Abstract

Purpose: To model the progressive effects of estrogen loss during menopause transition (MFT).

Methods: A multiscale model of calcium homeostasis and bone remodeling was developed to understand the effects of estrogen loss during menopause transition. The model couples intracellular signaling and endocrine feedbacks, and is parameterized to describe the dynamic changes in Ca, PO₄, TGFβ, and PTH in response to estrogen loss. Multiscale model components include:

- Intracellular signaling (+/-)
- PTH (+)
- ROB (+)
- Osteocytes, osteoblasts, osteoclasts
- Calcitriol (+)
- Bone remodeling

Results: The model successfully described the previously described therapeutic interventions and showed that estrogen loss has a significant impact on calcium homeostasis and bone remodeling. The model showed that estrogen inversely affects the renal excretion of calcium, thereby retaining calcium in the body. The model also showed that estrogen-mediated effect on OB apoptosis rate was estimated to very high values, thereby retaining calcium in the body. The model predicted that estrogen loss during menopause transition increases the risk of bone loss and fracture.

Conclusions: The multiscale model of calcium homeostasis and bone remodeling can be used to evaluate the impact of estrogen loss on bone health during menopause transition. The model offers a platform for understanding the complex dynamics in the context of other systemic changes.

METHODS

- Clinical data from literature review:
  - Magnitude and time-course of estrogen loss during the transition through menopause
  - Associated effects on bone remodeling markers:
    - Bone resorption marker (osteoclast function): urine cross-linked N-telopeptide of type I bone collagen (NTx)
    - Bone formation marker (osteoblast function): bone-specific alkaline phosphatase (BSAP)
  - Extending Ca homeostasis and bone remodeling model (Figure 1) to evaluate:
    - Longitudinal estrogen (E, relative fraction) described as ordinary differential equation with first-order elimination (E out = k in * E - k gen * E)
    - Age/41
    - k gen = 0.045, and k norm = 0.045
  - Predicted observed changes in BSAP and NTx over the time-course of estrogen loss
    - Estrogen inversely affects the renal excretion of calcium, thereby retaining calcium in the body. The model also showed that estrogen-mediated effect on OB apoptosis rate was estimated to very high values, thereby retaining calcium in the body. The model predicted that estrogen loss during menopause transition increases the risk of bone loss and fracture.

RESULTS

- Longitudinal Estrogen Effect:
  - First-order elimination
    - E out = k in * E - k gen * E
    - Age = 0.83 years

- Longitudinal Calcium, PTH and Bone Effects
  - Model Estimates (unitless):
    - E out = k in * E - k gen * E
  - Urine calcium excretion maximum (Tm) decreased linearly:
    - - 50% decrease with a 90% reduction in estrogen
  - Effect of estrogen on renal calcium reabsorption maximum (Tm) for urinary calcium excretion

- Comparison to Observed Clinical Data
  - Predicted observed changes in BSAP and NTx over the time-course of menopause transition and estrogen replacement in post-menopausal women (Figure 3, Panel B)
  - Nordin et al. reported a 2.1-fold increase in urine Ca excretion related to a 7.4% decrease in the tubular reabsorption maximum.  Model predicted an approximate 2.5-fold increase in urine Ca excretion related to a 7.6% decrease in the tubular reabsorption maximum (Figure 3, Panel B)
  - Riggs et al. reported increased PTH of −10% to 25% in women of age groups 50-59 and greater than 70 years old, respectively, compared to pre-menopausal women.  Model predicted PTH increases of 10-25% in 50-59-year-old women who entered menopause at the age of 50, with an asymptotic maximum of ~30% (Figure 3, Panel B)

DISCUSSION

- Model can be used to evaluate other drug candidates for estrogen loss
  - Research on direct effects on TGFβ and estrogen effects on bone modeling.
  - Estrogen-mediated effect on OB apoptosis rate was estimated to very high values, thereby retaining calcium in the body. The model also showed that estrogen-mediated effect on OB apoptosis rate was estimated to very high values, thereby retaining calcium in the body. The model predicted that estrogen loss during menopause transition increases the risk of bone loss and fracture.

SUMMARY

- Multiscale Model of Calcium Homeostasis and Bone Remodeling
  - Extension describes natural effects of aging in women
  - Estrogen preserves the structure and parameter estimates thereby retaining its ability to describe the previously described therapeutic interventions and disease states.
  - Provides additional model of simple the multiscale model of calcium homeostasis and bone remodeling.
  - Services as platform for incorporating these changes within the context of other therapeutic, disease, genetic, and other systemic changes.

References

[5] Riggs et al. reported increased PTH of −10% to 25% in women of age groups 50-59 and greater than 70 years old, respectively, compared to pre-menopausal women.  Model predicted PTH increases of 10-25% in 50-59-year-old women who entered menopause at the age of 50, with an asymptotic maximum of ~30% (Figure 3, Panel B)

FIGURES

- Figure 1: Published in Petersen and Riggs 2017
- Figure 2: Predicted fractional changes in estrogen during menopause transition (solid line). Observed data (circles) were taken from Sowers et al.
- Figure 3: Predicted longitudinal changes in (A) BSAP (solid line) and urine NTx (dashed line), and (B) plasma calcium (dashed line). TGFβ (solid line) and PTH (dotted line).
- Figure 4: Simulated longitudinal estrogen (A), PTH (B), BSAP (C) and NTx (D) for menopausal ages of 45 (dashed), 50 (solid), and 55 (dotted).