Skeletal Effects of Hormone Therapy in Women with Early Menopause

Translational Science Symposium
North American Menopause Society
Orlando, FL
October 4, 2016

Michael McClung, MD, FACP
Oregon Osteoporosis Center

Disclosure and Conflicts of Interest
Michael McClung, MD 2016

Global Advisory Boards of the following companies:
Amgen, Merck, Radius

Honorarium for speaking from Amgen and Merck

Bone Loss After Menopause

- Bone turnover rates increase
  - resorption > formation
- Bone loss occurs
- Architecture gradually becomes damaged
  - plates to rods
  - perforations
  - loss of cross-struts
  - thinning and increased porosity in cortical bone
- Bone strength decreases

At least 50% of trabecular bone loss after menopause occurs during the first 5 years after estrogen deficiency

Bone Mineral Density (T-score)

MENOPAUSE

Women

 Bone Mineral Density (T-score)  Bone Mineral Density (T-score)

10-15% decrease in spine BMD over 5-8 years beginning 1 year before cessation of periods

Loss in very elderly related to vitamin D deficiency and limited physical activity
Menopause and Bone Loss

- Pattern of bone loss is not affected by baseline BMD.
- BMD at menopause is a good predictor of BMD at age 65.

- Pattern of bone loss is not affected by age at menopause.
- BMD at early menopause is still a good predictor of BMD at age 65.

Premature menopause

Surgical menopause

Menopause and Fracture Risk

- The impact of early menopause on fracture risk is complex:
  - Until age 60, early menopause is a risk factor for fracture.
  - At age 60-65, women with history of early menopause have had more fractures than those with later menopause.
Menopause and Fracture Risk

- The impact of early menopause on fracture risk is complex:
  - Until age 60, early menopause is a risk factor for fracture
  - At age 60-65, women with history of early menopause have had more fractures than those with later menopause
  - However, after age 65, incident fracture risk, adjusted for BMD and age, is not increased by early menopause
    - 6,616 women in the Study of Osteoporotic Fractures who underwent either surgical (1,157) or natural (5,459) menopause
    - mean age at menopause (44.3 ± 7.4 vs 48.9 ± 4.9 y, P <0.001)
    - fracture rates were not significantly increased for surgical versus natural menopause, even among those who had never used estrogen
      - hip fracture: hazard ratio [HR], 0.87; 95% CI, 0.63-1.21
      - wrist fracture: HR, 1.10; 95% CI, 0.78-1.57
      - any nonvertebral fracture: HR, 1.11; 95% CI, 0.83-1.32

Skeletal Effects of Estrogen after Early Menopause

Estrogen and BMD in Early Menopause:
PEPI Trial

- 875 healthy women
- Ages 45-64 (Mean 55)
- At least 6 months past menopause

Estrogen and BMD in Early Menopause:
EPIC Study

- 110 postmenopausal women
- average age 53 years since menopause = 3.5
- Randomly assigned to estrogen* +/- progestin**
- Followed for 4 years, then therapy discontinued
- BMD response was related to years since menopause
  - CEE 0.625 mg/d or estradiol 2 mg/d days 1-22 and 1 mg days 23-28
  - MPA 5 mg/d or NETA 1.0 mg days 13-22
  - CEE 0.625 mg/d or estradiol 2 mg/d days 1-22 and 1 mg days 23-28
  - MPA 5 mg/d or NETA 1.0 mg days 13-22

* The Writing Group for the PEPI Trial. JAMA 1996;275:1399-1406
Lumbar Spine BMD Response to Estrogen
Relationship to Time Since Menopause

Early menopause: within 2 years
Late menopause: more than 5 years

HT: Conjugated estrogen 0.625 mg ± MPA 10 mg/d

Δ 4.5%

McClung M et al. Unpublished results

Timing of Estrogen Therapy

Bone Mass

- There is little evidence of the effects of estrogen in women with surgical menopause for benign conditions or following premature ovarian failure.
- What little evidence exists suggests that the BMD response to estrogen (and other bone-active drugs) is similar in these younger estrogen-deficient women.

61 women with surgical menopause average age 48 years since menopause – 8
Randomly assigned to esterified estrogens 1.25 mg +/- methyltestosterone 2.5 mg/d
Followed for 2 years

BMD response was similar to that in women with early natural menopause

McClung M et al. Unpublished results

Estrogen and BMD after Early Menopause

Estrogen and BMD in POI

145 women with primary ovarian insufficiency, average age 32 years, since onset 7 years.

All patients received transdermal estradiol (100 μg/d) plus oral medroxyprogesterone acetate 10 mg/d (12 days) for a 3-month run-in period before being randomized in a double-blinded fashion to the addition of transdermal T (150 μg/d) or placebo. Followed for 2 years.

Baseline BMD Z-score: -0.8 vs -0.4 for age-matched healthy controls.

BMD response was similar to that in women with early natural menopause.

Testosterone provided no additional benefit.

Timing of Estrogen Therapy

- Prospective cohort study of 6910 women, 65yr of age or older, without osteoporosis, stratified by patterns of estrogen use.
  - Never users (67%)
  - Past early users (started under age 60 yr with no current use; 23%)
  - Past late users (started at age 60 or later with no current use; 2%)
  - Current early users (started under age 60 yr with use both at baseline and 6 yr later; 6.7%)
  - Current late users (started at age 60 or later with use at baseline and 6 yr later; 1.5%)

- There was no evidence that past use of estrogen was protective against fractures.
- Women who started estrogen use before age 60 years and continued had the lowest rate of fracture.
  - In multivariate analyses, their risk of any non-spine fracture was reduced by 37% (28–49%) in comparison with never users.
  - Compared with never users, women who initiated estrogen use at age 65 or later had a statistically non-significant 25% reduction in the risk of non-spine fractures.

- **CONCLUSION:** Current estrogen use reduces fracture risk.
- Early, continuous estrogen therapy has the greatest effect on fracture risk.

Timing of Estrogen Therapy

<table>
<thead>
<tr>
<th></th>
<th>Incidence</th>
<th>RRR</th>
<th>Adjusted for BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used</td>
<td>27.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past user:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early start</td>
<td>25.1</td>
<td>0.95 (0.85–1.07)</td>
<td>1.04 (0.91–1.20)</td>
</tr>
<tr>
<td>Late start</td>
<td>27.0</td>
<td>1.16 (0.85–1.58)</td>
<td>1.13 (0.76–1.67)</td>
</tr>
<tr>
<td>Current user:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early start</td>
<td>17.3</td>
<td>0.63 (0.51–0.78)</td>
<td>0.83 (0.65–1.06)</td>
</tr>
<tr>
<td>Late start</td>
<td>20.0</td>
<td>0.75 (0.50–1.12)</td>
<td>0.71 (0.42–1.19)</td>
</tr>
</tbody>
</table>
Effects of Oral Contraceptive Use in Perimenopause on Fracture Risk

- Oral contraceptive use was associated with significant reduction in risk of vertebral fractures. 1,2
- Case control study: 1,204 case women aged 45 to 59 years with incident fractures and 2,275 control women. 3
  - participation was 69% for cases and 64% for controls.
  - study sample was 82% white
  - mean age 54 years
- most common fracture site for cases was the wrist/forearm (32%)
- Adjusted non-vertebral fracture risk did not differ between cases versus controls for OC use in the 10 years before menopause (OR 0.90, 95% CI 0.74, 1.11)

2. O’Neill TW et al. Osteoporos Int 1997;7:72-8

Skeletal Effects of Other Bone Active Drugs in Early Menopause

- Limited BMD data; little to no fracture data
- Raloxifene: not studied in early menopause; slows but does not prevent bone loss upon stopping estrogen
- Teriparatide: not indicated in absence of high risk for vertebral fracture
- Bisphosphonates and denosumab: effective prevents bone loss in early menopause

Alendronate and BMD in Early Menopause

- 447 healthy women
- 6-36 months past menopause (mean 25)
- Mean age 52

Zoledronic Acid Prevents Bone Loss in Early Menopausal Women

- Placebo
- ZOL 5 mg (Year 1 Only)
- ZOL 5 mg (Year 1 and 2)

Stratum I
- Within 5 years of menopause
Indications for therapy in postmenopausal women and men over age 50
1. after hip or spine fracture
2. BMD T-score in spine or proximal femur ≤ -2.5
3. BMD between -1 and -2.5 and one of following:
   a. 10 year risk of major fracture of 20% or more*
   b. 10 year risk of hip fracture of 3% or more*
* Calculated by FRAX® algorithm

No specific recommendation for preventing bone loss in women with early menopause

Osteoporosis Position Statement: endorsed NOF approach ¹
No specific recommendation for preventing bone loss in women with early menopause

Estrogen-progestin Position Statement ²
Recent data support the initiation of HT around the time of menopause to treat menopause-related symptoms; to treat or reduce the risk of certain disorders, such as osteoporosis or fractures in select postmenopausal women; or both.
No specific recommendation for preventing bone loss in women with early menopause

SUMMARY
- Bone loss related to estrogen deficiency occurs with natural or surgical early menopause
- This results in increased risk of fracture, at least until age 65
- Estrogen therapy is effective in preventing this bone loss
- In the absence of contraindications, hormone therapy until age 51 is recommended
  - bisphosphonate therapy for 3-5 years is an alternative
- After age 50, women with early menopause should be managed like other postmenopausal women