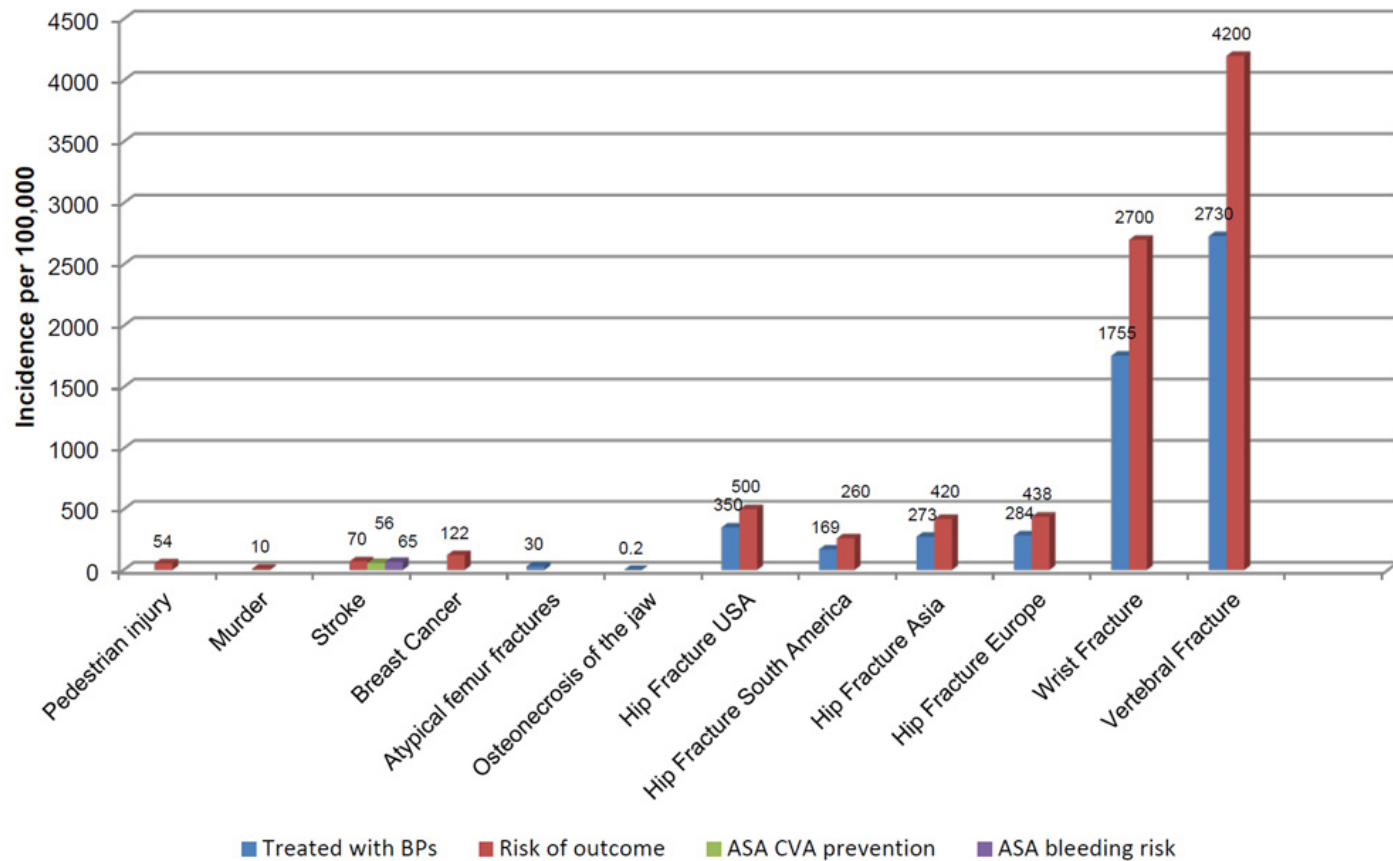
ONJ

- **Not a new diagnosis** Ist 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



J Bone Miner Res. 2016 Jan; 31(1): 16–35

FDA Statement November 12, 2008 for Atrial Fibrillation and Bisphosphonates One Controversy Solved

- 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.

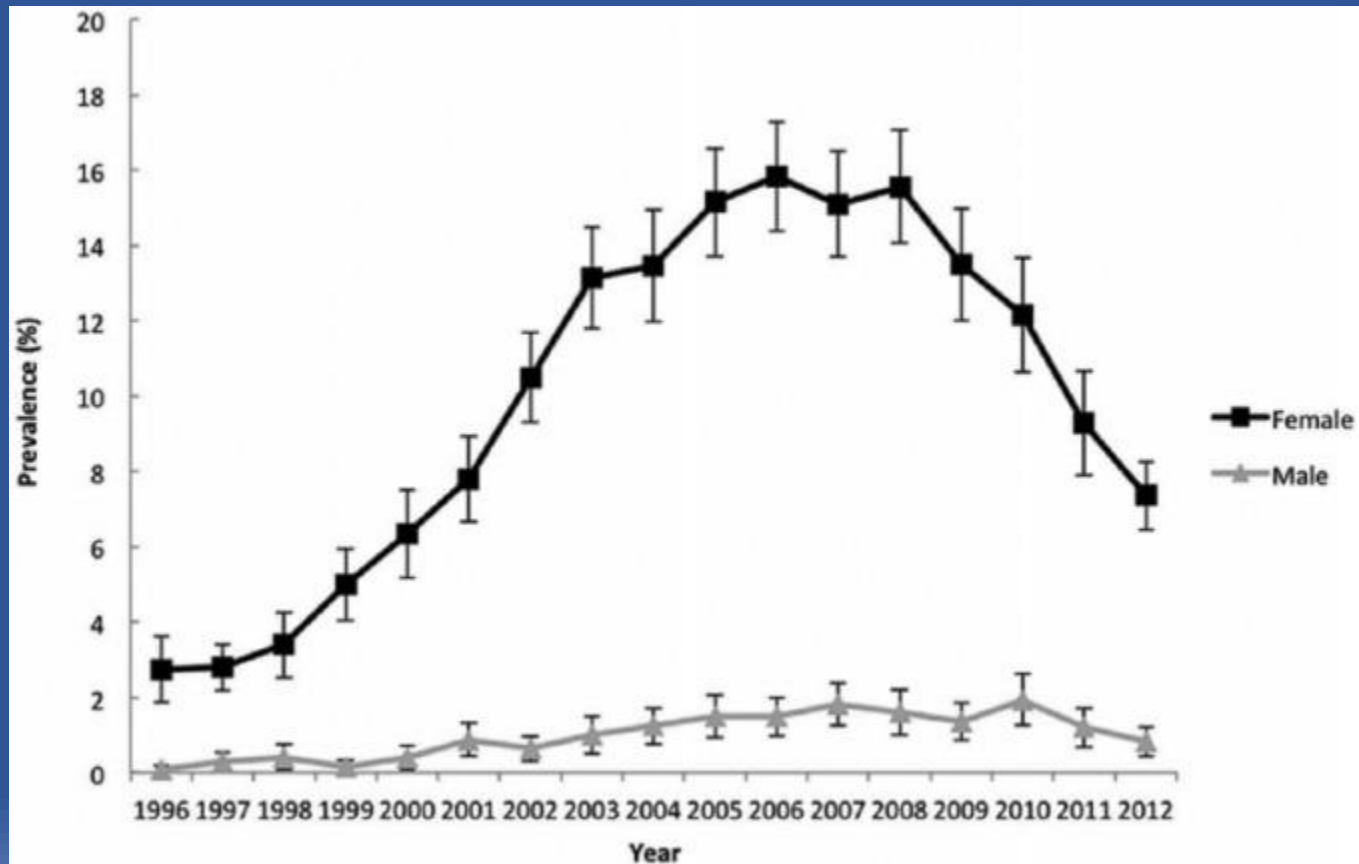
Impediments to Prevention and Treatment of Osteoporosis

- 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**.

- Sundeep Khosla, Elizabeth Shane. **A Crisis in the Treatment of Osteoporosis**. Journal of Bone and Mineral Research, 2016; DOI: 10.1002/jbmr.2888

Osteoporosis care at risk in the United States Osteoporos Int. 2008 Nov;19(11):1505-9. Epub 2008 Aug 29

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.

Andrade SE, Majumdar SR, Chan KA, et al. Low frequency of treatment of osteoporosis among postmenopausal women following a fracture. *Arch Intern Med.* 2003; 163:2052-2057.

Morris CA, Cabral D, Cheng H et al. Patterns of bone mineral density testing: current guidelines, testing rates, and interventions. *J Gen Intern Med* 2004; 19: 783-90

Michael Lewiecki E1, Wright NC2, Curtis JR3, Siris E4, Gagel RF5, Saag KG3, Singer AJ6,7, Steven PM8, Adler RA9. *Osteoporos Int.* 2018 Mar;29(3):717-722. doi: 10.1007/s00198-017-4345-0. Epub 2017 Dec 27.
Hip fracture trends in the United States, 2002 to 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 notation in the chart that follow up treatment is recommended

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?