Definition of Osteoporosis

- Current NIH definition: Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture\(^1\)
- Images from 3-D micro-CT bone scans\(^2\)

Osteoporosis prevalence

- 1/2 women & 1/4 men will have osteoporosis-related fracture
- Affects 55% of people over the age of 50
- 44 million Americans
- 80% are women
- Osteoporosis causes a fracture EVERY 20 SECONDS
- By the end of this presentation, 45 people will have acquired fractures due to Osteoporosis

BACKGROUND

- A prior fracture is associated with an 86% increased risk of future fracture ³
- Majority of postmenopausal women with a history of fracture WITHOUT OP treatment within the year following their fracture. ¹
- < 1/3 of estimated cases of OP actually diagnosed
- Only 1/7 of women with OP in the U.S. receiving treatment. ²

² AACE Osteoporosis Guidelines Endo Practice 2003. 9(6):545-564
Lifetime risks in men

- Osteoporotic fracture in men > 50 years: 30%
- Prostate cancer: 29%


Survival after hip fracture

Expected survival in the general population

Survival probability

Time after hip fracture (years)

Consequences of Vertebral Fractures

- Increased risk of further vertebral fracture
  - Height loss\(^1\)
  - Back related disability\(^2\)
  - Back pain\(^2\)
  - Kyphosis\(^1\)
  - Increased risk of nonvertebral fractures\(^1\)

Consequences of Hip and Nonvertebral Fractures

• Hip Fracture:
  – 67% of patients do not regain their pre-fracture level of function\(^1\)
  – 50% of patients require long-term assisted care\(^2\)
  – associated with a 10-20% reduction from expected survival, with most deaths occurring in the first year following the event \(^2\)

• Nonvertebral fracture
  – Varying reports on impact on mortality, depending on site, frequency and severity of fracture\(^2\)

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Risk Factor Assessment: Surgeon General’s Report Recommendations

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Medical Conditions/Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Older age (&gt;65 years)</td>
<td>• Hyperthyroidism</td>
</tr>
<tr>
<td>• Fracture after age 45</td>
<td>• Chronic lung disease</td>
</tr>
<tr>
<td>• First degree female relative with a fracture in adulthood</td>
<td>• Endometriosis</td>
</tr>
<tr>
<td>• Self report health as “fair” or “poor”</td>
<td>• Malignancy</td>
</tr>
<tr>
<td>• Current tobacco use</td>
<td>• Chronic hepatic or renal disease</td>
</tr>
<tr>
<td>• Weight &lt; 127 lbs</td>
<td>• Hyperparathyroidism</td>
</tr>
<tr>
<td>• Menopause prior to &gt; 45 years of age</td>
<td>• Vitamin D deficiency</td>
</tr>
<tr>
<td>• Amenorrhea</td>
<td>• Cushing’s disease</td>
</tr>
<tr>
<td>• Lifelong low calcium intake</td>
<td>• Multiple sclerosis</td>
</tr>
<tr>
<td>• Excess alcohol consumption</td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td>• Poor vision despite correction</td>
<td>• Hemachromatosis</td>
</tr>
<tr>
<td>• Falls</td>
<td>• Oral glucocorticosteroids</td>
</tr>
<tr>
<td>• Minimal weight-bearing exercise</td>
<td>• Excess thyroxine replacement</td>
</tr>
<tr>
<td></td>
<td>• Antiepileptic medications</td>
</tr>
<tr>
<td></td>
<td>• Gonadal hormone suppression</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppressive agents</td>
</tr>
</tbody>
</table>

---
Age and Fracture Rates in Women

![Graph showing age and fracture rates in women](image)

Determinants of Bone Strength: Deterioration of Bone Structure

![Images of normal and deteriorated bone structure](image)

Images courtesy of J. Bilezikian, MD and David W. Dempster, PhD © 2000
**Bone Turnover**

- **Activation**
- **Resorption**
- **Quiescence**
- **Reversal**
- **Formation**

Adapted from: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism; 2nd Ed.

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**Risk Factor Assessment:**

**Former NOF Guidelines**

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Additional Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal history of fracture as an adult</td>
<td></td>
</tr>
<tr>
<td>• History of fragility fracture in 1st degree relative</td>
<td></td>
</tr>
<tr>
<td>• Low body weight (&lt;127 lbs)</td>
<td></td>
</tr>
<tr>
<td>• Current smoking</td>
<td></td>
</tr>
<tr>
<td>• Oral corticosteroids for &gt; 3months</td>
<td></td>
</tr>
<tr>
<td>• Impaired vision</td>
<td></td>
</tr>
<tr>
<td>• Estrogen deficiency at early age (&lt;45 years)</td>
<td></td>
</tr>
<tr>
<td>• Dementia</td>
<td></td>
</tr>
<tr>
<td>• Poor health/fragility</td>
<td></td>
</tr>
<tr>
<td>• Recent falls</td>
<td></td>
</tr>
<tr>
<td>• Low calcium intake (lifelong)</td>
<td></td>
</tr>
<tr>
<td>• Low physical activity</td>
<td></td>
</tr>
<tr>
<td>• Alcohol in amounts &gt; 2 drinks per day</td>
<td></td>
</tr>
</tbody>
</table>

[www.nof.org/physguide/risk_assessment.htm](http://www.nof.org/physguide/risk_assessment.htm)
Fracture Risk Assessment: FRAX Impact of the World Health Organization Project

• WHO Project
  – To develop a methodology to estimate fracture probability, validated in men and women of different ethnicities in different world regions
  – Performing a "mega-analysis" of data obtained from cohorts involving a total of over 60,000 subjects
  – Clinical risk factors for fracture that are independent of BMD can be combined with BMD to estimate the 10-year fracture probability of fracture

http://www.iscd.org/Visitors/osteoflash/index.cfm

FRAX

• Computer-based algorithm (www.shef.ac.uk/FRAX)
• Utilizes clinical risk factors to estimate 10-year fracture probability
• Can be used alone or with femoral neck BMD
• Uses Poisson regression to derive hazard ratios of death as well as fracture which are continuous and permit 10 year probability of major osteoporotic fracture (hip, clinical spine, humerus, wrist) and of hip fracture
WHO Methods

• Meta-analysis
• Mega-analysis
• Validation
• Country-specific incidence rates
• Development of country-specific intervention thresholds
Probability of Fracture in FRAX

Calculated for men and women from age, BMI, dichotomized variables of:

- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Ever long-term use or oral glucocorticoids
- Rheumatoid Arthritis
- Other causes of Secondary Osteoporosis
- Daily alcohol consumption of 3 or more units per day
Limitations of FRAX

- Dose-response of clinical risk factors
- Risk of fracture increases progressively with number of prior fractures
- Multiple factors not included: biochemical markers of bone turnover, fall risk factors
- Previous exposure to pharmacologic therapy limits applicability
- Paucity of large international databases
- Femoral neck, single reference standard
- Age

WHO Caveats

- Not used if on treatment
  - How much time off medication can you use FRAX
  - Bone loss, bone turnover markers
- Family history
  - What about parent with multiple vertebral fractures
- Vertebral fracture
  - Clinical vertebral fracture stronger risk factor than morphometric
- Caucasian female T-score
  - AA T-score on Hologic
  - Male
Management Recommendations from FRAX Guideline Group: Controversial

• Women with prior fragility fracture should be considered for treatment, but men should be referred for BMD.
• Men>50 and all PM women with WHO risk factor or BMI<19kg/m² can use FRAX without BMD
• Patients with low risk of major OP fracture should be “reassured”
• If high risk, can be treated with without BMD
• Conflicting risks for Major osteoporotic or Hip fracture

FRAX International Applicability

• Other than US, ethnic minorities not represented
• Countries not represented need to extrapolate degree of fracture risk and apply algorithm
• Cost-effectiveness of treatment is relative, value-laden
The Future of FRAX?

- Evolution of increased International applicability
- Expand clinical considerations to include “dose”: smoking, steroids, EtOH)
- Number of fractures
- Better explain 10 year risks to patients
- Issues with insurance coverage
- CLINICAL JUDGMENT

NOF Guidelines 2008:

Treatment for postmenopausal women and men over 50

- After hip of spine fracture
- BMD T score in spine or proximal femur -2.5 of less
- BMD between -1.0 and -2.5 AND one of the following (based on FRAX algorithm):
  - 10 year risk of major fracture of 20% or more
  - 10 year risk of hip fracture of 3% or more
Osteoporosis 2010: A Year of Heated Controversies

• Subtrochanteric fractures: Association with bisphosphonate treatment?

• Calcium Supplementation and CV Risk

• New treatment: Denosumab

• ACR Glucocorticoid Guidelines

Subtrochanteric Fractures: Relationship to Bisphosphonate Treatment?

• Starting in 2005, case reports describing unusual, low energy subtrochanteric fractures in women on alendronate for 5-10 years- unique radiologic pattern

• Specific xray: simple transverse or short oblique fracture with unicortical beaking in areas of thickened cortices

• FDA communication 3/10/10 – “Be aware of the possible risks”

• Black: Reviewed 284 records among 14,195 in secondary analysis of three large randomized bisphosphonate trials – 12 fractures in 10 patients classified as subtroch or diaphseal. Hazard ratio of 1.03 compared to PBO

• “The occurrence…was very rare even among women treated with bisphosphonates for as long as 10 years…but the study was underpowered.”

• ACR “Hotline” – “insufficient data to warrant discontinuing these drugs in osteoporotic patients…appears to be diminished benefit in patients taking bisphosphonates for more than 5 years”
Do Calcium Supplements Increase CV Risk?

- ASBMR: Ian R. Reid: New analysis of WHI cohort 16,000 - “We calculate that for every 1000 people treated with calcium for 5 years, it will lead to 4 additional MI’s, 4 additional strokes and 2 additional deaths while preventing 3 fractures…”

- Meta-analysis: People taking calcium supplement showed statistically significant 24% excess relative risk for MI, 15% for stroke and 16% for MI or stroke

- ? Borderline transient hypercalcemia

The Benefits of (Adequate) Calcium Intake

- Calcium supplements reduce fracture risk\textsuperscript{1,2}
- High calcium intake might protect against cardiovascular disease\textsuperscript{3,4}
- Calcium supplements improve cardiovascular risk factors (Lipid concentration, body weight, blood pressure)

\textsuperscript{1}Bischoff-Ferrari, 2007; \textsuperscript{2}Tang, 2007; \textsuperscript{3}Bostik, 1999; \textsuperscript{4}Iso, 1999; \textsuperscript{5}Griffith, 1999; \textsuperscript{6}Reid, 2002; \textsuperscript{7}Reid, 2005
Calcium intake and fractures

- Results on fracture risk differ in large meta-analysis looking at calcium intake and calcium supplementation
- One analysis\(^1\) did not report any decrease in fracture risk with high calcium intake or supplementation
- A second analysis\(^2\) found a small decrease in the rate of bone mineral density and a small but significant reduction in fracture rates

\(^1\)Bischoff-Ferrari, 2007; \(^2\)Tang, 2007

The Adverse Effects of Taking Calcium Supplements

- Calcium supplements increase vascular calcification and mortality in patients with CKD (dialysis and pre-dialysis)\(^1\)–\(^3\)
- In healthy older women calcium supplements increases rates of myocardial infarction\(^4\)

\(^1\)Goodman 2000, \(^2\)Block 2007, \(^3\)Russo 2007, \(^4\)Bolland 2008
Myocardial Infarction

<table>
<thead>
<tr>
<th>Years</th>
<th>Calcium</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4097</td>
<td>4054</td>
</tr>
<tr>
<td>1</td>
<td>3870</td>
<td>3865</td>
</tr>
<tr>
<td>2</td>
<td>3539</td>
<td>3588</td>
</tr>
<tr>
<td>3</td>
<td>2670</td>
<td>2728</td>
</tr>
<tr>
<td>4</td>
<td>1294</td>
<td>1320</td>
</tr>
<tr>
<td>5</td>
<td>373</td>
<td>388</td>
</tr>
</tbody>
</table>

Hazard ratio 1.31 (95% CI 1.02 to 1.67), P=0.035

Calcium Supplementation Studies in Wang Systematic Review

- Baron, NEJM 1999: Calcium supplement (1200 mg/day) group in colorectal adenoma prevention trial: 930 men and women similar proportion hospitalized for cardiac disease or stroke
- Prince, RL, AIM 2006, 5 yr DB PBO controlled trial in elderly women: 1460 Australian women calcium citrate 1000 mg or PBO: after 5 years of rx, MI and composite CVD endpoints (MI, stroke, or sudden death) more common in supplement group, BUT when unreported events added from national database, endpoints no longer significant
- Reid, I, et al, AIM, 2008: RCT in New Zealand of 323 healthy, non-osteoporotic men: more self-reported composite vascular events in calcium supplement group than in PBO, but low event rates
Combined Vitamin D and Calcium Supplementation Trials in Wang Analysis

- Brazier et al, Clin Ther, 2005. 192 elderly women in France with Vit. D (<12 ng/mL) insufficiency randomized to 1000 mg calcium carbonate with 800 IU of Vit. D3 or PBO. Few CV events reported and similar in active supplement (6) and PBO group (5.)
- Hsai, J et al Circulation, 2007. WHI: 36,282 post-menopausal women randomly assigned to 1000 mg calcium and 400 IU Vitamin D or PBO. Combined supplementation with Vit D and Calcium did NOT affect CVD risk (RR for MI, CHD death and stroke
- Manson: Choice of Vitamin D dose “too low” in retrospect

Additional Evidence

ASBMR 2010 Annual Meeting
Metro Toronto Convention Centre, South Building
Toronto, Ontario, Canada
October 15-19, 2010

1163
Risk of Cardiovascular Events with Calcium/Vitamin D - a Re-Analysis of the Women's Health Initiative. Mark Bolland, Andrew Grey, Gregory Gamble, Ian Reid. University of Auckland, New Zealand

Bolland, M et al, “Risk of Cardiovascular Events with Calcium/Vitamin D – A Re-Analysis of the WHI” ASBMR 2010 Abstract 1163
Bolland, 2010

- Re-analyzed WHI limited access clinical trials dataset to determine adverse effects of CaD on CV events in subgroups
- Interaction between BMI and CV risk associated with CaD allocation
- >50% women in WHI used non-protocol calcium supplements

- Of the 44% not taking non-protocol calcium supplements at CaD randomization, CaD WAS associated with INCREASED incidence of MI, coronary revascularization, stroke and composite endpoints, sig for MI and revascularization.
- Women taking non-protocol CaD was NOT associated with altered CVD risk
- Non-obese women (BMI <30 kg/m²) CaD was associated with sig INCREASED risk of revascularization and composite endpoints (24-28%) and non-sig decrease MI (16%).
- Obese women, CaD was NOT associated with increased risk for any endpoint.
- CONCLUSION: In WHI, CaD was confounded by the use of non-protocol calcium supplementation, ? possible role of Vit D def in obese, ? Protective role of Vit D component of supplement?
### Cardiovascular Events in Non-Obese Women Not Using Non-Protocol Calcium Supplements

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CAD N=4708 (incidence)*</th>
<th>Placebo N=4603 (incidence)*</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical MI</td>
<td>103 (3.1)</td>
<td>87 (2.6)</td>
<td>1.19 (0.89-1.59)</td>
<td>0.24</td>
</tr>
<tr>
<td>Total MI†</td>
<td>113 (3.4)</td>
<td>96 (2.9)</td>
<td>1.18 (0.90-1.56)</td>
<td>0.23</td>
</tr>
<tr>
<td>Revasc</td>
<td>177 (5.3)</td>
<td>132 (4.0)</td>
<td>1.31 (1.04-1.64)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke</td>
<td>109 (3.2)</td>
<td>85 (2.6)</td>
<td>1.29 (0.97-1.72)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total MI/CHD death</td>
<td>135 (4.0)</td>
<td>117 (3.6)</td>
<td>1.17 (0.91-1.50)</td>
<td>0.22</td>
</tr>
<tr>
<td>Clinical MI/Revasc</td>
<td>210 (6.3)</td>
<td>167 (5.1)</td>
<td>1.25 (1.02-1.54)</td>
<td>0.03</td>
</tr>
<tr>
<td>Clinical MI/Stroke</td>
<td>205 (6.2)</td>
<td>168 (5.1)</td>
<td>1.24 (1.01-1.52)</td>
<td>0.04</td>
</tr>
<tr>
<td>Total MI/CHD death/Revasc</td>
<td>239 (7.2)</td>
<td>197 (6.0)</td>
<td>1.21 (1.00-1.47)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Events per 1,000 woman-years. †Includes MI diagnosed from EKG changes alone.

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**ASBMR**

American Society for Bone and Mineral Research

Statement on Potential Cardiovascular Risks Associated with Calcium Supplements

August 11, 2010

A recent report suggesting a link between calcium supplements and an increased risk of cardiovascular events has sparked concern among patients, health care professionals, and the public. In response to these concerns, the ASBMR has reviewed the current available literature. Some studies have suggested a possible increase in risk, while others have not provided evidence of increased risk. Until further studies are done and more information is available, the ASBMR advises that anyone taking or considering taking calcium supplements be aware of the following key points.

**Key Points**

1. There are numerous long-term studies of calcium plus vitamin D that have shown no increased risk of cardiovascular events.
2. Patients currently taking calcium supplements should not necessarily discontinue their use. Rather, they should consider the decision to use these supplements with their health care provider and understand that if it were decided to use calcium supplements, they should be used along with adequate dietary intake of calcium. Supplemental calcium should be used only when adequate dietary intake of calcium cannot be achieved.
3. The benefits and harms of supplements should be discussed with the patient.
4. Patients who are at high risk of osteoporosis or vitamin D deficiency, such as older adults, should continue to take calcium and vitamin D supplements.
5. Patients should continue to take their medications as prescribed.

The U.S. Food and Drug Administration (FDA) has begun a costly analysis of calcium supplements. The ASBMR will continue to study this important clinical issue and release additional information as soon as it is available.

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About ASBMR

The American Society for Bone and Mineral Research (ASBMR) is the largest professional, scientific, and medical society worldwide dedicated to promoting excellence in bone and mineral research and to facilitating the translation of that research into clinical practice. The ASBMR has a membership of nearly 5,000 physicians, basic research scientists, and clinical investigators from around the world.

For additional information please contact Ana L. Berman, MD at aberman@asbmr.org.
ASBMR Statement

Key Points
1. There are numerous large studies of calcium plus vitamin D that have shown no increased risk of cardiovascular events.
2. Persons currently taking calcium supplements should not necessarily discontinue their use. Rather, they should discuss the decision to use these agents with their health provider, and understand that food remains the best source of calcium. Supplements should be used only when adequate dietary intake of calcium cannot be achieved.
3. The beneficial effects of calcium are found with relatively low doses. More is not necessarily better. Individuals should discuss the amount of their calcium intake with their health provider.
4. In almost every modern study of osteoporosis treatment, adequate calcium and vitamin D were required for medications to have anti-fracture efficacy.
5. Elderly individuals and others with impaired renal (kidney) function who take calcium supplements may be at higher risk of cardiovascular problems.

ACR Glucocorticoid Guidelines:

Glucocorticoid-Induced Osteoporosis

- Most common drug-induced osteoporosis
- Vertebral fractures in 30-50% of glucocorticoid-treated patients
- Dose, duration dependent
- Fractures occur at higher BMD’s
- Glucocorticoids inhibit osteoblast (OB) development, inhibit OB maturation, direct osteocyte effects, enlarged lacunae, increase osteoclast maturation, calcuria, impact adrenal and gonadal hormones
Recommendations - Monitoring

- Consider serial bone mineral density testing
- Consider annual serum 25OH vitamin D level
- Assessment of incident fragility fracture
- Annual height measurement
- Assessment of medication compliance

Pharmacologic Recommendations - Low Risk Postmenopausal Women and Men ≥50 Years

- Alendronate for 7.5 mg or more prednisone daily
  OR
- Risedronate for 7.5 mg or more prednisone daily
  OR
- Zoledronic acid for 7.5 mg or more prednisone daily

- Starting glucocorticoid therapy with an anticipated duration of ≥3 months
  OR
- Prevalent glucocorticoid therapy of ≥ 3 months duration

- Low risk - FRAX 10 year major osteoporotic fracture risk <10%
**Pharmacologic Recommendations - Medium Risk**

**Postmenopausal Women and Men ≥50 Years**

- Alendronate for any dose of glucocorticoids
- OR
- Risedronate for any dose of glucocorticoids
- OR
- Zoledronic acid for 7.5 mg or more prednisone daily

- Starting glucocorticoid therapy with an anticipated duration of ≥3 months
- OR
- Prevalent glucocorticoid therapy of ≥3 months duration

- Medium risk - FRAX 10 year major osteoporotic fracture risk 10-20%

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**Pharmacologic Recommendations - High Risk**

**Postmenopausal Women and Men ≥50 Years**

- Alendronate for any dose of glucocorticoids
- Risedronate for any dose of glucocorticoids
- Zoledronic acid any dose of glucocorticoids
- Teriparatide for any dose of glucocorticoids duration > 1 month

- For high risk patients- any anticipated duration justifies initiating prescription therapy; for prednisone duration < 1 month, teriparatide recommended for 5 mg daily and higher

- High risk - FRAX 10 year major osteoporotic fracture risk >20% or prevalent fracture
Premenopausal Patients

• The panel felt that there was limited data on premenopausal patients

• Following recommendations are for those with a history of prevalent fracture

Absence of recommendation does not equal no treatment for this population

Premenopausal Non-child-bearing Potential Women and Men <50 Years with History of Fragility Fracture

• Anticipated duration glucocorticoid >1 month and <3 months
  – Alendronate if prednisone 5 mg daily or more
  – Risedronate if prednisone 5 mg daily or more
  – Zoledronic acid if prednisone 7.5 mg daily or more

• Anticipated duration glucocorticoid ≥ 3 months
  – Alendronate
  – Risedronate
  – Zoledronic acid
  – Teriparatide
Premenopausal Women of Child Bearing Potential With Prior Fragility Fracture

For those with an anticipated duration of >3 months or ≥3 months of prevalent glucocorticoid use

- Alendronate if prednisone 7.5 mg daily or more
  OR
- Risedronate if prednisone 7.5 mg daily or more
  OR
- Teriparatide if prednisone 7.5 mg daily or more

Differences from 2001 to 2010

- Expanded recommendations for counseling and monitoring
- Updated pharmacologic recommendations delineated for postmenopausal women and men over age 50 years, premenopausal women not of childbearing potential and men under the age of 50 years with a history of a fragility fracture, and premenopausal women of childbearing potential with a history of a fragility fracture
- The newer therapies zoledronic acid and teriparatide are now recommended along with alendronate and risedronate for the treatment of GIOP, while the previously included therapies estrogen replacement and testosterone are no longer endorsed
- Recommendations now guided by patient’s overall clinical risk instead of T-scores alone
Counsel and assess risk factors those starting or on prevalent glucocorticoid therapy

Determine Patient Risk Category

Low Risk*
- Alendronate, Risedronate or Zoledronic acid for those on ≥7.5 mg daily glucocorticoids

Medium Risk*
- Alendronate and risedronate for any dose glucocorticoids and zoledronic acid for ≥7.5 mg daily glucocorticoids

High Risk
- Alendronate, risedronate, zoledronic acid for any dose or duration of glucocorticoids, and teriparatide for 5 mg or more prednisone daily duration 1 month or less and for any dose of glucocorticoids with a duration greater than 1 month

Monitor patients on prevalent glucocorticoid therapy

Approach to Premenopausal Women and Men Under Age 50 Years Starting or on Glucocorticoid Therapy

Counsel and assess risk factors of those starting or on prevalent glucocorticoid therapy (refer to Table 2)
Denosumab: 2010

- Denosumab approved in June 2010 for treatment of post-menopausal osteoporotic women at high risk for fracture
- Fully human monoclonal antibody directed against RANKL: Interferes with formation, activation and survival of osteoclasts
Bone Resorption is Dependent on RANK Ligand, the Primary Mediator of Osteoclast Activity

**RANK Ligand is Essential for Osteoclast Formation, Function and Survival**

- CFU-M
- Pre-Fusion Osteoclast
- Multinucleated Osteoclast
- Activated Osteoclast

Growth Factors
Hormones
Cytokines


---

**Proposed Mechanism of Action for Denosumab**

- CFU-M
- Pre-Fusion Osteoclast
- Multinucleated Osteoclast
- Osteoclast

Growth Factors
Hormones
Cytokines

• 3886 women treated with Denosumab, 3876 with PBO
• All received calcium >1000 mg and Vit D
• At 3 years, denosumab led to 68% reduction in new vertebral fractures, 40% reduction in hip fractures and 20% reduction in non-vertebral fractures vs. PBO
• Denosumab BMD increases 8.8% in LS, 6.4% in hip and 5.2% in femoral neck.
• Decrease in CTX marker of resorption attenuated at end of dose interval : reversibility

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Denosumab no. (%)</th>
<th>Placebo no. (%)</th>
<th>Difference in Rates (95% CI)</th>
<th>Relative Risk or Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New vertebral fracture</td>
<td>86 (2.3)</td>
<td>264 (7.2)</td>
<td>4.8 (3.9 to 5.8)</td>
<td>0.32 (0.26 to 0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvertebral fracture</td>
<td>238 (6.5)</td>
<td>293 (8.0)</td>
<td>41.5 (0.3 to 2.7)</td>
<td>0.80 (0.67 to 0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>26 (0.7)</td>
<td>43 (1.2)</td>
<td>0.3 (-0.1 to 0.7)</td>
<td>0.60 (0.37 to 0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Other fracture end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New clinical vertebral fracture</td>
<td>29 (0.8)</td>
<td>92 (2.6)</td>
<td>1.7 (1.1 to 2.3)</td>
<td>0.31 (0.20 to 0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple (&gt;2) new clinical vertebral fracture</td>
<td>23 (0.6)</td>
<td>59 (1.6)</td>
<td>1.0 (0.5 to 1.5)</td>
<td>0.39 (0.24 to 0.63)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Percent Changes in Bone Mineral Density

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Denosumab (N=3,886)</th>
<th>Placebo (N=3,887)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>3605 (92.8)</td>
<td>3607 (93.1)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Serious</strong></td>
<td>1004 (25.8)</td>
<td>972 (25.1)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Fatal</strong></td>
<td>70 (1.8)</td>
<td>90 (2.3)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Leading to study discontinuation</strong></td>
<td>93 (2.4)</td>
<td>81 (2.1)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Leading to discontinuation of a study drug</strong></td>
<td>192 (4.9)</td>
<td>202 (5.2)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2055 (52.9)</td>
<td>2108 (54.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Cancer</td>
<td>187 (4.8)</td>
<td>166 (4.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0</td>
<td>3 (0.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>0 NA</td>
<td></td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>144 (3.7)</td>
<td>125 (3.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Infection</td>
<td>159 (4.1)</td>
<td>133 (3.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>186 (4.8)</td>
<td>178 (4.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>56 (1.4)</td>
<td>54 (1.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>47 (1.2)</td>
<td>38 (1.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>31 (0.8)</td>
<td>30 (0.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29 (0.7)</td>
<td>29 (0.7)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Adverse events occurring in at least 2% of subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>118 (3.0)</td>
<td>65 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Falling</td>
<td>175 (4.5)</td>
<td>219 (5.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Flatulence</td>
<td>884 (2.2)</td>
<td>53 (1.4)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Percent Changes in BMD for All Evaluated Skeletal Sites at Month 12

- **Alendronate 70 mg QW**
- **Denosumab 60 mg Q6M**

### Denosumab Safety Issues

- Safely with impairment, to GFR >30, but low bone density in patients may NOT be osteoporosis
- Hypocalcemia, ONJ, dermatologic reactions
- "Serious infections requiring hospitalization"
- Use with other biologics, immunosuppressives, transplant patients?
- Reversibility
Vitamin D and Skeletal Health

Vitamin D: What Is It?

- **1,25 dihydroxyvitamin D** (1,25[OH]$_2$D) is a hormone produced by the kidney, under the control of PTH from precursors derived from dietary vitamin D intake and UV skin-production of vitamin D.
- **It is not really a vitamin**, but the name was given many years ago, before anybody knew the function of this molecule.
- Vitamin D receptors are present in bone, kidney, intestines, and many other cells.
Types of Vitamin D

Vitamin D\(_2\)
- Formed by irradiation of ergocalciferol, found in plants
- Provided by some dietary sources and multivitamins
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form
- D\(_2\) is less potent than D\(_3\)

Vitamin D\(_3\)
- Naturally occurring form in humans
- Formed by action of ultraviolet light on vitamin D precursors in skin
- Present in certain nutrients
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form

Sources of Vitamin D

- Sunlight exposure
  - Major source of vitamin D\(^1\),\(^2\)
  - Vitamin D production is affected by season, duration of exposure, sunscreen use and skin pigmentation.\(^2\)
  - Age\(^2\)
- Endogenous production
  - Ability of skin and kidneys to form and process vitamin D\(^4\)
- Dietary intake
  - Minor source of vitamin D.\(^2\)
  - Vitamin D is rare in foods other than fatty fish and fortified food products, such as milk and breakfast cereals.\(^3\),\(^4\)
  - Supplements containing vitamin D alone are not readily available.\(^4\)

Vitamin D: Its Role in PTH and Calcium Homeostasis

- Vitamin D insufficiency leads to increased release of PTH, which stimulates:
  - Bone resorption
  - Release of calcium and phosphorus from the bone
  - Synthesis of renal calcitriol
- Vitamin D increases/promotes:
  - Intestinal calcium absorption (principally in the duodenum)
  - Reabsorption of renal calcium

---

The Interrelationship of Calcium, Vitamin D, and PTH

Low Calcium Intake  Low Vitamin D Status

- Insufficient Calcium Absorption
- Increased Intestinal Calcium Absorption
- Increased 1,25(OH)2D
- Increased PTH
- Fall in Serum Calcium
Vitamin D Status: Impact on Calcium Absorption and PTH

Fasting PTH

Calcium Absorption

Mean serum 25(OH)D level, nmol/L

- Predosed with 25(OH)D for 3 weeks prior to study
- No pretreatment with vitamin D or 25(OH)D

*P<0.001.

Consequences of Vitamin D Insufficiency

Calcium absorption

- When vitamin D status is sufficient, absorption of dietary calcium is approximately 30% to 40%.
- As vitamin D status declines, absorption of dietary calcium declines to about 10% to 15%.

PTH

- Low levels of vitamin D leads to increased release of PTH, which increases bone resorption and decreases bone mass.

Bone Mass

- Given its effect on calcium absorption, vitamin D insufficiency is associated with bone loss and an increased fracture risk.

References:
Impact of Vitamin D Insufficiency on Skeletal Health

Vitamin D insufficiency is associated with:\n
- Impaired calcium absorption
- Increased release of PTH
- Increased bone remodeling
- Bone loss leading to osteoporosis

In severe cases, deficiency results in more severe hyperparathyroidism, hypophosphatemia, proximal muscle weakness, bone pain and osteomalacia.


Relationship Between Serum Intact PTH (iPTH) and 25(OH)D Values

The 25(OH)D Continuum Controversy

“deficiency”

“insufficiency”

“normal”

0 10 20 30 40 50 60  
(ng/mL)

0 25 50 75 100 125 150  
(nmol/L)


Vitamin D: Definition of Insufficiency

Although there is no formal consensus on a definition of vitamin D insufficiency, many experts consider a 25(OH)D level of less than 30 ng/ml (75 nmol/l) to be vitamin D insufficient.

The Majority of Americans Are Not Receiving Adequate Levels of Vitamin D

- According to a NHANES III survey of 3,444 women aged 51 years and older, over 70% of women 51 to 70 years were estimated not to meet adequate intake guidelines for vitamin D based on daily intake from diet and supplements (400 IU).
- Nearly 90% of women older than 70 years were estimated not to meet guidelines (600 IU).

NHANES = National Health and Nutrition Examination Survey.


Vitamin D Intake (Diet + Supplement) NHANES III

![Vitamin D Intake Bar Chart]

*Percent consuming adequate intake or above from diet + supplement significantly different from diet alone, P<0.05.

Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

LOWESS = locally weighted regression plot.

Reference range of 25(OH)D: 30-70 ng/mL.

LOWESS regression plot of lower extremity function vs vitamin D levels

![Timed Sit-to-Stand Test Chart]

Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

LOWESS = locally weighted regression plot.
Reference range of 25(OH)D = 22.5–64.6 ng/mL.
N = 4,100; P=0.001.


Why 400 IU?

- Index disease for vitamin D deficiency was rickets or osteomalacia.¹
- It is known that vitamin D prevents rickets.²
- Absence of rickets or osteomalacia was implicitly considered to be evidence of vitamin D sufficiency.¹
- 1919–1920: Rickets developed in dogs reared indoors and fed purified diets; preventable with cod-liver oil.³
- The recommended dietary allowance for vitamin D was set at 400 IU because that was the quantity in 1 teaspoon of cod-liver oil.²

Defining the Upper Limit of Vitamin D Intake

- Cases of vitamin D toxicity have been reported in patients receiving >10,000 IU/day for at least 1 month.
- No toxic effects were observed in individuals given 4,000 IU/day administered orally for 5 months.¹

Cleveland Clinic

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