Osteoporosis in Youth, Aging and Illness

Premier Fitness
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Why is an Oncologist interested in the problem of osteoporosis? You’ll find out...
Case Presentation
35 year-old world-class long distance runner

Bronze medalist in Athens Olympics (2004)

In peak of physical health

For several weeks prior to 2008 Beijing Marathon had twinges of pain in second metatarsal of right foot

Three miles into Marathon felt a pop in her right foot, stopped in severe pain and dropped out of the race

Findings....
X-ray of foot... (Normal)
MRI of foot

Hair-line transverse fracture
X-ray of foot three weeks later...

Barely visible hair-line fracture
The Triad of the Female Athlete

- Eating disorder
- Amenorrhea
- Osteoporosis

The Osteoporosis is counter-intuitive because of so much weight bearing.

Amenorrhea is a function of low circulating estrogenic compounds, poor caloric intake and low body fat (storage site for estrogens).

What happens to their bones when young female athletes do not eat enough?
Effect of Controlled Caloric Intake on Markers of Bone Turnover in Female Military Recruits

Stress Fractures 1986-2000 in NCAA Division I Athletes

The Female Athletic Triad – in and out of balance

Nattiv Medicine & Science in Sports and Exercise Special Communication, pp 1867-82, 2007
Treatment of Osteoporosis in the Young Female Athlete

- Recognizing entity by performing DEXA scan after first stress fracture especially if amenorrhea present
- Calcium and Vitamin D supplementation; lack of body fat makes storage of D problematic
- Consideration of birth-control pills to supplement deficit in natural circulating estrogens
- Usual pharmacologic interventions (bisphosphonates, teriparatide, calcitonin) have not been studied in young women; safety and efficacy not assured
Osteoporosis in Young Female Athletes: Summary

- Stress fractures in long-distance women runners very common
- Prodrome of foot pain for several days prior to actual fracture common
- Bone mineral density likely depressed because of hormonal changes associated with athletic training and altered caloric intake; and absence of body fat to store Vitamin D
- Little scholarly work done on how to define bone disease in young women and how aggressive intervention could prevent stress fractures
- On her website, Deena promises to drink milk and eat yogurt – likely a totally inadequate band aid
Osteoporosis: Definition

NIH Definition:

“Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture”

Epidemiology of Osteoporosis in the US

- 44 million Americans, 80% of whom are women
  - 10 million have established osteoporosis
  - 34 million have osteopenia or low bone mass
  - 1.5 million fractures occur per year in US

In spite of case presentation, the vast majority of women with osteoporosis are post-menopausal.

Osteoporosis is Common Among US Women

- 10 million Americans have established osteoporosis, 80% of whom are women\(^1\)
- 1.5 million fractures occur per year in US

\[\text{Females in General Population}^2\]

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>% With Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>14.8%</td>
</tr>
<tr>
<td>60-69</td>
<td>21.6%</td>
</tr>
<tr>
<td>70-79</td>
<td>38.5%</td>
</tr>
<tr>
<td>≥80</td>
<td>70.0%</td>
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Risk Factors for Osteoporotic Fractures

Genetic/Nonmodifiable

- Age
- Female sex
- Asian or white ethnicity
- Previous fragility fracture
- Family history of hip fracture or osteoporosis
- Small frame

Potentially Modifiable

- Menopause-related estrogen deficiency
- Low body weight
- Calcium/vitamin D deficiency
- Inadequate physical activity
- Excessive alcohol intake
- Cigarette smoking
- Long-term glucocorticoids

Vertebral Fractures Have Significant Consequences for Patients, Including Dorsal Kyphosis

Vertebral Fractures

- Associated with
  - Acute and chronic pain
  - Kyphosis and height loss
  - Impaired function
  - Increased morbidity and mortality
  - Increased fracture risk

Hip and Other Non-Vertebral Fractures Have Significant Consequences

- Hip fracture associated with
  - Loss of ambulatory status in 30% of patients
  - Increased morbidity and mortality
  - Increased fracture risk
  - Major reason for admission to chronic care facilities

- Non-vertebral fractures
  - Pain
  - Increased risk of future fractures

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Risk of death over time with hip fracture: with and without subsequent treatment

Hazard ratio, 0.72 (95% CI, 0.56–0.93)
P = 0.01

Cumulative Incidence (%)

0 2 4 6 8 10 12 14 16 18

Month

No. at Risk
Zoledronic acid
Placebo

1054 1029 987 943 806 674 507 348 237 144
1057 1028 993 945 804 681 511 364 236 149

Lyles K et al. N Engl J Med 2007;357:1799-809
Clinical Presentation of Osteoporosis

- Usually asymptomatic and undiagnosed

- Signs and symptoms
  - Low-trauma fractures of spine, wrist, or hip
  - Loss of height
  - Kyphosis (rounded back)
  - Acute or chronic back pain

- Diagnostic tests
  - Bone mineral density measurement
  - Spine x-ray or morphometry

**WHO Bone Density Criteria for Diagnosing Osteoporosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>BMD T-Score: Number of SD Below Mean in Healthy Young Women*</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>−1 or above</td>
</tr>
<tr>
<td>Low bone mass [osteopenia]</td>
<td>Between −1 and −2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>−2.5 or less</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>−2.5 or less with fragility fractures</td>
</tr>
</tbody>
</table>

Reduction by 1 SD equals a 10% to 12% decrease in BMD
1 SD change increases fracture risk by 1.5- to 2.0-fold

Who should be screened for osteoporosis?

Recommend BMD testing for

- All women 65 years of age and older
- Younger postmenopausal women with one or more risk factors (other than being white, postmenopausal, and female)
- Postmenopausal women who present with fractures (to confirm the diagnosis and determine disease severity)

No testing for premenopausal women recommended at present, even for serious athletes
Nonpharmacologic Interventions

- Goal of nonpharmacologic interventions is to prevent future fractures through lifestyle change
  - Diet and dietary supplements
    - Calcium
    - Vitamin D
  - Exercise
  - Fall prevention
  - Smoking Cessation

Data to support these recommendations...

Hip Bone Mineral Density (BMD): Calcium + Vitamin D Supplementation vs. Placebo

Benefit modest and transient

Exercise relatively modest compared to that of serious athletes; body fat content average as well.

Feskanich et al JAMA 288: 2300, 2002
Impact of Smoking on Development of Osteoporosis

Complicated study: dots below the line show effect of smoking...the more smoking the greater the effect

Decision to Treat Is Affected by Several Factors

- Current AACE position on treatment intervention
  - Women with postmenopausal osteoporosis
    - Women with low-trauma fractures and low BMD
    - Women with BMD T-scores of \(-2.5\) and below
  - If risk factors are present, women with borderline-low BMD (T-scores of \(-1.5\) and below)
  - Women in whom nonpharmacologic preventive measures are ineffective (bone loss continues or low trauma fractures occur)

- Individual clinician judgment is important

- Forthcoming guidelines are likely to be based on absolute fracture risk probability over 10 years rather than on BMD alone

AACE = American Academy of Clinical Endocrinologists

Classes of Pharmacologic Agents Currently Approved for the Treatment of Osteoporosis

- **Antiresorptive agents**
  - Bisphosphonates
    - Weekly oral alendronate
    - Weekly or monthly risedronate
    - Monthly oral or quarterly IV ibandronate
  - Calcitonin (Miacalcin by injection or nasal spray)
  - Selective estrogen receptor modulators (SERMs) (Evista)

- **Anabolic agents**
  - Parathyroid hormone (Forteo)

- **Estrogen therapy and hormone therapy**
  - (Indicated for prevention only)
Effects of Bisphosphonates

- ↓ Bone turnover
- ↑ BMD at lumbar spine and hip
- ↓ Risk of vertebral and hip fractures
- Sustained effects with continued treatment
- Best-studied class of agents used in osteoporosis
- Long-term safety record

Real-World Obstacles in the Management of Osteoporosis

- Insufficient rates of diagnosis
- Low awareness among physicians and patients of the imperative to treat
- Global challenge of adherence to therapy in chronic diseases, compromising effectiveness
- Poor adherence is two-fold problem
  - Low persistence: patient stops taking medication
  - Poor compliance: patient does not follow dosing instructions

Rationale for Less-Frequent and Easier-to-Follow Dosing Regimens

- For many clinicians, bisphosphonates are the standard of care in osteoporosis because of their rapid efficacy and long-term safety.
- Poor adherence to daily, weekly, and monthly regimens of oral bisphosphonates results in compromised effectiveness.
- A once-yearly IV bisphosphonate therapy can deliver real-world effectiveness by assuring adherence for the entire dosing interval.
First of Two Large Studies Putting Principle of Infrequent Zolendronic Acid to the Test: Zolendronic Acid in Healthy Post-Menopausal Women

7765 patients randomized

- 3889 received Z A
- 3876 received placebo

3248 completed study
3269 completed study

The final groups were then analyzed...

Black D et al.  
_N Engl J Med_  
2007;356:1809-1822
Incidence of Hip Fractures during the 3-Year Study Period

Hazard ratio, 0.59 (95% CI, 0.42–0.83)
P=0.002

Cumulative Incidence (%)

Month

No. at Risk
Zoledronic acid 3875 3807 3674 3553 3494 3387 3161
Placebo 3861 3806 3694 3577 3499 3397 3144

Percent Change over Time in Bone Mineral Density in Hip

Most Recent Study Published on Outcomes Following Hip Fracture

2127 patients randomized

- 1065 randomized to ZA
- 1062 randomized to placebo

770 patients finished study
746 patients finished study

The final groups were then analyzed...

Refractures Over Time: ZA versus Placebo

Risk of death over time with hip fracture: with and without subsequent treatment

Hazard ratio, 0.72 (95% CI, 0.56–0.93)
P=0.01

Cumulative Incidence (%)

Month

No. at Risk
Zoledronic acid | Placebo
---|---
1054 | 1057
1029 | 1028
987 | 993
943 | 945
806 | 804
674 | 681
507 | 511
348 | 364
237 | 236
144 | 149

The Problem of Bone Mineral Loss in Cancer Patients

- Widespread use of hormonal manipulation in treatment of cancer greatly exacerbates problem
  - Aromatase inhibitors (Arimidex, Femara, Aromasin) in the treatment of breast cancer
  - Lowering testosterone levels by drugs or surgery in the treatment of prostate cancer

- Prophylactic treatment with bisphosphononates can prevent this loss...
Changes from baseline bone mineral density (BMD) over time in the lumbar spine over time in patients treated for 36 months with anastrozole or tamoxifen {+/-} zoledronic acid

Use of Bisphosphonates with Androgen Deprivation


(Not available in US)
Intravenous Reclast for Osteoporosis

- Most aggressive approach currently available
- Avoids side effects of oral bisphosphonates
- Cost competitive
- Once-a-year dosing very convenient
- Insurance reimbursement in a state of flux but improving
- Available at my office
- Requires prescreening for medical issues (dental health, adequacy of kidney function and vitamin D stores) by physician
Dental Issues??

- Osteonecrosis of Jaw
- Seen almost exclusively in cancer patients (rare)
- Substrate is pre-existing dental and gum disease

We screen for this, hold therapy until dental work is finished
Emerging rare isolated case reports of the development of “insufficiency” fractures in post-menopausal women on long-term (> 8 years) Alendronate (Actonel)

- Not seen with other bisphosphonates
- Risk factors murky at present
- Because of compliance issues not many women have stayed on long-term oral bp’s
- Reclast will make it easier to stay on long-term therapy
- No reason yet not to take these drugs

Finally...the scoop on a brand new drug
Denosumab (Prolia)

- First in a new class of drugs to treat osteoporosis
- Whole new mechanism of action: inhibits development of osteoclasts (cells in bone responsible for loss of calcium)
- No jaw damage
- Monoclonal antibody with potential to suppress the normal immune system
  - Risk of infection
  - Risk of cancer
  - Drug too new to quantify real risk, if any
- Awaiting final FDA approval (likely)
- Be the first among your friends to have heard about this potentially blockbuster drug
Denosumab: Incidence of New Vertebral, Nonvertebral, and Hip Fractures

C Time to First Hip Fracture

Cumulative Incidence (%)

Placebo

Denosumab

No. at Risk
Placebo  3906  3799  3672  3538  3430  3311  3221
Denosumab  3902  3796  3676  3566  3477  3397  3311

Why did more placebo patients in the Reclast trial develop hip fractures?? Demonstrates risk of interpreting data...
Effect of Denosumab on BMD among men undergoing hormone deprivation as part of treatment for prostate cancer

Effect of Denosumab compared with that of Clodronate (Bisphosphonate available only in Europe) and Reclast

In this study in these patients only Prolia was able to raise BMD.
Conclusions

- Osteoporosis is a major public health issue with significant morbidity, mortality, and health care costs.
- Prevalence increasing as population ages.
- Effective therapies are available, but treatment and adherence patterns are suboptimal in the real-world setting.
- Better diagnosis and longer-acting therapies with few adverse events that address obstacles to adherence may improve real-world outcomes.

Young thin female athletes need to be aware of emerging literature on the “triad” check Vitamin D levels and consider bone mineral density measurement.
For more information....

- Contact us at....

- James J. Stark, MD, FACP at 397-4200...just down the driveway...

Or visit me on the web:

www.StarkOncology.com