EPIDURAL STEROIDS AND BONE DENSITY: WHAT’S THE EVIDENCE

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Brief review of glucocorticoids and Epidural Steroids (ESI)
Skeletal and non-skeletal effects of glucocorticoids
Review of the evidence of skeletal effects of Epidural Steroids
Clinical implications and fracture prevention
Duluth?
Babbitt reports 38 below zero this morning; roundup of Northland low temperatures

For the second morning in a row, it appears that Babbitt was the cold spot in the Northland - with a low Tuesday morning of 38 degrees below zero.

By: News Tribune staff, Duluth News Tribune

For the second morning in a row, it appears that Babbitt was the cold spot in the Northland - with a low Tuesday morning of 38 degrees below zero.

Babbitt recorded a low of 29 below zero on Monday morning, the coldest reading in the region that day.

Here's a roundup of Tuesday morning's low temperatures as reported by the National Weather Service

- 38 below zero - Babbitt
- 36 below zero - Embarrass
- 35 below zero - Crane Lake
- 34 below zero - Brimson, Gunflint Lake
- 33 below zero - Ely, Bigfork
- 22 below zero - Grand Marais harbor, Grand Rapids, Brainerd, Hinckley
- 21 below zero - Duluth airport, Butternut, Upson, Clam Lake
Text from residency classmate last Tuesday:

Jan 22, 2013 7:12 AM

My inpts are Eating breakfast in the common area right now with the news on. They're doing the weather report and I hear it's -40 something in Duluth. One of the patients asked another one where They were talking about. The other one said Id rather be in the hospital than in Duluth.
GLUCOCORTICOIDS (GC)

- GC: class of steroid hormones under HPA control
  - CRH (hypothalamus) ➔ ACTH synthesis in pituitary gland ➔ adrenal cortex production of cortisol
  - Cholesterol derivative
GLUCOCORTICOIDS (GC)

- GC receptors ubiquitous in cytoplasm
- Many effects due to genomic mechanisms
- Regulate metabolism, immune response
Powerful anti-inflammatory and autoimmune effects

Commonly used to treat many conditions (RA, COPD, IBD, Lupus, Asthma)

Initially thought to be miracle cure
CUSHINGOID FEATURES
SYSTEMIC GC SIDE EFFECTS

- HTN
- Altered glucose metabolism
- Mood swings
- Cushingoid features
- Thinning of skin
- Easy bruising
- Acne
- Gastritis, ulcers

- Osteoporosis
- Impaired wound healing
- Muscle weakness
- Fluid retention
- Osteonecrosis
- Adrenal suppression/crisis
### Potential side effects or complications of epidural steroid administration

<table>
<thead>
<tr>
<th>Category</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine</strong></td>
<td>Adrenal suppression, Hypercorticism, Cushingoid syndrome, Hyperglycemia, Precipitation of diabetes mellitus, Immunosuppression, Hypokalemia, Amenorrhea, Menstrual disturbances, Retardation of growth</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Hypertension, Fluid retention, Congestive heart failure, Deep vein thrombosis</td>
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<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Osteopenia/osteoporosis, Avascular necrosis of bone, Pathologic fracture, Muscle wasting and atrophy, Muscle pain, Joint pain</td>
</tr>
<tr>
<td><strong>Psychological</strong></td>
<td>Mood swings, Insomnia, Psychosis, Anxiety, Euphoria, Depression</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Ulcerative esophagitis, Hyperacidity, Peptic ulceration, Gastric hemorrhage, Diarrhea, Constipation</td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
<td>Retinal hemorrhage, Posterior subcapsular cataracts, Increased intraocular pressure, Exophthalmus, Glaucoma, Damage to optic nerve, Secondary fungal and viral infection</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td>Facial flushing, Impaired wound healing, Hirsutism, Petechiae, Ecchymosis, Hives, Dermatitis, Hyperpigmentation, Hypopigmentation, Cutaneous atrophy, Sterile abscess</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Hyperglycemia, Glycosuria, Redistribution of fat, Negative nitrogen balance, Sodium and water retention</td>
</tr>
<tr>
<td><strong>Nervous system effects</strong></td>
<td>Headache, Vertigo, Insomnia, Restlessness, Increased motor activity, Ischemic neuropathy, Seizures</td>
</tr>
<tr>
<td><strong>Other adverse effects</strong></td>
<td>Epidural lipomatosis, Fever</td>
</tr>
</tbody>
</table>
SYSTEMIC EFFECTS OF EPIDURAL STEROID ADMINISTRATION

- Adrenal suppression
  - Kay et al 1994
- Elevated blood glucose
  - Even et al 2012
- Fluid retention leading to CHF
  - Manchikanti 2002
Therapeutic benefit includes decreasing pain, improving function, and avoiding surgery.
- Radiculopathy
- Herniated intervertebral disc
- Spinal stenosis with neurogenic claudication

Less efficacy for axial pain.

Parr 2012, Manchikanti 2012, Benjamin 2012
GLUCOCORTICOID EFFECT ON BONE

- Increase apoptosis of osteoblasts and osteocytes
- Reduction of bone formation
- Decrease apoptosis of osteoclasts
- Inhibit calcium resorption in GI tract and renal tubules

Debbey 2012, Canalis 2007
GLUCOCORTICOID-INDUCED OSTEOPOROSIS (GIOP)

- Bone loss biphasic with GC use
  - 3-5% in first year, 0.5-1.0% each subsequent year
- Bone loss more pronounced in trabecular bone (spine, ribs, proximal femur)
- 30% of patients with > 6 months oral GC use develop osteoporosis
- GC also decrease bone quality and increase osseous fragility

Canalis 2007
GIOP

- 30% of patients on chronic GC therapy develop incident fracture
- 2-5X risk in vertebral fracture
  - 1.3 – 2.6X increase in risk of overall fracture
- Fracture risk gradually returns to baseline after treatment stopped
BMD relationship and incidence of radiological spinal deformities in post-menopausal women with GIOP compared with postmenopausal osteoporosis; Van Staa TP, et al 2003
Premenopausal women with asthma treated over 1 year period
- Inhaled triamcinolone daily
- Measured BMD and markers of bone turnover (baseline, 6 months, 1, 2, 3 yrs)
  - Serum osteocalcin, PTH, urinary Ca²⁺ and N-telopeptide
    - Israel 2001
INHALED GLUCOCORTICOIDs

- Triamcinolone associated with dose-dependent decrease in bone density at the total hip and trochanter
- No dose-related effect in the spine or femoral neck
- No relationship with steroid dose/BMD and serum or urine markers of bone turnover
DOES THIS REALLY MATTER FOR INTERVENTIONAL PHYSICIANS?

- Chronic daily oral or inhaled GC use

- What about intermittent epidural steroid injections?
  - Less systemic exposure, less frequent use
What data is out there?
ESI AND BONE DENSITY

- Manchikanti 2002 review – *Pain Physician*

- “at this time, no studies show such a relationship between steroids utilized in neural blockade and osteoporosis or avascular necrosis.”
Prospective evaluation of 204 patients undergoing neural blockade

- Group 1 – neural blockade without steroids
- Group 2 – neural blockade with steroids
  - Mean dose 146 mg depo-medrol

Injections consisted of caudal/transforaminal ESI, MBB, intra-articular injections, radiofrequency neurotomy, adhesiolysis

- Manchikanti et al 2000
Patients monitored serially from baseline to 1 year

No changes in BMD or body weight associated with neuraxial steroid use
MORE RECENT DATA

- Focused on postmenopausal women
- Population most vulnerable to bone loss
- Most common patient receiving ESI

- 1,000 ESI patients
- 64% women, average age 66, average number of injections 2.1 over 5 years
  Al-Shoha et al, Spine 2012
Yi et al, *Pain Physician* 2012

- Retrospective analysis of 352 postmenopausal women with low back pain that received ESI
  - Recorded number and duration of injections, steroid dosage
  - Looked at BMD, AP and lateral thoracic and lumbar X-rays after treatment
62% with no fracture
38% with fracture
  - Spine most common location, then proximal femur
- Increased age correlated with higher fracture risk and lower bone density
- Increased height and weight correlated with higher BMD
No consistent correlation between BMD and total number of ESIs, total dose of steroid, or treatment duration

Multiple limitations
Khan et al, *Pain Physician* 2012

- Retrospective analysis of 90 postmenopausal women with low back pain
  - Group 1: NSAIDs, muscle relaxers
  - Group 2: Received ESI > 4 times
    - 10-40mg triamcinolone over 1-2 week intervals
- BMD measured before treatment and one year post treatment
Number of ESIs 5.6
Total dose triamcinolone 212 mg

ESI group showed trend towards decreased bone density in femoral neck (-2.87%) and total femur (-1.57%)
  - Not significant
Spine BMD did not change in epidural steroid group
No change in non-ESI group BMD at any location
Prospective, observational study

Selective inclusion criteria:
- At least 10 year post-menopausal white women with L4-5 nerve root compression, no other bone disease or recent steroid use
- 54 patients enrolled, 28 completed study
  - Remainder excluded due to non-compliance
“Control” group: 460 post-menopausal women with normal baseline BMD and serial BMD measurements

- No steroid exposure
Underwent L4-5 ESI with 80mg triamcinolone

- Measured BMD of total hip, femoral neck, and spine
- C-terminal telopeptide of type 1 collagen (CTX) and bone-specific alkaline phosphatase (BSAP)
- Measured at baseline, 3 months and 6 months post-injection
Total hip BMD decreased 0.018 g/cm² *(p = 0.002 compared to baseline)
- Control group 0.003 gm/cm² decrease
- Injection group had significant decrease compared to control group (p = 0.007)
Al-Shoha, *Spine*

- Spine BMD decreased 0.011 gm/cm² (NS)
  - Control group similar
- Femoral neck BMD decreased 0.011 gm/cm² (NS)
  - Control group similar
CTX and BSAP increased from 0-6 months (NS)
- BSAP increase was significant between 3 and 6 months
EFFECT OF EPIDURAL STEROID ON BONE

- Appears to be systemic effect (not local)
  - Correlates with inhaled corticosteroid effect on bone
  - Greater changes seen in hip than spine
    - 6 fold increase in bone loss
  - Changes in serum biomarkers

- Only one injection with short term follow up
How much does decrease in BMD lead to increase in fracture risk

- May not be clinically significant, though risk of fracture shown to increase with decreasing BMD
Is this a transient finding?
  - Will it resolve on it’s own?
  - Is there similarity to transient osteoporosis of the hip?
    - Seen in pregnancy, middle-aged men
Estimating fracture risk

- **FRAX® tool**: 10 year probability of hip or major osteoporotic fracture
  
  [http://www.shef.ac.uk/FRAX/tool.aspx](http://www.shef.ac.uk/FRAX/tool.aspx)

  - Takes multiple risk factors into account
FRAX® RISK FACTORS

- Age
- Race
- Sex
- Weight
- Height
- Previous fracture
- Parent with hip fracture
- Rheumatoid Arthritis
- Previous glucocorticoid use
- Secondary osteoporosis
- Smoker
- Alcohol (3 or more drinks per day)
- Bone mineral density
Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian)  Name/ID: 

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 65  Date of birth: Y: [ ] M: [ ] D: [ ]

2. Sex
   - Male
   - Female

3. Weight (kg) 55

4. Height (cm) 162

5. Previous fracture
   - No
   - Yes

6. Parent fractured hip
   - No
   - Yes

7. Current smoking
   - No
   - Yes

8. Glucocorticoids
   - No
   - Yes

9. Rheumatoid arthritis
   - No
   - Yes

10. Secondary osteoporosis
    - No
    - Yes

11. Alcohol 3 or more units per day
    - No
    - Yes

12. Femoral neck BMD (g/cm²)
    T-Score: -1.5

Calculate

BMI 21.0
The ten year probability of fracture (%)

with BMD

- Major osteoporotic 8.0
- Hip fracture 0.9
Please answer the questions below to calculate the ten year probability of fracture with BMD.

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12. Femoral neck BMD (g/cm²)
    - T-Score: -1.5

**BMI 21.0**

The ten year probability of fracture (%)

- Major osteoporotic: 13
- Hip fracture: 1.7
Several treatment modalities

- Exercise
- Education and lifestyle modification
- Dietary supplementation
- Medications
FRACTURE PREVENTION: EXERCISE

- Associated with significant improvement in BMD in premenopausal women
- Postmenopausal women: associated with mild increases, maintenance or attenuation of BMD
  - Net positive in BMD relative to control subjects
  - Weight-bearing exercise (resistance training in particular)

- Guadalupe-Grau 2009
FRACTURE PREVENTION: EDUCATION AND LIFESTYLE MODIFICATION

- Smoking cessation, limit EtOH intake decrease fracture risk

- Falls increase fracture risk independently
  - Appropriate rehab should target balance, mobility and posture to decrease fall risk
    - Patient education
    - Appropriate ambulation aids
Calcium and vitamin D supplementation help stabilize BMD in patients on chronic GC therapy

- Ca intake of 1000-1200 mg/d, vitamin D at least 800 IU/d
- Minimum serum level of 50 nmol/L 25(OH)D3

Canalis 2007, Tang 2007
Bisphosphonates consistently shown to prevent GC-induced bone loss, decrease fracture risk

Teriparatide even more effective
  - Counters GC-induced apoptosis of osteoblasts and osteocytes

Canalis 2007
CONCLUSIONS

- Limited prospective data on Epidural Steroids and Bone Health
  - Epidural steroids appear to have deleterious systemic effect on bone health
  - More prospective trials with longer term follow-up needed to better characterize problem
FUTURE DIRECTIONS

- Ways to prevent Epidural Steroid-induced bone loss
- Looking at other patient populations
- Identification of biomarkers, bone quality measures to better predict risk of fracture
What to do in practice:

- Limit number of steroid injections
- Think about risk factors and take preventative measures if indicated
- Communicate with other providers
  - BMD monitoring, treatment options
REFERENCES

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