Diagnosis and Treatment of Osteoporosis: What’s New and Controversial in 2019?

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No Disclosures

Osteoporosis Warm-Up: Which of the Following is True?

1) FRAX may be used to predict fracture risk before starting a drug holiday.
2) A healthy 65 yr old woman with a hip T-score of -1.9 should have a repeat test in 2-3 years.
3) The maximum recommended calcium intake is 2500 mg/d.
4) Bisphosphonate prescriptions have fallen by 30% since 2008.
5) Pre-treatment BMD has no impact on bisphosphonate effectiveness
What’s New in Osteoporosis

• The “crisis” in treatment and compliance
• Better risk identification and stratification
• New potential concerns about treatments
• When to start and stop bisphosphonates
• Rational use of newer drugs

What Would You Do?

1) Start daily calcium 1000 mg + vitamin D 800 iu
2) Start alendronate 70 mg or risedronate 35 mg per week
3) Start raloxifene 60 mg/d
4) Both 1) and 2)
5) Both 1) and 3)
What is Osteoporosis?

“A disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk.” \textit{WHO, 1993}

Normal bone  \hspace{5cm} Osteoporosis


\textit{Direct Research LLC, Medicare PPS Master Files and Medicare 5 Percent Sample LDS SAF, analysis by Peter M. Stever, PhD.}
New York Time June 1, 2016

Fearing Drugs’ Rare Side Effects, Millions Take Their Chances With Osteoporosis

By GINA KOLATA  JUNE 1, 2016


A Clear Example of the Therapeutic Gap: Post-Hip Fracture Treatment

- 97,000 commercially insured hip fracture patients, 2004-15 OP
- OP med use 6 mo. after surgery
- Discouraging results: 10% use in 2004 and 3% in 2015…
- Post-op zoledronic acid reduces fractures and mortality!

Desai, Jama Open. 2018; Lyles, NEJM. 2007

Under Recognition and Inadequate Treatment of Osteoporosis

- Among women with fracture or BMD<-2.5 about a third are evaluated and treated…
- Ask about fracture history, note vertebral fractures, use chart reminders for DXA
- One easy fix: identify all hip and vertebral fractures in your practice and treat if appropriate!

Soloman, Mayo Clin Proc, 2005
Shibli-Rahhal, Osteo Internat, 2011

A Quick Review: Risk Factors for Fracture

• The Big Three: older age, postmenopausal female, and Caucasian/Asian

• Other important risk factors
  - Family history of fracture (hip)
  - Low body weight (<127# in women)
  - Smoker, 3 or more drinks/d
  - Certain drugs (steroids, Als) and diseases (RA, sprue)
  - Previous fracture (especially hip or spine)

• Low bone mineral density (BMD)
  - T-score above -1=normal, below -2.5=osteoporosis
A Quick Review: Interpretation of DXA Bone Mineral Density

- Absolute mineral (calcium) content using x-rays
- Relative to a healthy reference population
- T-score is the number of standard deviations above or below average 30 year old female
  - T greater than -1.0 = “normal”
  - T between -1.0 and -2.5 = “low bone mass” (previously “osteopenia”)
  - T less than -2.5 = “osteoporosis”
- Z-score is number of SDs above or below others of the same age (use in those <50)

Hip BMD and Fracture Risk at Age 70

<table>
<thead>
<tr>
<th>T-score</th>
<th>5 year</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; -1</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>-1 to -2</td>
<td>1%</td>
<td>8%</td>
</tr>
<tr>
<td>-2 to -3</td>
<td>4%</td>
<td>16%</td>
</tr>
<tr>
<td>&lt; -3</td>
<td>9%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Who Should Be Tested and Treated? NOF and ACP Practice Guidelines

- Preventive measures for everyone: adequate calcium/vitamin D, exercise, avoid bad habits
- Screening hip BMD: women >65 (or >50 with risk factors), anyone >50 after fracture, men >70*
- If >70, consider vertebral assessment (DXA VFA)*
- Recommended pharmacologic treatment thresholds:
  - Anyone with hip or spine fracture
  - T-score (any site) < -2.5
  - T-score -2.5 to -1 and a FRAX 10 yr risk >3% hip or >20% major fractures*

*Not endorsed by ACP Guidelines

Repeat Screening: Risk at Age 65 of Developing Osteoporosis Over Next 15 Years

<table>
<thead>
<tr>
<th>BMD Result Femoral Neck</th>
<th>15 Yr Risk for Osteoporosis</th>
<th>Time to 10% BMD = –2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &gt; –1.0</td>
<td>0.8%</td>
<td>16.8 y</td>
</tr>
<tr>
<td>T = –1.01 to –1.49</td>
<td>4.6%</td>
<td>17.3 y</td>
</tr>
<tr>
<td>T = –1.50 to –1.99</td>
<td>20.9%</td>
<td>4.7 y</td>
</tr>
<tr>
<td>T = –2.00 to –2.49</td>
<td>62.3%</td>
<td>1.1 y</td>
</tr>
</tbody>
</table>

Gourlay, NEJM 2012
Implications for Follow-up Testing

• BMD results higher than –1.5 at age 65 can safely defer repeat screening until age 80
• BMD between –1.5 and –2 at age 65 merits repeat screening BMD at 5 years
• BMD results –2 to –2.5 merits rescreening at 2 years
• Caveat: applies to untreated US white women >65 at average risk

Gourlay, NEJM 2012

Medical Work-up in Primary Care

• Very little data, lots of opinions
• A reasonable start:
  – Vitamin D (25-OH, not 1,25-OH)
  – Serum calcium, Cr, TSH
• Additional tests that may be helpful:
  – Sprue serology, SPEP, UEP
• Unlikely to be helpful: PTH, urine Ca

Jamal et al, Osteo Inter, 2005
Non-Drug Therapy To Prevent Osteoporosis?

Non-pharmacologic Interventions: Do Not Underestimate Benefits

- Smoking cessation, avoid alcohol abuse
- Physical activity: modest transient effect on BMD but reduced fracture risk
- Hip protector pads effective (but poor compliance even in nursing homes...)
- Fall prevention: targeted PT, stop sedating meds
  - RCT: home based PT reduced falls by 36%

Liu-Ambrose, JAMA 2019
Calcium and Vitamin D

- Chapuy, 1992
  - Elderly women in long-term care
  - 30% decrease in hip fracture

- Porthouse, 2005:
  - Women >70 with 1+ risk factor
  - No benefit on hip, non-spine (RR=1.0, CI: 0.7, 1.4)

- USPSTF meta-analysis: 11% fewer fractures (together not alone)

Can Your Calcium Pills Kill You?

- Meta-analysis of 15 calcium/D RCTs: CHD increased 30%
  - Not 1st endpoint, cherry-pick subjects, contradicts WHI

- Little supporting mechanistic data
  - No effect on surrogates (coronary calcium, IMT)
  - Dietary calcium not implicated

- ASBMR Task Force: “evidence is insufficient to conclude that calcium supplements cause adverse CV events…”

Bolland, BMJ, 2011
Bockman, JCD, 2011
How Much Is Enough? The IOM Report

• Calcium (elemental)
  – 1200 mg/d for women >50 and men >70; no more than 2500 mg/d
  – Dietary sources preferred (estimate intake using 300 mg/d plus 300-400 per dairy serving)
  – Supplement use: nephrolithiasis but not CVD

• Vitamin D (non-skeletal benefits not established)
  – 600-800 IU/d (maximum 4,000/d)
  – Recommends serum levels 20-50 ng/ml

Institute of Medicine Report, 2010

Calcium and the US Preventive Task Force? Widely Misunderstood…

• “Insufficient evidence to assess risks/benefits for daily routine supplementation with calcium >1000 mg/d and vitamin D3 >400 IU”

• “Recommend against routine supplements with calcium 1000 mg or less and vitamin D 400 IU or less…”

  Not applicable if inadequate intake!

• Unclear if vitamin D supplements effective for fall prevention

USPTF, Ann Intern Med 2013
**Bisphosphonates: What Is Known**

- Four approved generic agents in US: alendronate, risedronate, ibandronate, and IV zoledronic acid
  - No head-to-head fracture studies; network meta-analysis show similar efficacy
- New vertebral fracture reduced 50-60%
- Non-spine fractures (including hip) reduced 30-50% if
  - Existing vertebral fracture OR
  - Low hip BMD (T-score < -2.5)
- NNT for 3 yr: 9 for vertebral, 90 for non-spine fracture

*Black and Rosen, NEJM 2016*

**Bisphosphonates: What Is Known and What is Uncertain**

- After hip fracture: 40% reduction in non-spine fracture (and mortality) with IV zoledronic acid
  - Similar effect regardless of BMD
  - NNT for 3 yr: 19 to prevent one non-spine fracture
- Efficacy if no hip or vertebral fracture and T > -2.5?
  - Trial evidence that oral alendronate and risedronate do not prevent non-spine fracture...

*Lyles, NEJM 2007
Cummings, Jama 1998
McClung, NEJM 2001*
Effect of Alendronate on Non-spine Fracture Depends on Baseline BMD

Baseline hip BMD

<table>
<thead>
<tr>
<th>Baseline BMD</th>
<th>Relative Hazard (± 95% CI)</th>
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<tbody>
<tr>
<td>T -1.5 – -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T -2.0 – -2.5</td>
<td>0.97 (0.72, 1.29)</td>
</tr>
<tr>
<td>T &lt; -2.5</td>
<td>0.69 (0.53, 0.88)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.86 (0.73, 1.01)</td>
</tr>
</tbody>
</table>

Cummings, Jama 1998

RCTs of Women with Osteopenia? Just One (Zoledronic Acid)

- 2000 women >65, hip BMD -1 to -2.5 and no previous fracture
- Randomized to ZOL or placebo for 6 yr
- 34% fewer non-spine
- 55% fewer vertebral
- 35% fewer hip
- NNT for 6 years: 15

Reid, NEJM 2018
Risedronate HIP Study: Two Groups

Group 1
- 5445 age <80; hip BMD T-score < -3.0
- 39% decreased hip fracture risk

Group 2
- 3886 age >80; risk factors for hip fx
- No significant effect on hip fracture risk

McClung, NEJM, 2001

More Bad News for Oral Bisphosphonate: Poor Compliance

- 50-60% persistence after one year
- Reasons for non-compliance?
  - Burdensome oral administration (fasting, remain upright for 30 minutes)
  - Upset stomach and heartburn can occur
  - Newer concerns about serious side effects
- Good news: Asking about side effects and positive re-enforcement increases oral med compliance by 59%

Clowes, JCEM, 2004
RCT of Nurse Visits to Discuss Medication Compliance

![Graph showing cumulative survival with nurse visits improving adherence by 59%]

Clowes, JCEM, 2004

Does Dosing Interval Matter?

- Poor quality data:
  - Daily to weekly improves compliance
  - Unclear if weekly to monthly helps
- Consider yearly dosing: zoledronic acid
  - IV bisphosphonate with very long half-life
  - Fracture reduction 25-60% with 3 annual injections (may work even if pre-treatment BMD >-2.5)
  - Precautions: acute phase reaction, renal insufficiency

Black et al, NEJM, 2007
Recent Concerns about Potent Bisphosphonates

- Associated with potent bisphosphonate use:
  - 94% treated with IV bisphosphonates
  - 4% of cases have OP, most have cancer
  - 60% caused by tooth extraction. Other risk factors unknown. Infection?

- Key points: extremely rare (<1/10,000), early identification, conservative treatment

- Dental exam recommended before Rx, but no need to stop for dental procedures

Khan, JBMR 2015
ADA Guidelines, 2011
Other Things to Worry About

- Atrial fibrillation (zoledronate acid and alendronate RCTs)
  - No association in other trials
  - Likely spurious
- Esophageal cancer
  - Case series (FDA author) and two conflicting cohorts,
  - Probably spurious
- Subtrochantic fracture (with atypical features)
  - Undoubtedly real...

Atypical Femoral Fractures (AFF)

- Thousands of reports in long-term bisphosphonate users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
- Over-suppression stress fractures?
- Other risk factors? (steroids, RA, DM, Asian...)

ASBMR Task Force, JBMR 2013
Critical Unknowns About AFFs

• Mechanism and exact relationship with BP use?
  – RR vary from 2 to over 40
  – NNTH for 3 yr of use is between 800-43,000

• Risk with increasing duration of use?
  – May increase after 5-8 years

• Risk after stopping treatment?
  – After 1 yr, AFF risk fell 70% in Sweden. Really?

Black et al NEJM, 2016 and Schilcher et al, NEJM 2011, 2014

3 Critical Unknowns About AFFs

• Mechanism and real relationship with BP use?
  – RR for BP user vary from 2 to >40
  – NNTH: Treat 800-43,000 for 3 yr to cause 1 AFF

• Does treatment duration matter?
  – AFF risk increases after 5-8 years of use

• Risk after stopping?
  – After 1 yr, AFF risk fell 70% in Sweden...

Black et al, NEJM, 2016
Schilcher et al, NEJM 2011, 2014
What Would You Do Now?

- Mrs. C. felt strongly about therapy, and has now been on Ca/D and weekly alendronate for 5 years
- Misses her weekly dose about 8-10 times per year
- No new fractures
- Repeat hip BMD: T-score -2.4 (was -2.2)
- How would you advise her?

What Would You Do Now?

1) Urge better compliance and continue current oral bisphosphonate
2) Switch to IV bisphosphonate
3) Switch to denosumab q 6 mo
4) Stop bisphosphonate, continue Ca/D
Bisphosphonates Recycle

- Bind to the bone surface
- Released when osteoclasts act
- Reattach to bone surface
- More potent, more recycling

How Long to Treat with Bisphosphonates?
Benefits Vs. Risks

- Duration of fracture protection after stopping?
- FIT Long-term Extension (FLEX) study
  - Treated with weekly ALN for 5 yr. (N=1099)
  - Re-randomized to ALN or PBO for 5 yr.
- Horizon Extension
  - Treated with annual ZOL for 3 yr. (N= 1233)
  - Re-randomized to ZOL or PBO for 3 yr.

Black et al, Jama 2006; Black et al, JBMR 2012
**FLEX Change in Femoral Neck BMD:**
% Change from FIT Baseline

![Graph showing mean percent change over years for FIT and FLEX groups.](image)

- Placebo
- ALN (Pooled 5 mg and 10 mg groups)

**Start of FLEX**

P < 0.001 ALN vs PBO

**Fracture Risk During FLEX**

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=437)</th>
<th>ALN (n=662)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-vertebral</td>
<td>20%</td>
<td>19%</td>
<td>1.0 (0.8, 1.4)</td>
</tr>
<tr>
<td>Hip</td>
<td>3%</td>
<td>3%</td>
<td>1.1 (0.5, 2.3)</td>
</tr>
<tr>
<td>Vertebral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphometric</td>
<td>11%</td>
<td>10%</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>Clinical</td>
<td>5%</td>
<td>2%</td>
<td>0.5 (0.2, 0.8)</td>
</tr>
</tbody>
</table>

Similar results with ZOL in Horizon Extension....
Are There Subgroups That May Benefit from BP Treatment Beyond 5 Years?

- High risk of vertebral fracture
  - Previous vertebral fracture (particularly recent)
  - Osteoporotic BMD at any site
- High risk of non-spine fracture
  - Previous hip fracture
  - Osteoporotic hip BMD after 5 yr of ALN.
    - FLEX: 5 additional years of ALN reduced non-spine fracture 50% if BMDfn < -2.5 (interaction p=0.02)

Schwartz et al, JBMR, 2010

Guidance for Drug Holidays

- American College of Physicians
  - Stop after 5 yr of bisphosphonate
- National Osteoporosis Foundation (NOF)
  - Consider stopping after 5 yr if “low risk”
- ASBMR Task Force
  - Algorithm with fracture risk factors + BMD

Monitoring Drug Holidays

- No specific guidance on duration or monitoring
- How to assess?
  - Repeat BMD might be helpful after 3-5 years (FLEX), but not sooner.
  - Calculate FRAX? No studies
- No data or consensus about re-initiation of anti-resorptive agents or use of newer agents...

Bauer JBMR, 2017; Adler JBMR, 2016
2019 Summary: Who Should Be Treated and When to Stop?

• US treatment guidelines:
  – Existing hip or vertebral fracture? Yes!
  – T-score < -2.5? Yes!
  – “Low bone mass” + FRAX score that exceeds absolute threshold? Oral BPs may not work

• Drug holiday after 5 yr of bisphosphonate? Maybe
  – No hip/vertebral fracture; no fracture on therapy
  – BMD T-score > -2.5 before stopping
  – How long? Monitor? Risk stratify after 3-5 yr

Other Anti-resorptive Agents

• Some clearly less effective than bisphosphonates
  – Calcitonin (poor quality studies)
  – Raloxifene (prevents vertebral fractures only; breast cancer prevention?)

• Denosumab (antibody to RANKL) similar to BPs
  – SQ q 6 months, not cleared by kidneys
  – Expensive, rebound fractures after stopping
  – Both ONJ and AFF reported
Multiple Outcomes of Raloxifene Evaluation (MORE)

Design:
7705 women >55 with low BMD or fracture
Raloxifene (60 or 120 mg) vs. placebo for 3 yr.

Primary Endpoints:
New spine fracture: RR = 0.65 (0.53, 0.79)
Non-spine fracture: RR = 0.94 (0.79, 1.12)

Other Endpoints:
Breast cancer: RR = 0.24 (0.13, 0.44)

Women’s Health Initiative

• RCT of ERT, PERT or PBO among women age 50-79, 10,739 with hysterectomy. Primary prevention
• PERT, ERT arms stopped after 5-7 years
  – Follow-up 93% complete
• Endpoints: ERT vs. PBO
  – Hip RR = 0.61 (0.41, 0.91)
  – Non-spine RR = 0.70 (0.63, 0.79)
  – CVD RR = 1.12 (1.01, 1.24)

WHI Writing Group, Jama, 2004
Rank Ligand Inhibition: Denosumab

- Human monoclonal antibody against RANKL
- Extremely potent inhibition of osteoclast activity
- Preclinical studies: increased trabecular, cortical bone mass and increased strength
- Rapid inhibition for months following a single injection, rapid resolution when stopped

Denosumab Vs. Placebo: Fracture Risk (The FREEDOM Trial)

- Multicenter study funded by Amgen
- 7808 postmenopausal women with OP
- Denosumab, 60 mg SC every 6 months (n=3902) or placebo (n=3906)
- 3 years of follow-up (83% completed study)
- Primary outcome: new vertebral fracture
- Secondary outcomes: BMD, markers, non-spine fracture, hip fracture

Cummings et al, NEJM 2009
SQ Denosumab Vs. Placebo Every 6 Months for 3 Years (FREEDOM)

<table>
<thead>
<tr>
<th>Fracture Outcome</th>
<th>Dmab vs. PBO RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>0.32 (0.26-0.41)</td>
</tr>
<tr>
<td>Hip</td>
<td>0.60 (0.37-0.97)</td>
</tr>
<tr>
<td>Any Non-spine</td>
<td>0.80 (0.77-0.95)</td>
</tr>
</tbody>
</table>

Cummings et al, NEJM 2009

The Future: Anabolic Agents

• Most treatments inhibit bone resorption > formation
• Anabolic agents (fluoride, intermittent PTH, abaloparatide) stimulate formation > resorption
• SQ teriparatide (PTH 1-34) or albaloparatide for 18 mo. reduces vertebral and non-spine fracture
  – No hip fracture data
• After anabolic need bisphosphonate for maintenance
• Expensive, daily injections: use with severe OP, when other agents have failed?

Neer, NEJM, 2001
Miller, Jama, 2016
New and Controversial: Romosumab (Sclerostin Antibody Inhibition)

- Anabolic + Anti-resorptive = Dramatic Effects on BMD
- ARCH: RCT of 4393 postmenopausal women with low BMD and vertebral fractures
- Monthly SQ romosumab vs. oral alendronate for 12 mo, then open label ALN for 12 mo
- After 24 mo: 48% fewer vert fx, 38% fewer hip fx
- BUT more CVD in romo group (2.5% vs 1.9%) so Black Box Warning; ONJ and AFF reported; cost

Saag, NEJM 2017

Osteoporosis 2019 Conclusions

- Treatment rates are low and are dropping rapidly...
- Screening and appropriate treatment = fewer fractures
  - Particularly important for secondary prevention
  - Find and treat patients after hip fracture!
- Bisphosphonates: remain treatment of choice
  - Use when spine/hip fracture or T<-2.5. >-2.5?
  - Adherence counseling. Consider yearly dosing
  - Duration of therapy: 3-5 years then off for many
- Denosumab, anabolics and sclerostin antibody effective but less clear when to use. Pipeline is empty...
Thanks for Listening
Questions or Comments?