Steroid-Induced Osteoporosis: "First, Do No Harm"

Karen E. Hansen, M.D.
Assistant Professor of Medicine
Rheumatology Section
University of WI

This CME program is sponsored by an unrestricted educational grant from Proctor & Gamble
Hippocrates, Father of Medicine

- *I will neither give deadly drug to anybody who asks for it, nor will I make a suggestion to this effect.*
Learning Objectives

1. Understand the prevalence of steroid use in clinical practice
2. Recall the adverse effects of steroids on bone
3. List treatment options for steroid induced osteoporosis
Who takes steroids?

- Over 5.5 million prescriptions issued by general practitioners in the United Kingdom in 1993
- An estimated 1% of adult Americans take steroids
- Among 65,786 patients in one large practice, continuous use of steroids was recorded in
  - 0.5% of people ages 12-94 years
  - 1.7% of women age > 55 years

Walsh, BMJ 1996; 313:344-6
Prevalence of CIO

- Most common form of drug-related osteoporosis
- Most common form of secondary osteoporosis in both men and women
- Between 30–50% of people taking steroids > 3 months experience fragility fractures
  - Vertebrae or ribs
  - Pelvis
  - Other sites

Tannenbaum, J Clin Endocrinol Metab 2002;87:4431-37
Johnson, Arch Int Med 1989;149:1069-1072
Emphysema and Asthma
CIO and Chronic Obstructive Pulmonary Disease

*P<0.05 vs. ISU or NSU; **P<0.005 vs ISU. McEvoy CE, et al, 1998.

<table>
<thead>
<tr>
<th></th>
<th>Systemic steroid users (n=125)</th>
<th>Never steroid users (n=117)</th>
<th>Inhaled steroid users (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At least one vertebral fracture</strong></td>
<td><img src="#" alt="Yellow bar" /></td>
<td><img src="#" alt="Yellow bar" /></td>
<td><img src="#" alt="Yellow bar" /></td>
</tr>
<tr>
<td><strong>Multiple vertebral fractures (&gt;2)</strong></td>
<td><img src="#" alt="Blue bar" /></td>
<td><img src="#" alt="Blue bar" /></td>
<td><img src="#" alt="Blue bar" /></td>
</tr>
<tr>
<td><strong>Severe vertebral fractures</strong></td>
<td><img src="#" alt="Red bar" /></td>
<td><img src="#" alt="Red bar" /></td>
<td><img src="#" alt="Red bar" /></td>
</tr>
</tbody>
</table>

*P<0.05 vs. ISU or NSU; **P<0.005 vs ISU. McEvoy CE, et al, 1998.
Rheumatoid Arthritis
Risk Factors for Bone Loss in RA

- 1110 patients with RA from five centers
- All patients enrolled in ARAMIS
- Questionnaire regarding fractures over past 13 years, and risk factors for fracture
- 50 variables investigated in univariate analysis, comparing 226 cases with fracture to the remaining controls
- Multivariate analysis with stepwise logistic regression to determine most important risk factors for fracture

Michel, J Rheumatol 1993;20:1666-9
Prednisone is the Most Important Risk Factor for Fracture in RA

- 7% increased risk of fracture per year of prednisone use
- Use for > 5 years was associated with a fracture rate of 33%

Michel, J Rheumatol 1993;20:1666-9
Is the Treatment Worse than the Disease?

- Obesity
- Diabetes
- Hypertension
- Mood Changes, Insomnia
- Cataracts, Glaucoma
- Infection
- Muscle Weakness
- Skin fragility
- Gastritis
- Avascular Necrosis

**Osteoporosis**

30–50 % of patients on chronic steroid therapy sustain osteoporotic fractures
Osteoporosis is not a benign disease, particularly when compounded with another chronic disease.
70 Year-Old Woman With Newly Diagnosed Temporal Arteritis
Complications of Osteoporosis

- Pain
- Height loss
- Kyphosis
- Activity limitations
- Constipation and other abdominal symptoms
- Psychological symptoms
- Another fracture
- Restrictive lung disease
The Consequences of Fracture

- Morbidity: pain, fear, limited mobility
- Mortality: one in four with hip fracture die within the following year
- Money: the financial cost of treating osteoporotic fractures is estimated at $10-15 billion annually

NIH Consensus Statement on Osteoporosis, 2000
http://consensus.nih.gov/cons/111/111_statement.htm#introduction
Gold, Bone 1996;18(S3):185-189
Mechanisms by Which Steroids Harm Bone
Cardinal Histologic Features of Steroid-Induced Osteoporosis

- Decreased bone formation rate
- Decreased trabecular wall thickness
- Decreased osteoblast function
- In situ death of portions of bone

Manolagas, JBMR 1999;14:1061-1066
Bone Remodeling Cycle

Normal

With Steroids

1  Osteoclast
2  Osteoblast
3  Osteoblast
4  Osteoclast

1  Osteoclast
2  Osteoblast
3  Decreased Osteoblast number
4  Premature osteoblast apoptosis

Manolagas SC. J BMR 1999; 14:1063.

Incomplete repair of bone
Treatment with steroids causes:

- three fold increase in osteoblast apoptosis
- dramatically increased osteocyte apoptosis
- early increase in osteoclastic bone resorption
Other Potential Contributing Factors that Lead to Bone Loss with Steroids

1. Sex Steroid Deficiency
2. Defective vitamin D metabolism with secondary hyperparathyroidism
3. Hypercalciuria
4. Underlying disease
5. Immobility related to underlying disease

Adler, Arch Intern Med 2003;163:2619-2624
Rapid BMD Decline Due to Glucocorticoids in Rheumatoid Arthritis

% Change Lumbar Trabecular Bone Mineral Density (BMD)

Placebo (n = 17)

Prednisone (n = 13)

Cessation of steroids

Fracture Risk with Steroids

- Retrospective cohort study using UK General Practice Research Database
- Controls matched to steroid users for age, gender
- 244,235 steroid users and 244,235 controls
- Mean age 57 years, 59% female
- Most frequent indication for steroids: respiratory disease (40%)

Van Staa TP, JBMR 2000;15:993-1000
Fracture Risk During Steroid Therapy

Van Staa TP, JBMR 2000;15:993-1000
Relative Risk of Fracture after Cessation of Steroids

Suggests osteoblast recovery
Fracture Risk and Dose of Corticosteroids

Relative risk of fracture compared with control

- Hip fracture
- Vertebral fracture

Fracture Rates in Subjects with and without Steroid Use

Overview of GIOP

- Initial rapid bone loss within the first months
- Trabecular (spine) bone preferentially affected
- Bone loss may partially reverse with cessation of steroid
Who is at Risk for GIOP?

- Both men and women

- Older adults more likely to fracture since baseline bone mass may be closer to fracture threshold

- Underlying steroid-requiring disease may also increase bone loss and/or fracture risk
Physician Perception Regarding Toxicity: rank the importance of 11 side effects of steroids

Buckley, J Rheumatol 1998;25:2195-202
Do Physicians Treat CIO?

- Harrington: 30%
- Walsh: 10%
- Peat: 5%
Initial Clinical Work-Up of Steroid Induced Osteoporosis

Risk factors for bone loss

Physical exam

Laboratories

Bone density test
Guidelines for BMD Measurement

- Baseline BMD prior to/within 6 months of initiating therapy
- Follow-up every 6 months until bone mass shows no decline, then annually thereafter
- Be sure to measure spine bone mass, since loss of trabecular (vertebral) bone is more rapid

ISCD Guidelines, J Clin Densitom
Diagnosis of CIO: Biochemical Assessment

- 25-hydroxyvitamin D
- Intact PTH
- 24-hour urinary calcium
- Testosterone, FSH, LH
- Complete blood count
- creatinine
- calcium
- alkaline phosphatase
- liver enzyme
- phosphorus
Treatment
Management of CIO: Goals of Treatment

Prevent bone loss

Reduce fracture risk

Alleviate pain associated with existing fracture(s)

Maintain/increase muscle strength

Initiate lifestyle changes as needed
Meta-Analysis of Randomized, Controlled Trials Using Vitamin D

- $1^0$: Change in Lumbar Spine BMD at 12 months
- $2^0$: Fracture Rates

- Pooled analysis of vitamin D and calcium versus no therapy or calcium only
- Pooled analysis of vitamin D with/without calcium versus bisphosphonate / calcitonin / fluoride

Amin, Arthritis Rheum 1999;42(8):1740-1751
Vitamin D versus Calcium or No therapy

- 11 studies comprising 560 subjects
- 9 compared vitamin D with calcium to calcium only (n=5) or no therapy (n=4)
- Vitamin D doses range from 400 IU daily to 100,000 IU weekly

Amin, Arthritis Rheum 1999;42(8):1740-1751
Vitamin D versus Calcium or No therapy

- Pooled effect size of vitamin D plus calcium was 0.60 (CI 0.34-0.85) with a 3.2% increase in spine BMD
- Pooled effect size of vitamin D alone was 0.57 (CI 0.36-0.78)
- Fracture rates did not reach statistical significance, pooled effect size –0.89 (p=0.08)

Amin, Arthritis Rheum 1999;42(8):1740-1751
Meta-Analysis of Vitamin D for GIOP
Comparisons to No Rx/Calcium

Warady 1994
Adachi 1996
Buckley 1996
Talalaj 1996
Bijlsma 1988
Sambrook 1993
Emkey 1994
Sambrook 1997
Reginster 1999
Pooled Effect

Hormone Replacement Therapy
HRT Increases Spine Bone Density Among Steroid Users

- 200 women with RA, including 21% on steroids
- Mean daily prednisone dose of ~7 mg
- Randomized to estradiol 50 μg patch or calcium 400 mg
- BMD of spine and hip at baseline, 12 and 24 months
- High withdrawal rate during study (26.5%)
- Steroid group analyzed separately, lower body weight and baseline bone mass in steroid users (p<0.05)

Estrogen for GIOP Prevention

No fractures in either group

HRT
Calcium

(n = 18)
(n = 16)

(n = 17)
(n = 15)

P<0.05

P=ns

% Change
Lumbar BMD

% Change
Femoral BMD

Calcium

Months

Hall, Arthritis Rheum 1994;37:1499–1505
Regulate Myostatin...
And Take the Brakes Off Muscle Growth!

Pop 'Em Out Muscles
See Swoleheads. Look Fat & Leap!

How to Cheat on Your Diet and Win!

Expose
Best, Cheats Support Companies Play on Men

5 Ways to Go-Stick Your Bench Press

The Pro-Steroid Roundtable
Testosterone Therapy

- 15 asthmatic men on long-term steroids with low serum testosterone
- Randomized to 12 months of IM testosterone 250 mg monthly or placebo
- Cross over to opposite therapy at 12 months, with 4 month “wash out” for those initially on testosterone
- One gram calcium for all subjects
- BMD every 4 months

Reid, Arch Intern Med 1996;156:1173-77
Testosterone Replacement Therapy in the Treatment of CIO

Changes in lumbar spine BMD (%) at 1 year

-5.0
-2.5
0.0
2.5
5.0

Testosterone
Control

$p=0.005$ vs. baseline BMD; $p=0.05$ between-group difference

Reid, Arch Intern Med 1996;156:1173-77
Calcitonin
A Comparison of Calcium, Calcitriol, and Calcitonin

- 103 patients starting long-term steroids randomized to one year of:
  - Calcium, calcitriol, and calcitonin nasal spray 400 IU
  - Calcium and calcitriol 0.5-1.0 mg
  - Calcium 1,000 mg

- BMD every 4 months
- Spine radiographs at baseline, 1 and 2 years

Sambrook, NEJM 1993;328:1747
Calcitonin Maintains Spine Bone Mass

P<0.05 for difference between groups 1 and 2

P ns for difference between groups 1 and 2

Calcium, Calcitriol, Calcitonin
Calcium, Calcitriol
Calcium
Nasal Calcitonin Prevents Steroid Induced OP

- 31 subjects with PMR initiating prednisone > 10 mg daily
- Randomized to nasal calcitonin 100 IU or placebo nasal spray
- Calcium 800 mg daily
- Randomization stratified for age, sex, initial BMD, and initial steroid dose
- Primary outcome by ITT analysis: change in spine BMD at 12 months

Adachi, Brit J Rheumatol 1997;36:255-259
Calcitonin Prevents Bone Loss

Adachi, Brit J Rheumatol 1997;36:255
Bisphosphonates
Alendronate for the Prevention and Treatment of Steroid Induced OP

- 477 patients taking ≥ 7.5 mg prednisone daily
- Randomized to placebo or 5 or 10 mg of alendronate
- All subjects were given calcium 800-1000 mg and vitamin D 250-500 IU daily
- 48 week study
- Radiographs and BMD at baseline and 48 weeks

Efficacy of Alendronate in Increasing BMD

* $P < 0.001$ vs. control; ** $P < 0.01$ vs. control; † $P < 0.001$ vs. baseline, ‡ $P < 0.01$ vs. baseline; Saag KG, et al, 1998.
Efficacy of Alendronate: Two Years Follow-Up

Change in BMD from baseline (%)

- Lumbar spine
- Femoral neck
- Trochanter

*P<0.001 vs. control; **P<0.01 vs. control; †P<0.05 vs. control. Saag KG, et al, 1998.
Reduction in Fractures with Alendronate

New Fractures

48 weeks

Percent

0 0.5 1 1.5 2 2.5 3 3.5 4

Aledronate
Placebo

Risedronate Prevents Steroid Induced Bone Loss

- 228 patients
- Ages 18-85 years old
- Onset of $\geq 7.5$ mg of prednisone daily within past 3 months, with expected duration of $\geq 12$ months
- Double-blind, placebo-controlled trial using 5 mg risedronate daily
- Calcium 500 mg daily
- Vitamin D $\leq 500$ IU daily for those with deficiency

Risedronate Prevents Lumbar Spine Bone Loss

p < 0.05 vs (*) baseline and (†) control

6 % have vertebral fracture

17 % have vertebral fracture

Risedronate Prevents Femoral Neck Bone Loss

p < 0.05 vs (*) baseline and (†) control

Risedronate Increases Bone Mass in Subjects Already on Long-Term Steroids

- 290 men and women ages 18-85 years
- Prednisone ≥ 7.5 mg daily for ≥ 6 months

- Randomized to
  - risedronate 2.5 or 5 mg daily
  - placebo

- Calcium 1 gram, vitamin D 500 IU daily
- 12 month study with primary endpoint: change in lumbar spine bone density

Reid, JBMR 2000;15:1006-1013
Risedronate Increases BMD in Patients on Long-term Glucocorticoid Therapy

* p ≤ 0.05 vs baseline; † p ≤ 0.05 vs control

Risedronate Reduces Fracture Rates in Patients taking Glucocorticoid Therapy

Incidence, one year (%)

Control  Risedronate 5 mg

Patients Continuing Treatment

Patients Initiating Treatment

Combined

Absolute risk reduction = 11% (combined)
All patients were taking >7.5 mg oral prednisone or equivalent
Effect of Risedronate on Vertebral Fracture Rates

## Bisphosphonates in the Management of CIO: A Meta-Analysis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of pooled trials</th>
<th>Change in lumbar spine BMD (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>18</td>
<td>+1.96</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>11</td>
<td>+2.11</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>18</td>
<td>+5.31†</td>
</tr>
</tbody>
</table>

*Compared with no treatment or with calcium alone
†\(P=0.0001\) compared with calcitonin or vitamin D
FDA Approved Treatments for Steroid Induced Osteoporosis

Alendronate (Fosamax)

Risedronate (Actonel)
Intravenous Ibandronate

- 115 men and women
- Lumbar spine T-score below -2.5
- Steroid therapy continuously for 2 years
- Steroid dose ≥ 7.5 mg daily

Ringe, Osteoporos Int 2003;14:801
Intravenous Ibandronate

- Open-label single center trial
- All patients received calcium 500 mg daily
- Patient pairs, matched for baseline characteristics, were assigned to
  - Daily oral alfacalcidol 1 mcg
  - IV ibandronate 2 mg every 3 months

Ringe, Osteoporos Int 2003;14:801
Lumbar Bone Mass over 36 Months

Mean Change, %

Ibandronate
Alfacalcidol

p<0.001

Months
Ibandronate Reduces Rate of New Compression Fracture

p=0.043, 62% reduction

Percent with New Vertebral Fracture

36 Months

alfacalcidol  ibandronate
Cyclical Etidronate and Prevention of Corticosteroid-Induced Bone Loss

Roux et al (N=117) Adachi et al (N=141)*

*P<0.05 between-group difference

Etidronate: Pooled Results from Three Randomized Trials

Pamidronate

- 32 patients beginning steroids ≥ 10 mg daily for ≥ 3 months
- Randomized to one of three groups
  - Pamidronate 90 mg iv once plus calcium
  - Pamidronate 90 mg iv then 30 mg q 3 months plus calcium
  - Calcium 800 mg once daily

  - 9 patients per group with similar baseline characteristics

Boutsen, JBMR 2001;16:104-112
Change in Bone Mass at 12 Months

no new fractures in either group with radiographs at baseline and 12 months
Parathyroid Hormone for Steroid Induced Osteoporosis

- 51 postmenopausal women with T-score < -2.5
- All taking HRT for at least one year
- All taking prednisone for the past year
- Randomized to PTH or no therapy
- All given calcium 1500 mg daily
- All given 2 multivitamins daily

Lane, J Clin Invest 1998;102:1627-1633
The Premenopausal Woman and Bisphosphonates

- Bisphosphonates cross the placenta in rats
- Bisphosphonates given to pregnant rats decreased post-implantation survival, body weight, and fetal ossification
- Bisphosphonates caused prolonged hypocalcemia and protracted parturition
- Bisphosphonates given to pregnant rabbits had no adverse outcomes
The Premenopausal Woman and Bisphosphonates

- The terminal half life of alendronate in humans is > 10 years
- Mobilization of calcium from the maternal skeleton is crucial for fetal development
- However, a limited number of pregnancies reported to Merck in patients on alendronate show no adverse effects
- Bisphosphonates are considered “Pregnancy Category C
- Use of bisphosphonates should be considered carefully in pre-menopausal women who may in future become pregnant
Time Points to Begin GIOP Rx

• Primary Prevention
  At initiation of glucocorticoid therapy

• Secondary Prevention
  After detection of low BMD, but before fractures

• Tertiary Prevention
  After osteoporosis insufficiency fractures
ACR Task Force on Osteoporosis: Initiating Long-Term (>6 months) Corticosteroid Therapy

- Baseline BMD
- Calcium, vitamin D supplementation
- Patient education
- Modify other risk factors

T score ≤ -1
- Initiate bisphosphonates
- 2nd line- consider calcitonin

T score > -1

6-12 months follow-up:
- Repeat BMD
- Decrease >5%: change/add medication
- Stable or increased: no change in therapy

If Hypogonadal, Consider HRT

Calcium and Vitamin D
Consider bisphosphonate to prevent OP
Repeat DXA in 6-12 months

American College of Rheumatology Task Force on Osteoporosis Guidelines, 2001
What shall I do if the duration of steroids is uncertain?

- The US Preventive Task Force recommends screening DXA for all women > 65 years old, and for women between age 60-65 who have low body weight or do not take estrogens.
- The ISCD recommends that men receive a screening DXA at age 70.
- A DXA will be paid for if a patient is taking steroids, has suffered a low-trauma fracture, or has a dorsal kyphosis.
First, Do No Harm

Any patient on steroids presents an opportunity to perform primary, secondary or tertiary treatment of steroid induced bone loss.
Calcium Plus Vitamin D₃

The Effects of Inhaled and Oral Steroids on Bone Mass in Asthmatics

<table>
<thead>
<tr>
<th></th>
<th>Lumbar Spine BMD</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose Inhaled Steroid</td>
<td>0.916</td>
<td>0.914 g</td>
</tr>
<tr>
<td>High Dose Inhaled Steroid</td>
<td>0.848 g</td>
<td>0.835 g</td>
</tr>
<tr>
<td>&lt; 2.5 Steroid Tapers yearly</td>
<td>0.917</td>
<td>0.925</td>
</tr>
<tr>
<td>&gt; 2.5 Steroid Tapers yearly</td>
<td>0.844</td>
<td>0.802</td>
</tr>
</tbody>
</table>

Matsumoto, Chest 2001;120:1468-1473