Asthma and Osteoporosis and Osteopenia

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Inhaled Corticosteroids:
Is Osteoporosis a Concern?

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Learning Objectives

- Why are subjects with COPD or asthma at risk of bone loss.
- How do we define osteoporosis and what are the known risk factors.
- What are the treatments of osteoporosis.
- How should the risk of osteoporosis influence treatment strategies for respiratory disease.
Learning Objectives

• Factors influencing bone density in allergic disease and naturally.
• Inhaled corticosteroids and growth in children and osteoporosis in adults. What are the factors involved?
• Management of bone disorders in asthma and allied disorders.
Potential Conflicts of Interest

- Speaker Bureau: AstraZeneca
- Stock: < $20,000 AstraZeneca, ImmunoGen
- Research Paid to University: Forest, Boehringer Ingelheim, Genentech, Merck
- Research Paid to Practice with < $10,000 personal: Genentech
- Legal: Case review < $5,000 not related
- Journal: Allergy Watch, JACI
- Organizations: AMA, ACP, ACCP, AAAAI
Definition of 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

• Decrease of T score by $> 2.5$ Standard Deviations ($T$ score compares individual to idealized young subject or peak bone mass)
Low-power scanning electron micrograph of trabecular bone

Epidemiology of Osteoporosis

• 40% of white women > 45 years of age
• 15% of white men > 50 years of age
• 1.5 million fractures/year in US
  – 1.7 million hip fractures/year worldwide 1990
  – 6.3 million hip fracture/year worldwide 2050
• One third of subjects with hip fracture become totally dependent, 15-20% mortality within one year
Risk Factors for Osteoporosis

- Age > 60 years
- Female gender
- Caucasian or Asian ethnicity
- Diet deficient in calcium
- Low body mass
- Minimal weight bearing exercise
Risk Factors for Osteoporosis

- Positive family history
- Life style issues (smoking, EtOH)
- Infertility
- Menopause
- Endocrine disorders
Dual Energy X-Ray Absorptiometry (DEXA)

- Preferred method of bone density assay
  - least cost
  - most accurate
  - less radiation exposure

- Precision of current instruments 1-3%
  - change > 2.8 X precision, 95% confidence int

- Precision affected by marrow fat (underest) and anatomy of spine (overest)
Bone Loss and COPD

- Severe COPD (mean FEV1 31%)
- < 50 years of age
- No other cause of bone loss, adequate calcium and recommended Vitamin D ingestion
- 62 patients studied: 68% had osteoporosis or osteopenia; 29% had osteopenia/38% osteoporosis
- Glucocorticoid use did not explain increased occurrence

Respir Med 2006
Inhaled Corticosteroid Use and Bone Mineral Density

- Progressive annual BMD loss as dose inhaled TCA dose increased from 400 mcg to >800 mcg/d X 3 yr (premenopausal Female)
- Seven studies reviewed in Cochrane analysis showed no effect on BMD with ICS (primarily < 60 years of age, M>F 2:1, duration months up to a year)

NEJM 2001;345:941-47
Conchrane Database 2002
Inhaled Corticosteroid Use and Bone Mineral Density

- 196 adults with mild asthma, 119 women, in general practice setting
  - 20-40 years of age
  - Minimal or no prior use of nasal, systemic or topical dermal corticosteroids

- Cumulative dose of ICS negatively correlated with BMD (Dose X Duration)
  - Decrease of 0.16 SD with doubling ICS

Lancet 2000;335:1399-403
Inhaled Corticosteroid Use and Bone Mineral Density

• One in three asthmatics in UK receive ICS (majority BDP in current study)
  – Approximately 30% receive more than 800 micrograms per day

• 2000 micrograms per day for 7 years or 1000 micrograms per day for 14 years would result in a decrease of 1 SD in BMD (Double the risk of fracture)

Lancet 2000;335:1399-403
Lumbar Spine BMD Z-Score

![Graph showing the relationship between current dose of inhaled steroid (mg/d) and BMD Z-score (adjusted mean ± 2SEM).](image)
Femoral Neck BMD Z-Scores In Subpopulations

Resp Crit Care Med 1999;159:1183
Dual Energy X-Ray Absorptiometry (DEXA)

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Bone Densitometry

- Desk top low-dose X-ray using phosphor technology storage
  - $40/ test
  - Primarily cortical bone
- Ultrasound devices
  - Heel, calcaneous bone
  - Accuracy improving
Myths About Corticosteroid Therapy and Osteoporosis

- “low dose” systemic Rx is safe
- Every other day systemic Rx is safe
- Bone effects require long term Rx
- Topical CS (ICS) Rx has no systemic side effects
Truths About Corticosteroid Therapy and Osteoporosis

- Inhaled corticosteroid Rx is safer than systemic
- Some individuals are at greater risk than others (risk factors for osteoporosis may help to identify some subjects at risk)
- Various ICS differ in effects on bone but safest is unknown
Stratify Risk of Osteoporosis

• Low risk
  – ICS < 0.8-1 mg/day for adults
  – ICS < 0.4-0.5 mg/day for children
  – Include nasal ICS
  – No other risk factors other than ICS

Ledford, JACI 1998;102:353
Recommendations for Low Risk Subjects

- Maintain adequate calcium intake
- Encourage exercise, particularly weight bearing
- Consider Vitamin D supplementation
- Discourage cigarette smoking and significant EtOH
- Ensure euthyroid, consider measuring TSH
Daily Calcium Recommendations

- 800 mg/day for 1-10 years of age
- 1200 mg/day for 11-12 years of age
- 1200 mg/day for pregnancy and lactation
- 1000 mg/day for adults > 24 years of age
- 1500 mg/day for postmenopausal women
Vitamin D Recommendations

- Levels at upper limits of normal recommended for individuals at risk (>800 units /day, achieve 75 nmol/L 25OHVitD or > 40-60 ng/ml)
- Pharmacologic dosages controversial
- 1,25 (OH)2 Vitamin D controversial
- Maximum “safe” dose 2000 IU/day
Stratify Risk of Osteoporosis

• Moderate risk
  – ICS > 0.8-1.0 mg/day > 6 weeks for adults
  – ICS > 0.4-0.5 mg/day > 6 weeks for children
  – Include nasal ICS
  – May have one other risk factor

Ledford, JACI 1998;102:353
Recommendations for Moderate Risk Subjects

- Follow low risk recommendations
- Measure annual height
- Consider estrogen replacement or estrogen receptor modulator if peri/postmenopausal
- Consider bone densitometry
- Consider TSH
Stratify Risk of Osteoporosis

• High risk
  – Chronic systemic CS (daily or qod)
  – Systemic CS > 4 weeks continuously
  – Systemic CS bursts > 4 per 12 months
  – >2 other risk factors with chronic, moderate to high dose ICS
Recommendations for High Risk Subjects

- Follow low risk and moderate risk recommendations
- 24 hour urine for calcium and creatinine if receiving systemic CS therapy
- Bone densitometry
- Consider referral or detailed medical evaluation

Ledford, JACI 1998;102:353
Calculation of Risk of Fracture

- [http://www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/)
- 12 questions including bone densitometry
- Provides calculation for 10 year hip fracture or any osteoporotic fracture
- If 10 year hip fracture risk $\geq 3\%$ or other osteoporotic fracture $\geq 20\%$, treatment suggested
- Only will accept 40 years to 90 years for age
Medical Evaluation of Osteoporosis

- Serum calcium, creatinine, phosphorus, alkaline phosphatase, transaminases
- TSH
- Estradiol level if premenopausal with irregular menses
- Free testosterone in men
- 24 hour urine for calcium and creatinine
- 25-OH Vitamin D and PTH level
Therapies of Osteoporosis

- Thiazide diuretics (hypercalciuric)
- Hormone replacement therapy
- Bisphosphonates (alendronate 70mg/wk, ibandronate 150mg/mo or 3mg/iv q 3 mo, risedronate 35mg/wk, zoledronic acid 5mg/iv once a year)
- Calcitonin (nasal spray and injection)
- Selective estrogen receptor modulators (raloxifene)
Other Therapies of Osteoporosis

- Testosterone
- Pharmacologic dosages of Vitamin D
- Teriparatide
- Growth hormone
- Fluoride
- 1,25 (OH)2 Vitamin D
- Denosumab (monoclonal against RANK ligand, a stimulant of osteoclasts)
Bisphosphonates, estrogen, parathyroid hormone, raloxifene prevent vertebral fractures
- Evidence for calcitonin was fair
- Evidence for zoledronic acid was fair
- Etidronate increased risk of esophageal ulcer

Data not sufficient to determine relative efficacy and safety
Teriparatide or Alendronate in Corticosteroid Induced Osteoporosis
NEJM 2007;357:2028

- 428 M/F with osteoporosis and prior prednisone 5 mg for 90 days, Rx for 18 mo
- BMD Spine
  - Teriparatide 7.2% increase
  - Alendronate 3.4% increase
- Vertebral Fx
  - Teriparatide 0.6%
  - Alendronate 6.1%
Teriparatide or Alendronate in Corticosteroid Induced Osteoporosis

NEJM 2007;357:2028

- Teriparatide with transient hypercalcemia and some local reaction
- Effects of teriparatide may be blunted by prior bisphosphonate Rx due to need for osteoclast activity
  - High risk patients should be treated with teriparatide initially
Issues Related to Treatment

- Osteonecrosis with bisphosphonates
  - 865 cases to date, 26 with oral use
- ?Duration of Rx?
- DVT with estrogen Rxs including SERMs
- Ureterolithiasis with calcium, Vit D
- Sarcoma with teriparatide
- Cancer, vascular disease, cholestasis with testosterone
- Esophageal ulceration with bisphosphonates
Osteoporosis Therapeutic Comparisons

![Graph showing increase in bone density and reduction in bone resorption for different treatments.]

- **Calcitonin**
  - Increase in bone density: 10%
  - Reduction in bone resorption: 5%

- **Estrogen**
  - Increase in bone density: 60%
  - Reduction in bone resorption: 40%

- **Alendronate**
  - Increase in bone density: 30%
  - Reduction in bone resorption: 30%

- **Fluoride**
  - Increase in bone density: 20%
  - Reduction in bone resorption: 20%
Monitoring of Treatment

- Repeat densitometry of limited value due to minimal increase in early treatment with antiresorptive agents but long term benefit of decreased fractures
  - May be helpful in higher risk or use of agents which increase bone (teriparatide)
Strategies to Minimize Osteoporosis

- Discontinue systemic CS
- Lower dose of ICS
- Use ICS sparing agent (IT, LTM, Omalizumab)
- Exclude other Dxs which complicate or emulate asthma
- Increase awareness of osteoporosis
- Recognize, diagnose and Rx osteoporosis