Welcome to UVM ECHO: Corticosteroids and Osteoporosis

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Liz Cote
Introduction to ZOOM for ECHO

• Please mute microphone when not speaking
• Please use camera as much as possible
• Test both audio & video before joining
• Communicate clearly during session:
  • Can use “raise hand” feature to comment
  • Speak clearly
  • Use chat function for technical issues
• Didactic session will be recorded for review or if you miss a session
• RECORDING OF SESSION TO BEGIN
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• Interest Disclosures:
  • None
Agenda

• Objectives
• Summary from last session (2 min)
• Didactic Presentation (20 min)
• Case presentation
  • Clarifying questions
    • Participants first – then faculty panel
• Discussion of case
  • Concluding with the cohort’s recommendations
• Summary
• Closing Announcements
Objectives

• Review osteoporosis work up (as it pertains to medications)

• Discuss corticosteroid effect on bone

• Review osteoporosis work up and treatment in patients taking corticoid steroids
<table>
<thead>
<tr>
<th>Category</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>−1.0 or above</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)(^{a})</td>
<td>Between −1.0 and −2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>−2.5 or below</td>
</tr>
</tbody>
</table>

\(^{a}\) Fracture rates within this category vary widely. The category of “osteopenia” is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.
In addition to the WHO bone mineral density criteria, these may also be used to diagnose osteoporosis...

<table>
<thead>
<tr>
<th></th>
<th>2020 AACE Diagnosis of Osteoporosis in Postmenopausal Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>T-score $-2.5$ or below in the lumbar spine, femoral neck, total proximal femur, or $1/3$ radius</td>
</tr>
<tr>
<td>2.</td>
<td>Low-trauma spine or hip fracture (<em>regardless of bone mineral density</em>)</td>
</tr>
<tr>
<td>3.</td>
<td>T-score between $-1.0$ and $-2.5$ and a fragility fracture of proximal humerus, pelvis, or distal forearm</td>
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<tr>
<td>4.</td>
<td>T-score between $-1.0$ and $-2.5$ and high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds</td>
</tr>
</tbody>
</table>

Abbreviations: AACE = American Association of Clinical Endocrinologists; FRAX® = fracture risk assessment tool; TBS = trabecular bone score.
Table 7
Assessment for Fracture Risk and Osteoporosis in Postmenopausal Women

- Medical history and physical examination to identify:
  - Prior fracture without major trauma (other than fingers, toes, skull) after age 50 years
  - Clinical risk factors for osteoporosis
    - Age ≥65 years
    - Low body weight (<57.6 kg [127 lb])
    - Smoking
    - Early menopause
    - Excessive alcohol intake (more than 3 drinks daily)

- **Secondary osteoporosis**

- Height loss of kyphosis
- Risk factors for falling (see Table 9)
- Patient’s reliability, understanding, and willingness to accept interventions
- Lateral spine imaging with standard radiography or vertebral fracture assessment in patients with unexplained height loss, self-reported but undocumented prior spine fractures, or glucocorticoid therapy equivalent to ≥5 mg of prednisone per day for 3 months or more
- Bone mineral density measurements in those at increased risk for osteoporosis and fractures and willing to consider pharmacologic treatment if low bone mass is documented:
  - All women 65 years of age or older
  - Younger postmenopausal women
    - With a history of fracture(s) without major trauma
    - Starting or taking long-term systemic glucocorticoid therapy
    - With radiographic osteopenia
    - With clinical risk factors for osteoporosis (low body weight, cigarette smoking, family history of spine or hip fractures, early menopause, or secondary osteoporosis)
- In women who are candidates for pharmacologic therapy, laboratory evaluation to identify coexisting conditions that may contribute to bone loss or interfere with therapy (or both).
To identify coexisting medical conditions that cause or contribute to bone loss, an appropriate medical evaluation is indicated for all women with postmenopausal osteoporosis. Some causes of secondary osteoporosis include the following:

<table>
<thead>
<tr>
<th>Endocrine or metabolic causes</th>
<th>Nutritional/Other conditions</th>
<th>Drugs</th>
<th>Disorders of collagen metabolism</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>Alimentation</td>
<td>Anti-estrogen drugs</td>
<td>Ehlers-Danlos syndrome</td>
<td>AIDS/HIV</td>
</tr>
<tr>
<td>Diabetes mellitus Type 1/2</td>
<td>Anorexia nervosa</td>
<td>Aromatase inhibitors</td>
<td>Homocystinuria due to cystathionine deficiency</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>Calcium deficiency</td>
<td>Chemotherapy/Immunosuppressants</td>
<td>Marfan syndrome</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>Chronic liver disease</td>
<td>Depo-Provera</td>
<td>Osteogenesis imperfect</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Malabsorption syndromes/malnutrition (including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass)</td>
<td>Glucocorticoids</td>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Total parenteral nutrition</td>
<td>Gonadotropin releasing hormone agents</td>
<td></td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Vitamin D deficiency</td>
<td>Heparin</td>
<td></td>
<td>Immobilization</td>
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<tr>
<td>Porphyria</td>
<td></td>
<td>Lithium</td>
<td></td>
<td>Major depression</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>Proton pump inhibitors</td>
<td></td>
<td>Myeloma and some cancers</td>
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<tr>
<td></td>
<td></td>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
<td>Organ transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiazolidinediones</td>
<td></td>
<td>Renal insufficiency/failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid hormone (in supraphysiological doses)</td>
<td></td>
<td>Renal tubular acidosis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systemic mastocytosis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thalassemia</td>
</tr>
</tbody>
</table>

Note: This is table 11 from the AACE guidelines.

Corticosteroids
Epidemiology

- Glucocorticoid induced osteoporosis is the most common cause of secondary osteoporosis

- NHANES data from 1999-2008
  - 1.2% of responders reported use of a glucocorticoid
  - 30% of users reported use for >5 years
  - Bisphosphonates were reported in 8.6% of these patients
• GCs adversely affect 3 phases of bone remodeling
  • Decreased osteoblastogenesis
  • Increased apoptosis
  • Increased osteoclastogenesis

Glucocorticoid-Induced Osteoporosis. NEJM, 2018
When to Worry? Right away!!!

• The loss of bone mineral density is bi-phasic; it occurs rapidly (6 to 12% loss) within the first year and more slowly (approximately 3% loss yearly) thereafter

• The risk of fracture escalates by as much as 75% within the first 3 months after initiation of therapy, typically before there is substantial decline in BMD

Bone Loss in Response to Long-Term Glucocorticoid therapy.
Bone Miner 1990.
Low-Dose Prednisone Induces Rapid Reversible Axial Bone Loss in Patients with Rheumatoid Arthritis A Randomized, Controlled Study

- The greatest risk of fractures is noted during the first 3-6 months after beginning steroid therapy
- There is reversibility of this process

Laan RF. Ann Intern Med 1993
Risk of fracture and dose of steroids

- Relative risk of vertebral fracture doubles among patients who receive 2.5 to 7.5 mg of prednisolone daily
- Vertebral fractures are the most common fractures associated with glucocorticoids

Van Staa TP et al. *J Bone Miner Res* 2000
Additional Steroid Groups

• Inflammatory Diseases:
  • Complicated by the effect of the disease itself on bone loss
  • Case-control study in RA patients with/without pred- increase in fractures in the pred group

• Adrenal Insufficiency:
  • Controversial
  • Cross-sectional studies show lower BMD in patient’s with Addison’s disease
  • No fracture data

• Inhaled Glucocorticoids
  • Data is inconsistent
Initial Fracture Risk Assessment

• All adults taking prednisone at a dose of >2.5 mg/day for > 3 months should be evaluated within 6 months of starting therapy

<table>
<thead>
<tr>
<th>Risk Factors Included in FRAX®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of residence</td>
</tr>
<tr>
<td>Ethnicity (U.S. models only—white, black, Hispanic, and Asian)</td>
</tr>
<tr>
<td>Age (accepts ages between 40 and 90 years)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Weight (kg) and height (cm) used to calculate body mass index; a converter from English to metric units is provided within the FRAX® tool</td>
</tr>
<tr>
<td>Family history (either parent with a hip fracture)</td>
</tr>
<tr>
<td>Personal history of fragility fracture, including radiographic vertebral fracture</td>
</tr>
<tr>
<td><strong>Glucocorticoid use (prednisolone 5 mg daily or more for 3 months or longer, current or past)</strong></td>
</tr>
<tr>
<td>Rheumatoid arthritis (confirmed diagnosis)</td>
</tr>
<tr>
<td>Smoking (current)</td>
</tr>
<tr>
<td>Alcohol use (2 or more units daily)</td>
</tr>
<tr>
<td>Secondary osteoporosis (specifically mentioned are type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease)</td>
</tr>
<tr>
<td>BMD. Femoral neck BMD should be entered. The model also works without BMD.</td>
</tr>
</tbody>
</table>

Abbreviations: BMD = bone mineral density; FRAX® = fracture risk assessment tool.

“Because the effects of causes of secondary osteoporosis on fracture risk are assumed to be mediated through changes in BMD, a “yes” answer to this question does not change fracture risk if BMD is entered into the risk tool.

How do we identify patients at risk?

• BMD testing is recommended for patients age >40
• Calculate a FRAX score
  • Glucocorticoid use—reflexes the risk associated with pred at doses of 2.5 to 7.5 mg/day
  • Patients who receive >7.5 mg of pred/daily- the FRAX-predicted risk of major osteoporotic fracture should be increased by 15% and the risk of hip fracture increased by 20%
Limitations to this screening process...

- Tools to estimate the risk of fracture among patients who are younger than 40 years of age are lacking.

- Fracture risk is likely underestimated in patients on high dose prednisone (> 30 mg/day or cumulative doses > 5 g/year).

- The FRAX score calculation uses bone mineral density at the hip and glucocorticoid have the greatest negative effect on trabecular bone.
Initial Pharmacologic Treatment

All adults taking prednisone at a dose of > 2.5 mg/day at >3 months

Arthritis Rheumatol. 2017Aug
Pharmacologic treatment to prevent glucocorticoid-induced fracture guidelines

- Any patient with a previous osteoporotic fracture who is receiving glucocorticoids (>2.5 mg/day)
- Men >50 years old and postmenopausal women receiving glucocorticoids and have BMD T-score <-2.5 at either the spine or femoral neck
- Adults age 40 or older treat if the 10-year risk of major osteoporotic fracture is at least 10-20% or if the risk of hip fracture is at least 1-3% using FRAX
  - After increasing the risk by 15% and 20%, respectively, for a prednisone dose >7.5 mg/daily
Non-pharmacologic recommendations for patients receiving glucocorticoids

• Minimize use of glucocorticoids!!

• Ca 1200 mg/daily and vitamin d 1000-2000 IU/daily
  • Glucocorticoids increase the excretion of urinary calcium

• Routine lifestyle recommendations
  • Weight-bearing exercise
  • Maintenance of normal weight
  • Smoking cessation, limitation of alcohol consumption
Treatment

- Bisphosphonates are considered first line treatment for glucocorticoid induced osteoporosis
- Alendronate, Risedronate, Zoledronic Acid are approved by the FDA for this indication
- Multiple RCTs have demonstrated these medication to increase BMD in patients who receive glucocorticoids
- The average percentage of bone mineral density increase is less than that seen in post-menopausal women
Bisphosphonates for steroid-induced osteoporosis

• Cochrane review, 12 randomized trials
• 1342 participants
• 43% lower risk of new vertebral fractures in bisphosphonate group compared to calcium/vitamin d
• NNT to prevent one vertebral fracture =31

From the updated AACE 2020 Guidelines:

- Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than −3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk (Grade B; BEL 1; downgraded due to limited evidence).

- Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic patients with high fracture risk, as defined in R23 (Grade A; BEL 1).

- R25. Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk, as defined in R23 (Grade A
Alternatives to bisphosphonates

• Teriparatide, recombinant human parathyroid hormone
  • approved by the FDA for treatment of glucocorticoid osteoporosis
• Denosumab, humanized monoclonal antibody to the receptor activator of RANKL
  • Approved by the FDA in May 2018 for glucocorticoid induced osteoporosis

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**Table 2.** Incident vertebral and nonvertebral fractures in subjects with glucocorticoid-induced osteoporosis

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Subjects taking alendronate (n = 214)</th>
<th>Subjects taking teripar tide (n = 214)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 radiographic vertebral</td>
<td>13 (7.7)</td>
<td>3 (1.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥1 clinical vertebral</td>
<td>4 (2.4)</td>
<td>0</td>
<td>0.037</td>
</tr>
<tr>
<td>≥1 nonvertebral</td>
<td>15 (7.0)</td>
<td>16 (7.5)</td>
<td>0.843</td>
</tr>
<tr>
<td>≥1 nonvertebral fragility</td>
<td>5 (2.3)</td>
<td>9 (4.2)</td>
<td>0.256</td>
</tr>
</tbody>
</table>

Third-Line Agents

- Raloxefine- approved by the FDA for corticosteroid induced osteoporosis
- Shown to increase BMD at the spine in patients taking steroids
- Fracture data is lacking
Special Populations

• Childbearing Aged Women
  • Generally avoid treatment- concern for long-term retention of agents and affect on fetal skeleton
  • If absolutely needed (h/o previous fracture or high risk fracture on steroids) consider use of medications with shorter half life and less retention in bone ie teriparatide

• Medications to prevent fracture are not recommended in pregnant women
References

• Overman RA, Yeh JY, Deal CL. Prevalence of oral glucocorticoid usage in the United States: a general population perspective. Arthritis Care Res (Hoboken). 2013 Feb;65
• Gonzalez, Anne V. et al. Long-term Use of Inhaled Corticosteroids in COPD and the Risk of Fracture. CHEST , Volume 153 , Issue 2 , 321 - 328