New Guidelines for Osteoporosis Prevention and Management

Professor Peter R Ebeling AO
MBBS MD FRACP

Head, Department of Medicine
School for Clinical Sciences
Monash Health Translation Precinct
Monash University, Clayton, Victoria

The Annual Women’s and Children’s Health Update
Brisbane, 22nd July 2017

Potential Conflicts

• Departmental research funding from Merck, Novartis, Amgen and Eli-Lilly

• Honoraria to Department from Amgen, Viiv Healthcare and Merck

The Crisis in the Treatment of Osteoporosis

Declining Osteoporosis Treatment Rates Post-hip Fracture

Media Tries to Provide a Positive Message

Half of Hip Fracture Patients Give Us Advance Notice

Opportunities for GP intervention

Hip fracture is all too often the final destination of a thirty year journey fuelled by decreasing bone strength and increasing falls risk.”


"Millions of Americans are missing out on a chance to avoid debilitating fractures from weakened bones, researchers say, because they are terrified of exceedingly rare side effects from drugs that can help them."
WHO Criteria for Osteoporosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; -1</td>
</tr>
<tr>
<td>Osteopaenia</td>
<td>-1 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ -2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>≤ -2.5 and ≥ 1 fracture</td>
</tr>
</tbody>
</table>

For every 1 SD \( \bar{U} \) from normal, the relative risk of fracture increased by 1.5- to 2.5- fold

* Reference standard for "normal" BMD is a 30-year-old healthy woman


### Vitamin D + Ca in Institutionalised Elderly

3270 women, mean age 84, living in nursing homes, randomised to 1.2g Ca + 800 IU Vit D or placebo for 18 mths

![Graph showing fracture risk reduction](image)

Chapuy et al, NEJM, 1992

### Secondary Prevention: RECORD Trial

Recent low trauma fracture

<table>
<thead>
<tr>
<th>Setting</th>
<th>Comm</th>
<th>Dose</th>
<th>25OH D</th>
<th>Adherence</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>5292</td>
<td>62</td>
<td>38</td>
<td>800 IU</td>
<td>54%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Grant AM et al. Lancet 2005

### Effects of Vitamin D on Fractures

Importance of Vitamin D Dose

Effects on Hip and Non-vertebral Fracture

![Graph showing effects of vitamin D dose on fractures](image)

Bolland MJ et al. BMJ 2011;342:d2040

©2011 by British Medical Journal Publishing Group
MI Risk and Baseline Risk Factors

- Bolland M J et al. BMJ 2010

Cardiovascular Events in RCT of 5 Yrs Calcium vs Placebo & 4.5 Yrs Follow up in 1460 Postmenopausal Women


Health Benefits of Higher Dietary Calcium Intakes

- Khan B et al., J Bone Miner Res 2015;30:1758-66

Effects of Calcium on Myocardial Infarction

- Numerous large studies of Ca plus vitamin D have shown no increased risk of cardiovascular events
- However, concern exists that MI risk is increased
- Food remains the best source of calcium
- Supplements should be used only when adequate dietary Ca intake cannot be achieved
- Beneficial effects of calcium are found with relatively low doses (500-600 mg)
- In almost every osteoporosis treatment RCT, adequate Ca and vitamin D were also required
- Elderly individuals and others with impaired renal function who take calcium supplements may be at higher risk of CVD

Vitamin D Reduces Falls

- Meta-analysis showed that vitamin D supplementation reduces falls by 22% in ambulatory or institutionalised elderly individuals
- 15 patients would need to be treated with vitamin D to prevent one fall
- Should be part of multi-faceted falls prevention program
- Larger doses of 60,000 IU per mth, or 500,000 IU per yr, are associated with an increased falls risk

Bischoff-Ferrari HA et al., JAMA 2004, 2016

Position Statement – Risks and Benefits of Sun Exposure 2016 - CCV, ACD, OA, ANZBMS, ESA

- UV Index >3: A few minutes of mid-morning or mid-afternoon sun exposure to arms and hands (or equivalent area) on most days of the week should be sufficient to maintain adequate vitamin D levels
- UV Index <3 (May-August in southern states): Sun protection is not recommended
  - During these times, to support vitamin D production it is recommended that people be outdoors in the middle of the day with some skin uncovered on most days of the week
  - Being physically active while outdoors will further assist with maintaining vitamin D levels. A brisk walk at lunchtime or gardening are examples of being physically active outdoors

- Bolland M J et al. BMJ 2010
Vitamin D Supplements

Recommended daily vitamin D₃ dose: at least 800 IU/d

- Calcipress (cholecalciferol) 700 IU + 600 mg Ca
- CitroD (cholecalciferol 500 IU + 155 mg Ca)
- Ostevit Original D and Calcium (cholecalciferol 800 IU + 325 mg Ca)
- Secofit (cholecalciferol 500 IU + 155 mg Ca)
- Notoskis Calcium Complex (cholecalciferol 250 mg + 625 mg Ca)
- Nutricure's Own Calcium and Magnesium with Vitamin D (cholecalciferol 250 mg + cholecalciferol 200 IU)
- Humitan's BioHormon (cholecalciferol 250 mg + cholecalciferol 200 IU)
- Nutricure Calcium 500 (cholecalciferol 500 mg and cholecalciferol 600 IU)

- Vitamin D₃ supplement recommended

- Higher dose (>1000 IU) vitamin D supplements now available in OsteVit-D liquid, Bioceuticals D₃ drops forte, and from compounding pharmacists

- Biological Therapies - 50,000 IU capsules

Tailoring Therapy: Which Option for Who?

First-line drugs for osteoporosis are "anti-resorptive"

- Oestrogen + progestogen, if menopausal symptoms are present
- Selective oestrogen receptor modulating drugs (e.g. raloxifene)
- Oral bisphosphonates (alendronate, risedronate)
- Intravenous bisphosphonates (zolendronic acid)
- Subcutaneous denosumab injections (human RANK ligand Ab)

Second-line drugs

- Stimulates bone formation (subcutaneous PTH(1-34) or teriparatide injections)
- Strontium ranelate (uncertain mode of action; CV safety)

Effect of Denosumab on Fracture Risks at 36 Mths

FREEDOM Trial

New Vertebral Nonvertebral Hip

Incidence at Month 36 (%)

RR = 60%  P < 0.001
RR = 20%  P = 0.04

Denosumab Continues to Increase BMD Over 8 Years

FREEDOM Extension

Percent Change from Baseline

Denosumab

Placebo
**Why Change Therapy?**

- Sequential therapy for osteoporosis may be considered
  - When there has been significant bone loss or a fracture on antiresorptive therapy for >12 months
  - In the presence of adverse events
  - Insufficient adherence, e.g. the elderly
  - Dosing inconvenience or intolerance with oral bisphosphonate therapy
  - Patients with CKD where bisphosphonates are contraindicated
  - To consolidate increases in BMD following anabolic therapy

---

**PBS Reimbursement for Teriparatide in Patients with Severe Osteoporosis**

- Severe osteoporosis
- T score < -3.0
- 2 minimal trauma fractures
- One fracture occurred after 12 mths of antiresorptive drugs
- Or, intolerance to oral and intravenous bisphosphonates and denosumab
- Treatment initiated by specialist, but may be continued by GP - limited to 18 months per lifetime

---

**Head-to-head Studies of Denosumab vs Bisphosphonates in Both Pre-treated or Treatment-naive Subjects**

<table>
<thead>
<tr>
<th>Treatment Status</th>
<th>Denosumab vs Bisphosphonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treated</td>
<td>+1.6% vs +1.5%</td>
</tr>
<tr>
<td>Pre-treated</td>
<td>+1.6% vs +2.1%</td>
</tr>
<tr>
<td>Pre-treated</td>
<td>+1.5% vs ALN</td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>+1.0% vs ALN</td>
</tr>
<tr>
<td>ALN</td>
<td>+2.8% vs ALN</td>
</tr>
</tbody>
</table>

Data are least squares means and 95% confidence intervals. *p < 0.0001 denosumab vs BP.

1. Recknor C et al. ASBMR Poster P15905.

---

**Radiographic Features**

- Short-oblique configuration
- Diffuse cortical thickening
- Focal lateral cortical thickening ("beaking")
- No comminution
- Medial spike

---

**Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use during the 3 Years (2005–2008) Preceding the Fracture.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Women</th>
<th>Cases of Atypical Fracture</th>
<th>Age-Adjusted Relative Risk [95% CI]</th>
<th>Age-Adjusted Absolute Risk [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonate use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4,187,920</td>
<td>13</td>
<td>0.09</td>
<td>3.0 (reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>33,311</td>
<td>48</td>
<td>47.3 (19.6-97.1)</td>
<td>0.0004 (0.0001-0.0007)</td>
</tr>
<tr>
<td>Duration of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 yr</td>
<td>15,572</td>
<td>3</td>
<td>3.8 (1.3-10.3)</td>
<td>0.0002 (0.0000-0.0006)</td>
</tr>
<tr>
<td>1.0-1.9 yr</td>
<td>21,405</td>
<td>1</td>
<td>1.9 (1.2-3.1)</td>
<td>0.0068 (0.0000-0.0006)</td>
</tr>
<tr>
<td>≥2.0 yr</td>
<td>44,333</td>
<td>8</td>
<td>47.0 (15.8-128.3)</td>
<td>0.0006 (0.0001-0.0006)</td>
</tr>
<tr>
<td>Time since last use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 yr</td>
<td>33,311</td>
<td>42</td>
<td>8.9 (9.2-96.4)</td>
<td>0.0004 (0.0001-0.0006)</td>
</tr>
<tr>
<td>1.0-1.9 yr</td>
<td>78,096</td>
<td>2</td>
<td>5.1 (2.1-12.1)</td>
<td>&lt;0.0001 (0.0000-0.0001)</td>
</tr>
<tr>
<td>≥2.0 yr</td>
<td>75,369</td>
<td>3</td>
<td>5.1 (2.1-12.1)</td>
<td>&lt;0.0001 (0.0000-0.0001)</td>
</tr>
</tbody>
</table>


---

**Early Detection - Radionuclide Bone Scintigraphy**
Clinical Features I

- Prodromal pain in 70% (158 of 227)
- Concomitant GC use in 34% (26 of 76)
  - Incr fracture risk in one large series (OR 5.2)
- Bilateral fractures present in 28% (60 of 215)
- Bilateral radiological changes present in 28% (63 of 224)
- Delayed healing in 26% (29 of 112)

Physician and Patient Education

- The majority have a prodrome of thigh or groin pain
- Educate physicians and patients about this symptom
  - Physicians to ask patients on BPs and other potent antiresorptive agents about thigh or groin pain
- Urgent radiographic evaluation of both femora (even if pain is unilateral) is needed
  - If plain radiographs are normal, MRI or radionuclide scintigraphy scans should be performed

Jaw Osteonecrosis

- Originally called bisphosphonate-associated osteonecrosis of the jaw (2008 ADA Council advisory statement)
- Since then a few cases of ONJ have been described in patients treated with denosumab for osteoporosis, and more in patients treated with denosumab for metastatic breast and prostate cancer and with chemotherapeutic anti-angiogenic agents for cancer
- Medication-related ONJ (2014 statement)

Frequency of MRONJ – Benign Indications

- Retrospective assessment
  - ASBMR consensus rep. 1/10,000-1/100,000
  - German study 1/13,500
  - ADA < 1/100,000
  - Canadian study < 1/100,000
  - Kaiser-Permanente 1/952-1/1,337

- Prospective assessment
  - HORIZON (>10,000 pts) 2 BP/1 placebo (incl follow up study)
  - 2,000,000 pts used zoledronic acid so far
    - Not a single ONJ case reported
  - Risk in oncology trials is much higher 1-2%
  - In oncology trials, denosumab has the same risk of ONJ as zoledronic acid – also 13 pts in osteoporosis 7-year FREEDOM trial extension with denosumab

Risk Factors for ARONJ

- Age > 65 yrs
- Periodontitis
- Use of bisphosphonates > 2 yrs
- Smoking
- Denture wearing
- Diabetes mellitus
- Invasive bone procedures such as tooth extractions
Antiresorptive Drug Holidays

- “Insufficient evidence to recommend a holiday from Antiresorptive drug therapy or waiting periods before performing dental treatment for prevention of ARONJ”
- “Significant therapeutic benefits of AR agents in patients with osteoporosis far outweigh the small risk of developing ARONJ”

Hellstein JW et al. JADA 2011

Effect of Continuing or Stopping Alendronate After 5 Years of Treatment on Clinical Vertebral Fractures

Black et al JAMA 2006;296:2927-2938

Effect of Continuing or Stopping Zoledronate After 3 Years of Treatment: Spine, Total Hip BMD

Black et al J Bone Miner Res 2012;27:243-254

Effect of Continuing or Stopping Zoledronate After 3 Years of Treatment: Fractures

Black et al J Bone Miner Res 2012;27:243-254

Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of ASBMR

Adler RA et al., J Bone Miner Res 2016
Thank You!

Q & A