Menopause

Clinical Cases Applicability: menopausal symptoms (hot flashes, atrophy), osteopenia/osteoporosis, menopausal hormone, premature ovarian insufficiency

Learning Objectives:
1. Understand the physiologic changes in estrogen levels and the hypothalamic-pituitary-ovarian axis in menopause
2. Describe the pathophysiology of the various symptoms of peri-menopause/menopause
3. Discuss treatment options for the symptoms of menopause

What hormonal changes occur in perimenopause and menopause (defined as 1 year of cessation of menstruation)? How does this affect the HPO axis?
Perimenopause: Reduced ability of aging follicles to secrete inhibin (produced in granulosa cells of developing follicles) → lack of negative feedback from ↓inhibin → ↑FSH→↑ovarian follicular response→ maintain overall estrogen levels
Menopause: Ovarian follicles undergo accelerated loss until depletion of follicles → ↓ovarian steroid hormone (estrogen, progesterone) release → lack of negative feedback → ↑ GnRH release→↑ circulating FSH and LH

What are common symptoms of menopause? What is the pathophysiology?
Abnormal uterine bleeding- increased anovulatory cycles; With ↑unopposed estrogen levels→ increasing risk for developing hyperplasia/carcinoma
Vasomotor symptoms (hot flashes): occur in up to 80% of women; lasts 1-5 minutes, sudden wave of heat that spreads over the body, particularly the upper body & face; associated with sweating, palpitations, anxiety, sleep disturbance

- Dysfunction of the thermoregulatory nucleus of the hypothalamus (regulates perspiration & vasodilatation – nucleus activates heat dissipation mechanisms to maintain core body temperature in a regulated range, "the thermoregulatory zone")
- women with severe vasomotor symptoms → narrower thermoregulatory zone – minimal changes in core body temperature induce hot flash **(figure 1)**
- ↓estrogen → ↑norepinephrine & serotonin levels → Norepinephrine & serotonin lower the thermoregulatory set point and triggers the heat loss mechanisms **(figure 1)**

Bone loss: Normal bone remodeling– constant resorption of bone carried out by osteoclasts & bone formation by osteoblasts; Osteoblasts produce proteins RANKL and OPG (osteoprotegerin) **(figure 2)**

- RANKL binds to RANK – a receptor on the surface of the osteoclast progenitor cells → promotes development of osteoclasts→ leads to bone resorption
- OPG binds to RANKL preventing it from binding with RANK→decreased osteoclast development
- ↓estrogen → ↑ RANKL production outnumbers OPG → osteoclast development & bone resorption favored → ongoing bone loss over time

Cardiovascular disease: ↓ estrogen affects lipid profile, with slightly ↑ LDL → ↑ risk for CVD
Skin changes: dryness, wrinkles, thinning; ↓ collagen content, ↓sebaceous gland secretion, ↓ elasticity, ↓ blood supply
Vulvovaginal atrophy: dryness, itching, dyspareunia; ↓estrogen results in thinning of the vaginal epithelium; Loss of vaginal collagen, adipose tissue, rugae flatten; pH >4.5 (alkaline); for the vulva, ↓ sebaceous glands, subcutaneous fat loss → shrinkage & retraction of clitoral prepuce & urethra, introital narrowing
Urinary symptoms: incontinence, urgency, recurrent UTIs; ↓estrogen →thinning of urethral and bladder mucosa, ↑ risk of incontinence from decreased urethral mucosa coaptation or "seal"
Depression: ↑ risk of new-onset depression in the menopausal transition; unclear if secondary to ↓ estrogen or symptoms related to menopause (hot flashes, sleep disturbances, etc)

What are treatment options?
Menopausal hormone therapy: goal is to relieve symptoms, especially vasomotor symptoms; minimal dose for shortest amount of time possible

-For healthy symptomatic women in their 50s, overall risk for complications is low
-For women with an intact uterus, progestin therapy must be added to estrogen to prevent endometrial hyperplasia & carcinoma
- Risks with estrogen+progestin: ↑ risk of breast cancer, stroke, coronary heart events, venous thromboembolism
- Risks with estrogen only: ↑ risk of stroke & venous thromboembolism

Vaginal estrogen: low dose estrogen, minimal systemic absorption, improves urogenital symptoms
SSRIS/SNRIs, Clonidine, Gabapentin – alternatives for hot flashes
Herbal medications: black cohosh, phyto-estrogens (soy) –inconsistent evidence of efficacy

Figure 1

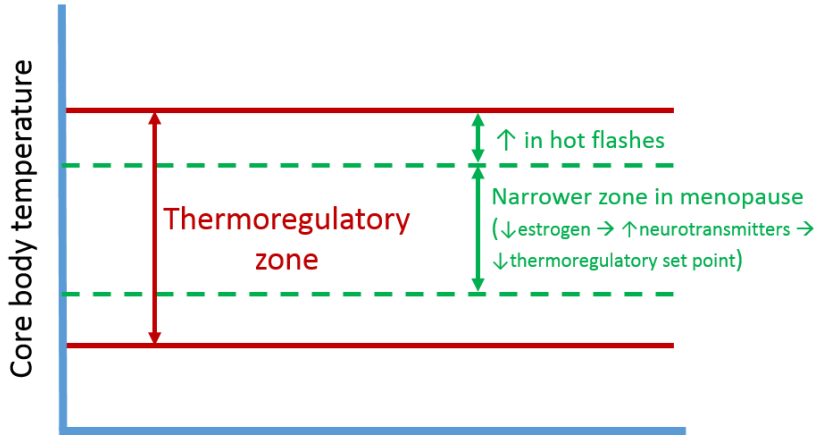
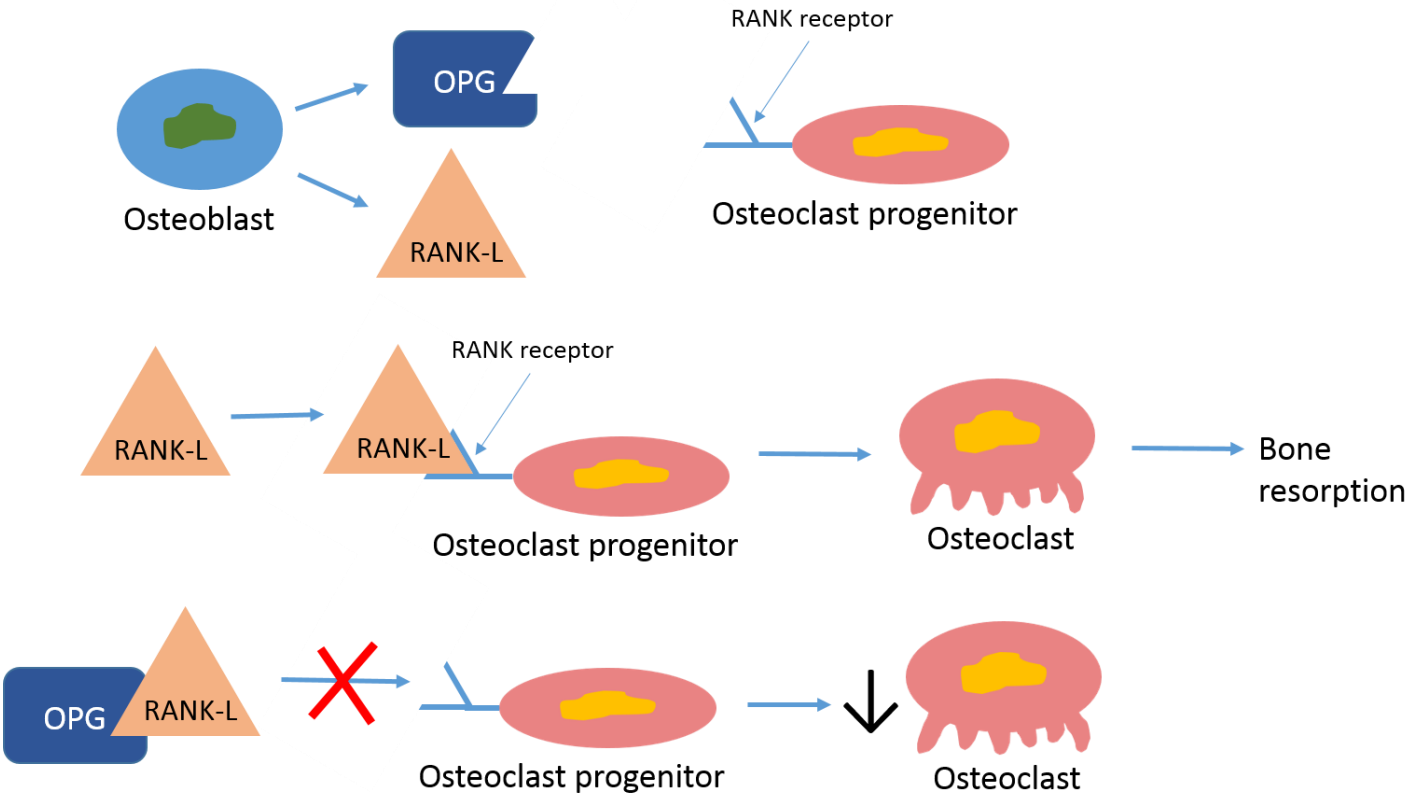


Figure 2



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