Osteoporosis

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Disclosures

• I attended a scientific advisory board meeting for Amgen, who paid travel expenses and I declined the honorarium.
Osteoporosis is common but it’s not simple

Hip fractures are one of the most important reasons that older patients lose their independence
Topics

- Vertebral fracture assessment and bone density
- Life-style recommendations
- Osteoporosis medications
Vertebral fractures

- ignored on ~50% of radiology reports
- risk for a new fracture is 4 times higher than in a person with the same age and BMD without a fracture
- new fractures cause pain in only 40% of cases
- patients have higher mortality and disability than patients without fractures
- should be prescribed medication to strengthen bone!
In NHANES, only 8% of those with a spine fracture by VFA reported a history of spine fracture by questionnaire. Among those who reported a spine fracture on the questionnaire, only 21% had a fracture by VFA.
Radius T-score does NOT equal Hip T-score

% of 75 y/o women with “osteoporosis” goes from ~20% to ~50%
Reproducibility

0 - 2% change (51%) : Within machine precision
2 - 4% change (34%) : Mild, non-significant change
4 - 6% change (6%) : Concerning but can’t be sure
>6% change (1.5%) : Significant change
Bone density does not always predict fractures

Can’t measure:

Intrinsic toughness of bone
Brittle bone
Micro-cracks
Micro-architecture
Ability of bone to repair damage
Lifestyle
Calcium: A sacred cow?
- Calcium 1000 mg/day and protein 1-1.2 mg/kg/day (European council)
- Do not use calcium supplements in community-dwelling women to prevent fractures (USPTSF)
- Daily recommended allowance for calcium in adults is 1200mg (Inst. of Medicine)
- It is recommended that a daily calcium intake of between 700 and 1200mg should be advised, if possible achieved through dietary intake (NICE)
EAT YOUR CALCIUM: 1000mg/day

Cheese: 200
Bok Choy: 100
Tofu: 250
Sweet potato: 90
Yogurt: 300
Latte: 300
Kale: 200
Almonds: 100
Spinach: zero
Vitamin D levels should be between 20 and 50 ng/ml

To achieve this give 800 to 1000 iu/day of vitamin D

In clinical trials excess vitamin D causes bone loss and hip fractures
Vitamin D levels in skateboarders from a beach in Hawaii

Binkley 2007
Vitamin D and Mortality

Mortality Hazard Ratios

Vitamin D quartiles, ng/ml

3-16
17-24
24-32
32-160

Daraghmeh, Atherosclerosis, 2016
Vitamin D, the Sunshine Supplement, Has Shadowy Money Behind It

The doctor most responsible for creating a billion-dollar juggernaut has received hundreds of thousands of dollars from the vitamin D industry.

Liz Szabo
Aug 18, 2018

Medicare paid $365 million for Vitamin D tests in 2016
How do medicines work to strengthen the bone?
Normal Bone Remodeling
Bone Remodeling at menopause
Treatment with estrogen/SERM
Treatment with bisphosphonate
Treatment with denosumab
Treatment with teriparatide
Guidelines may recommend unnecessary treatment
When to start medications?

- **Estrogen**: Peri-menopause
- **Raloxifene**: When tolerated after menopause (localized spine disease)
- **Bisphosphonates**: Hip T-score <-2.5 OR a fragility fracture (age independent)
- **Calcitonin**: Anytime (safe but 2nd choice)
- **Teriparatide**: Severe disease, any adult
- **Denosumab**: Patients with cancer
- **Romosozumab**: Severe (T<-3.5 for now)
For each medicine you start, you should have a plan for duration and follow-up.

This is critical for the injectables.
“When indicated among women aged <60 years or within 10 years after menopause, HRT may be recommended for additional benefit to musculoskeletal health”
Estrogen in women aged 50-59

N=3310

WHI, JAMA 04
Estrogen vs Alendronate

N=1609
Women younger than 60

Ravn, Ann Intern Med 99
### % Change in lumbar spine bone density

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr</th>
<th>N</th>
<th>Estrogen</th>
<th>Bisphosphonate</th>
<th>Both</th>
<th>Placebo</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Wimalawansa</td>
<td>98</td>
<td>72</td>
<td>7</td>
<td>7.3</td>
<td>10.4</td>
<td></td>
<td>Established osteoporosis; 4 yrs; etidronate</td>
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<tr>
<td>Bone</td>
<td>00</td>
<td>425</td>
<td>6</td>
<td>6</td>
<td>8.3</td>
<td>-0.6</td>
<td>Hysterectomized women; 2 yrs; alendronate</td>
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<tr>
<td>Greenspan</td>
<td>03</td>
<td>373</td>
<td>7.1</td>
<td>7.7</td>
<td>10.4</td>
<td>1.1</td>
<td>Elderly women; 3 yrs; alendronate</td>
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<tr>
<td>Evio</td>
<td>04</td>
<td>90</td>
<td>10</td>
<td>9.1</td>
<td>11.2</td>
<td></td>
<td>Osteoporosis; 2 yrs; alendronate</td>
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<tr>
<td>Ravn</td>
<td>99</td>
<td>1609</td>
<td>7.5</td>
<td>4</td>
<td></td>
<td>-2.8</td>
<td>Perimenopausal; 4yr; alendronate</td>
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Non-vertebral fracture incidence

N = 9704
Age > 65
Mean duration estrogen use at baseline = 24.4 yrs

Nelson, Arch Intern Med 2002
Raloxifene

• Good choice for woman with osteoporosis at the spine but not the hip

• Improves the quality of bone (like estrogen but unlike bisphosphonates)

• Reduces breast cancer. Over 8 years:
  
  Placebo  4.2 per 1000/yr
  Raloxifene  1.4 per 1000/yr
Raloxifene

- May make hot flashes worse
- Not effective in premenopausal women
- No effect on uterus
- Acts like estrogen on bone
- Decreases LDL cholesterol like estrogen
- Increases blood clotting like estrogen
- In women with serious coronary artery disease, same number of strokes but more were fatal. No difference in strokes in the 8 year osteoporosis trial
- Give at different time of day than thyroxine
Clinical fractures in Alendronate Trial

FIT trial

N = 4000
Without baseline vertebral fracture

Duration 4.5 yrs

Cummings, JAMA 1998
Zoledronic acid in hip fx patients

A Any Clinical Fracture

Hazard ratio, 0.65 (95% CI, 0.50–0.84)
P=0.001

Cumulative Incidence (%)

Month

No. at Risk
Zoledronic acid  1065  1013  950  895  762  628  473  316  212  129
Placebo        1062  1010  947  884  742  611  443  305  190  119

Lyles NEJM 2007
Zoledronate reduced fractures in patients with osteopenia

• New study from New Zealand
• N = 2000, 6 years (Q 2yr doses)
• >65 yrs, women, mean 71, T-score of one hip between -1 and -2.5 (but other hip could be lower). Median fx risk was 12%.
• Prevalent fracture in 23%

RESULT
• 190 vs 122 women with fractures
• (no difference for hip fractures)
Patients in FLEX: Fracture Risk

Cumulative Incidence of Fracture

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<tr>
<th></th>
<th>0</th>
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<td>ALN/PBO</td>
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FLEX(0) Time (Year) to Observe First Fracture in FLEX

At Risk:

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<tr>
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<th>333</th>
<th>306</th>
<th>285</th>
<th>243</th>
<th>220</th>
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</tr>
<tr>
<td>ALN/PBO</td>
<td>437</td>
<td>397</td>
<td>369</td>
<td>330</td>
<td>290</td>
<td>115</td>
</tr>
</tbody>
</table>
Osteoporotic range [Tscore <= -2.5 Total Hip] at baseline

Cumulative Incidence of Fracture

FLEX(0) 1 2 3 4 5
Time (Year) to Observe First Fracture in FLEX

At Risk:
ALN/ALN 10 mg 56 49 45 34 26 10
ALN/ALN 5 mg 59 50 44 37 32 5
ALN/PBO 76 62 57 50 39 15

Whitaker, FDA report 2011
Fossil bones have high BMD!
Incidence of atypical femur fracture

Rate/100,000/year

Duration bisphosphonate use, years

Dell, JBMR, 2012
Long-term bisphosphonates

Bone biopsies from ordinary osteoporotic patients on bisphosphonates from 1 to 17 years found strength peaked at 7 years and then declined to levels below baseline. Crack density increased progressively.

Pienkowski, Wood, Malluche.
ASBMR 2019
Teriparatide
Abaloparatide
Denosumab
Romosozumab

✧ Should be used only in severe cases.
✧ Should be given by practitioner with experience and knowledge of these drugs.
✧ Rebound bone loss with discontinuation means there must be a long-range plan and compliant patient.
Denosumab

- Increases bone density
- Reduces clinical fractures
- Stops bone resorption and also completely stops bone formation
- Some cases of atypical fractures and jaw osteonecrosis
- Rebound loss after it wears off in 6 mo.
Denosumab in CKD

High incidence of serious hypocalcemia

Seizures, laryngospasm, arrhythmias, tetany

No randomized trials in patients with chronic kidney disease

Unknown effects on vascular calcifications; case report of rapid development
Denosumab rebound

• In one study, subjects gained 12% over ten years
• After stopping they lost 13% during the next year
Discontinuation of Denosumab and Associated Fracture Incidence

Conclusion: Discontinuation of DMAb is associated with an increase in VFx rate to levels comparable to PBO.

Among subjects who sustained new VFx after DMAb cessation, there was a greater incidence of multiple new VFx than in PBO.

Brown ASBMR 2016
Before and after skipping a dose of denosumab
48 yr old woman with breast cancer treated with AI from 2010 to 2015 and denosumab from 2012-2015 with improvement in BMD. Within 6 months after stopping she developed multiple spine fractures.

Popp, Osteoporosis Int 2016
Exaggerated Increases in Bone Mass
2-Year Rat Study of PTH


But they got osteosarcoma
Teri/abalo-paratide Contraindications

- History of malignancy / radiation / Paget’s
- Abnormal SPEP or UPEP
- High alkaline phosphatase
- Hypercalcemia
- Hypercalciuria
- Vitamin D level >45ng/dl
- Hyperparathyroidism
- Hepatic disease
- Chronic Kidney Disease grade 4-5
- High uric acid
- Noncompliance
Adverse effects or teriparatide

- Hypercalcemia in 11%
- Hypercalciuria or kidney stones
- Gout
- 8% nausea/ dizziness / bone aches
Teriparatide discontinuation

Eastell, JBMR 2009
WNT signaling: a simplified view

Baron, Nature Med, 2013
Markers of bone formation
Markers of bone resorption
Markers of bone resorption
Markers of bone resorption