Estrogens and SERMS
The forgotten few!

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Outline

- Physiology of Estrogen and estrogen receptors
- Actions of estrogen on bone
  - BMD, fracture, other off target effects
  - Cohort and randomized trials of E2
- Role of SERMS in bone diseases
  - Raloxifene
  - Bazedoxifene
- Summary

How Does Estrogen Work in Bone?
Its Complex!!!
Modes of Action of Estrogen on Bone - Adults

- Anti-resorptive
  - Inhibit RANKL
  - Apoptosis of Osteoclasts
  - Inhibit NFκB signaling

- Anabolic
  - Stimulates bone formation in rodents
  - Humans unlikely suppresses formation

- Other
  - Stimulates ATGL in fat cells - reduction in adipocytes
Antiresorptive Therapy

- Reduce Bone Turnover
- Stabilize or Improve Microarchitecture
- Increase BMD
- Decrease in Fracture Risk

Hormone Products Available for Rx

- Estrogen
  - Full doses of conjugated EE or estradiol
  - Low doses EE
  - Alternate routes of administration
- Progestins
  - Micronized progesterone
  - Progesterone orally- ‘provera’
  - Progestin intrauterine device
- Vaginal estrogen
- Bioidentical hormones
  - Soy products, isoflavonoids, genistein

Bone Remodeling: Rankl/OPG

Estrogen Dose Equivalents

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Standard</th>
<th>Low Dose</th>
<th>Ultra-Low Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEE</td>
<td>0.625 mg</td>
<td>0.3 mg</td>
<td></td>
</tr>
<tr>
<td>Oral E2</td>
<td>1 mg</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td>Transdermal E2</td>
<td>0.05 mg</td>
<td>0.025 mg</td>
<td>0.014 mg</td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>5 µg</td>
<td>2.5 µg</td>
<td></td>
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</tbody>
</table>

CEE = conjugated equine estrogen; E2 = estradiol.
Graphic courtesy of Kathryn A. Martin, MD.
**Impact of Esterified Estrogens (EE) on Spine, Total Hip, and Total Body BMD**

**Effects of Micronized 17β-estradiol + Calcium on Spinal BMD**

**Impact of Standard CEE and CEE/MPA on Hip and Spine BMD: PEPI Trial Results**

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**Fig. 2**—Mean yearly change in metacarpal mineral in two groups of age-matched women taking an average of 25 μg mestranol daily, starting three years (group T) or six years (group S) after oophorectomy. Numbers of patient-treatment-years are given in parentheses.
Estrogen Use reduces non vertebral fractures

Figure 3. Probability of nonvertebral fractures. Probabilities are adjusted for age and weight.

Estrogen + Progesterone increases Spine BMD more than Alendronate
Women's Health Initiative Estrogen and Progestin Arm: Absolute Excess Risk

- Excess CHD events: 7/10,000 woman-years
- Excess stroke events: 8/10,000 woman-years
- Excess pulmonary emboli: 8/10,000 woman-years
- Excess invasive breast cancer: 8/10,000 woman-years

Source: Writing Group for the WHI Investigators 2002

Relative Risk Compared to Placebo

- Hip Fracture: 0.61*
- Breast Cancer: 0.77
- CHD: 0.91
- Total Mortality: 1.04
- Colorectal Cancer: 1.08
- Stroke: 1.39*

Favors Treatment Favors Placebo

* P < .05

Source: Adapted from WHI Steering Committee 2004
Estrogen Alone Did Not Effect CHD Events in WHI; After Cessation of Estrogen, Younger Women Who Had Taken CEE† Had Fewer CHD Events

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Placebo</th>
<th>CEE 0.625 mg</th>
</tr>
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<tbody>
<tr>
<td>50-59</td>
<td>56</td>
<td>33</td>
</tr>
<tr>
<td>60-69</td>
<td>168</td>
<td>161</td>
</tr>
<tr>
<td>70-79</td>
<td>121</td>
<td>125</td>
</tr>
</tbody>
</table>

*Statistically significant difference

[Placebo vs. CEE 0.625 mg]

**Low-Dose Estrogen**

**HOPE Trial**
- Women’s Health, Osteoporosis, Progestin, Estrogen (HOPE) trial
- 2600+ postmenopausal women with uterus, treated for 2 years
- 8 treatment groups and placebo
  - CEE 0.625 mg/d ± MPA 2.5 mg/d
  - CEE 0.45 mg/d ± MPA 2.5 mg/d
  - CEE 0.45 mg/d + MPA 1.5 mg/d
  - CEE 0.3 mg/d ± MPA 1.5 mg/d
  - Placebo
- Endpoints: vasomotor symptoms, BMD, endometrial safety

CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; BMD = bone mineral density

Source: Anderson 2004; LaCroix 2011

**HOPE Trial**
- Placebo vs. CEE 0.625 mg/d

**CEE and Spine BMD**

**HOPE Trial**

- CEE and Spine BMD
- Placebo vs. CEE 0.3 mg, 0.45 mg, 0.625 mg

**CEE and Hot Flashes**

**HOPE Trial**

- Percentage Hot Flash Frequency (Mean)
- Placebo vs. CEE 0.3 mg/d, 0.45 mg/d, 0.625 mg/d

Ultra–Low-Dose Estrogen

- ULTRA trial: Ultra–low-dose Transdermal Estradiol Assessment
  - Transdermal E2 (0.014 mg/day) vs placebo x 2 years
  - N = 417 women, mean age 67
  - Asymptomatic population – no effect on hot flashes
- Effective for hot flashes in trials of younger women (N = 425)


Ultra–Low-Dose Estrogen and BMD

ULTRA Trial

- BMD increased more in spine (2%) and hip (1.2%) vs placebo
- Greater bone effect with lower endogenous E


Discontinuation of ERT and Risk of Osteoporotic Fracture

Menopausal Hormone Therapy and Osteoporotic Fractures

Table 3. Hazard Ratio for Osteoporotic Fracture Among Ever Users of Menopausal Hormone Therapy (in Comparison With Never Use) According to the Route of Estrogen Administration and Recency of Use (n = 70,182), EDIN Cohort, 1962-2008

<table>
<thead>
<tr>
<th></th>
<th>Oral Estrogens</th>
<th>Cutaneous Estrogens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>HR^1</td>
</tr>
<tr>
<td>All osteoporotic fractures (n = 5,309)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>427</td>
<td>0.69</td>
</tr>
<tr>
<td>Treatment stopped &lt;5 years previously</td>
<td>291</td>
<td>0.99</td>
</tr>
<tr>
<td>Treatment stopped ≥5 years previously</td>
<td>368</td>
<td>1.00</td>
</tr>
<tr>
<td>Major osteoporotic fractures (n = 2,268)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>154</td>
<td>0.63</td>
</tr>
<tr>
<td>Treatment stopped &lt;5 years previously</td>
<td>151</td>
<td>0.67</td>
</tr>
<tr>
<td>Treatment stopped ≥5 years previously</td>
<td>482</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**Raloxifene**

- Selective estrogen receptor modulator
- Acts as an estrogen agonist on bone
- Acts as an estrogen antagonist on breast and uterus
- Approved for prevention and treatment of postmenopausal osteoporosis
- Adverse events: Hot flashes, venous thromboembolism, leg cramps


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**Effect of Raloxifene Treatment in Women With or Without Existing Fractures - MORE Trial 36 Months -**

- RR 0.45* (95% CI 0.29, 0.71)
- RR 0.70* (95% CI 0.50, 0.96)

*Placebo
- RLX 60 mg/d


* rounded off in paper

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**Effect of Raloxifene on Non-vertebral Fractures - MORE Trial 36 Months -**

- All Non-vertebral Fractures
- Hip Fractures
- Wrist Fractures
- Ankle Fractures

*Placebo
- Pooled RLX

Are there non-BMD effects of the SERMS on bone strength?

Significant alterations of trabecular bone material-level biomechanical properties with raloxifene.

Raloxifene alters energy to failure and toughness of cortical bone through changes in postyield displacement.
Figure 1. Chemical structure of bazedoxifene.

Significant Risk Reduction from Bazedoxifene for Non Vert Frx
Summary

- Estrogens are very effective in raising BMD and reducing vert and non-vert fracture risk
- Off-target effects of estrogen limit clinical utility (breast cardiovascular, thrombosis)
- SERMS are protective to the skeleton
- At least one SERM has non-vert fracture risk reduction
- There may be beneficial off-target effects; e.g., protection vs breast cancer
Molecular structures of the endogenous estrogen 17β-estradiol and of tamoxifen, 4-hydroxytamoxifen, raloxifene, ICI 182,780 (fulvestrant), toremifene, R,R-cis-diethyl-THC, and genistein.

Heldring N et al. Physiol Rev 2007;87:905-931

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Raloxifene: Effect on Nonvertebral and Hip Fracture

Pooled Data (60 mg and 120 mg*)

Nonvertebral Fractures

Hip Fractures

*P=0. 24

*P=0.71

Incidents of patients with nonvertebral fractures

Incidents of patients with hip fractures

n = placebo = 2570 women; Raloxifene (60 mg and 120 mg) = 5129

*Not FDA-approved dose

Ettlinger B et al. JAMA 1999;282:837-645

Raloxifene: Effect on Radiographic Vertebral Fractures (MORE)*

Incidents of patients with ≥1 vertebral fracture

RR, 0.7 (95% CI, 0.6-0.9)

100%

50%

0%

Placebo

Raloxifene

60 mg/d

n=1522

n=1490

(BMD < 2.5 and no preexisting vertebral fractures)

(n=3012)

(BMD < 2.5 and preexisting vertebral fractures)

(n=1539)

*postmenopausal women

MORE = multiple outcomes of raloxifene evaluation; RR = risk ratio

Women's HOPE Study: Bone Substudy Conclusions

- All doses of CEE and CEE/MPA demonstrated a statistically significant improvement in BMD relative to placebo
- All doses except .3 CEE at the femoral neck demonstrate a statistically significant improvement in BMD relative to baseline

FIG. 1—Mean yearly change in metacarpal mineral in women receiving mestranol (M) or placebo (P) starting two months (group Z), three years (group T), or six years (group S) after oophorectomy. Numbers of patient-treatment-years are given in parentheses. N.S. = Not significant.

FIG. 2. Incidence of non-vertebral fractures and corresponding fracture risk reductions by baseline prevalent fracture status: *RRR, relative risk reduction; HR, hazard ratio; CI, confidence interval. "Intent-to-treat population; n = 160." *p < 0.05 vs. placebo; **p = 0.00 for treatment by prevalent fracture status interaction.

EFFECTS OF RALOXIFENE AND ESTROGEN ON BONE

Fig. 2. BMD was measured by dual-energy x-ray absorptiometry at various skeletal sites in postmenopausal women treated for 6 months with 40 mg/day raloxifene (RLX; open bars; n = 24) or 0.625 mg/day CEE (solid bars; n = 30). All values are expressed as the mean percent change from baseline ± SE. *Significant differences from baseline (p < 0.05); # significant difference between groups (p < 0.05).
Raloxifene has less effect on BMD than alendronate

Changes in bone mineral density (BMD) from baseline to 12 months (N=107) with GC.


Changes in bone markers from baseline to 12 months (N=107).
