Vasomotor symptoms and Hormone therapy

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Vasomotor Symptoms

- Frequently termed hot flashes when occur during the day and night sweats when occur at night
- Characterized by sudden intense sensation of heat in the upper body, particularly the face, neck, and chest, that last 1-5 min
- Can be accompanied by perspiration, chills, anxiety, and occasionally, heart palpitations
- Number of episodes per day varies
- Vasomotor symptoms last for median of 7-10 y

Prevalence of Vasomotor Symptoms

- Most commonly reported symptom of the menopause transition; affects 60%-80% of women at some point during menopause transition
- Varies by menopause phase
  - —21% reported vasomotor symptoms in premenopause
  - —41% reported vasomotor symptoms in perimenopause
  - —42% reported vasomotor symptoms in postmenopause
- Varies by racial/ethnic group
  - —Black women > Hispanic women > White women > Chinese women > Japanese women

Physiology of Vasomotor Symptoms

- Not completely understood
- Likely involves complex interplay between central nervous system and peripheral physiologic processes
- Thermoregulatory center is altered after menopause by an increase in kisspeptin-neurokinin B-dynorphin (KNDy) neurons; activation of the neurokinin-3 receptor (NK3R) causes hot flashes; blockade of the NK3R reduces/eliminates them
- May also be affected by serotonin, epinephrine, and norepinephrine, as well as sympathetic and parasympathetic nerve activity

Nonprescription Therapies for Vasomotor Symptoms

- **Cognitive-behavior therapy, clinical hypnosis, and stellate ganglion block** have shown some efficacy in RCTs to be effective in reducing VMS
- **S-equol derivatives of soy isoflavones** may have some benefit, but evidence supporting use is mixed
- **Behavior modifications** to minimize symptoms (dressing in layers, avoiding triggers, cool ambient temperatures)

Prescription Therapies for Vasomotor Symptoms

- Treatment based on the person's tolerance of symptoms, health history, risk factors, and personal preferences
- **FDA-approved prescription treatments**
  - Hormone therapy
  - Paroxetine
- **Off-label prescription therapies**
  - Selective serotonin reuptake inhibitors
  - Serotonin-norepinephrine reuptake inhibitors
  - Gabapentinoids
  - Clonidine
  - Oxybutynin

Hormone Therapy

- Indications/contraindications
- Risks/benefits
- Preparations available

FDA-approved indications for hormone therapy

- **First-line therapy for relief of vasomotor symptoms in appropriate candidates**
- **To prevent bone loss and reduce fractures in postmenopausal women at elevated risk of osteoporosis or fractures**
- For women with hypogonadism, primary ovarian insufficiency, or premature surgical menopause without contraindication, hormone therapy is recommended for health benefits until the average age of menopause
- Low-dose vaginal estrogen therapy is recommended first line for isolated genitourinary syndrome of menopause to treat symptoms of vulvovaginal atrophy

Absolute Contraindications to Estrogen Therapy/Hormone Therapy

- Unexplained vaginal bleeding,
- Liver disease
- History of DVT or PE
- Known thrombophilia (although transdermal may be an option)
- History of estrogen-dependent neoplasia (with exceptions for some early endometrial cancers)
- History of coronary artery disease, stroke or TIA

Relative Contraindications to Estrogen Therapy/Hormone Therapy

- High triglycerides (>400mg/dl)
- Gallbladder disease
- Elevated breast cancer risk (>5% by NCI assessment)

NOTE: migraines are <u>not</u> a contraindication to hormone therapy

Cardiovascular Disease and Hormone Therapy

- Hormone therapy and coronary artery disease
  - **Hormone therapy started within 10 y of menopause or in women aged <60 y lowers all-cause mortality and does not increase the risk of coronary events**
  - May even reduce coronary events
  - Hormone therapy started later in menopause or in older women increases the risk of coronary artery disease
- Hormone therapy and stroke
  - **Stroke risk not increased with hormone therapy in women aged <60 y or within 10 y of menopause**
  - Hormone therapy may increase the risk of stroke in women starting hormone therapy after the age of 60 y
  - Transdermal estrogen or lower doses of oral estrogen may have a lower stroke risk (observational evidence)

Cardiovascular Disease and Hormone Therapy (cont)

- Hormone therapy and venous thromboembolism
  - **Increased venous thromboembolism risk with oral hormone therapy**
  - The risk does not appear to be increased with transdermal estrogens and may be lower with lower dose of oral estrogens (observational evidence)
  - Risk for venous thromboembolism increases with age and with BMI
    - 3-fold higher risk in women who are obese
  - Micronized progesterone may be less thrombogenic than progestins
  - No risk with vaginal estrogen therapy
- Hormone therapy not recommended for primary or secondary prevention of cardiovascular disease

Hormone therapy, the Women's Health Initiative, and breast cancer

- Increased risk of invasive breast cancer after 3 to 5 years of conjugated equine estrogen 0.625 mg + medroxyprogesterone acetate 2.5 mg therapy
- No increased risk of breast cancer was seen with 7 years conjugated equine estrogen 0.625 mg alone therapy
- Allows for more flexibility in duration of estrogen therapy use in women without a uterus

Hormone therapy and breast cancer

- **The effect of hormone therapy on breast cancer risk is complex and conflicting**
- The effect of hormone therapy on breast cancer risk may depend on
  - Type of hormone therapy, dose, duration of use
  - Regimen, route of administration
  - Prior exposure to hormone therapy Individual characteristics

Hormone therapy and cognition

- **Hormone therapy is not recommended for preventing or treating cognitive function or dementia**
- Conjugated equine estrogen + medroxyprogesterone acetate initiated in women aged older than 65 years in the Women's Health Initiative Memory Study showed a rare increased risk for dementia
- Estrogen therapy may have positive cognitive benefits if initiated early after surgical menopause
- Hormone therapy in the early postmenopause neutral on cognitive function
- Tentative support (observational studies) available for critical window hypothesis of hormone therapy in Alzheimer disease prevention

Estrogen and Estrogen-Progestogen Hormone Therapy

Categories of hormone therapy

- **Estrogen therapy**
  - Unopposed estrogen for postmenopausal women who have undergone hysterectomy
- **Estrogen-progestogen therapy**
  - For postmenopausal women with a uterus
  - Progestogen reduces the risk of endometrial adenocarcinoma from unopposed estrogen
- **Estrogen agonist/antagonist therapy**
  - For postmenopausal women with a uterus who prefer a progestogen-free option
  - Estrogen antagonist/agonist has a similar effect to progestogen on the uterine lining

Types of Systemic Estrogen Therapy

- **Conjugated equine estrogens**
  - On the US market >65 y
  - The most used in randomized clinical trials
  - More is known about efficacy and safety than any other estrogen product
  - Approved for prevention of osteoporosis
- **Synthetic conjugated estrogens**
  - US government does not view as a generic equivalent to CEE; approved generic equivalent in Canada
  - Not approved for prevention of osteoporosis
- **Estradiol**
  - Most widely used estrogen in Europe
  - Only estrogen available in a government-approved, bioidentical formulation
  - Approved for prevention of osteoporosis

Routes of Estrogen Therapy Administration - Oral

- **Most widely used form in North America**
- **Because of first-pass uptake and metabolism in the gastrointestinal tract and the liver**
  - Increase high-density lipoprotein cholesterol (HDL-C)
  - Associated with 25% increase in triglycerides
  - Increase in hepatic globulins, coagulation factors, and some inflammatory markers
  - Decrease in E-selectin, which may affect coronary artery disease

Routes of Estrogen Therapy Administration - Transdermal

- Based on observational data only, the use of lower doses and transdermal therapy appears to be associated with lower venous thromboembolic and stroke risk
- But . . . the lack of comparative randomized control trial data limits recommendations

Endometrial protection

- For systemic estrogen, endometrial protection requires an adequate dose and duration of a progestogen or use of the combination conjugated equine estrogen with bazedoxifene (Level I)
- Progestogen therapy is not recommended with low-dose vaginal estrogen—1-year safety data
- Appropriate evaluation of the endometrium should be performed for vaginal bleeding (Level I)

Types of Progestogen Therapy

- **Micronized Progesterone**
  - Compound identical to endogenous progesterone
  - Prometrium is the only FDA-approved bioidentical progestogen
  - Contraindicated in women with peanut allergy
  - Bedtime dosing advised because of sedating effects
- **Progestin**
  - Synthetic products with progesterone-like activity
  - Classified into two groups based on structure
  - Chemical structure similar to progesterone
    - Medroxyprogesterone acetate (MPA) is the most commonly used and studied in the United States for endometrial protection
  - Chemical structure similar to testosterone

Methods of Estrogen Progestogen Therapy Administration

- **Continuous-cyclic (sequential)**
  - Daily estrogen with progestogen added cyclically for 12-14 days each month
  - 80% of women will experience bleeding with progestogen withdrawal
- **Continuous-combined**
  - Daily estrogen and progestogen
  - Low rates of endometrial hyperplasia
  - Higher rates of amenorrhea
  - Decreased breakthrough bleeding after 2 years

Potential Adverse Events of Hormone Therapy

- Uterine bleeding (starting or returning)
- Breast tenderness (sometimes enlargement)
- Nausea
- Abdominal bloating
- Fluid retention in extremities
- Changes to the shape of the cornea (sometimes leading to contact lens intolerance)
- Headache (sometimes migraine)
- Dizziness
- Mood changes with estrogen progestogen therapy, particularly with progestin
- Angioedema
- Gallstones, pancreatitis

Monitoring Hormone Therapy

- **Annual return visits**
  - More frequent visits for new starts or those with adverse events
- **Annual mammogram**
- **Endometrial sampling is not required unless postmenopausal bleeding develops**
- **Clinical goal**
  - Use the appropriate hormone therapy dose, duration, regimen, and route of administration
  - Periodic reevaluation

Stopping Systemic Hormone Therapy

- Decision should be individualized on the basis of severity of symptoms and risk-benefit ratio considerations
- Meta-analyses of randomized, controlled trial showed absolute risks that increased with age or time from menopause included coronary heart disease, stroke, venous thromboembolism, and pulmonary embolism
- However, approximately 50% of women will experience recurrence of symptoms with discontinuation
- Low-dose, local estrogen therapy may be continued as long as vaginal symptoms are present

No general rule to discontinue hormone therapy after age 65

- The recommendation to use the Beers criteria to routinely discontinue systemic hormone therapy after age 65 is not supported by data
- Decisions regarding whether to continue hormone therapy beyond the age of 60 years should be individualized
  - After appropriate evaluation
  - Counseling about potential benefits and risks
  - Ongoing surveillance (Level III)

Conclusions

The experts agree about hormone therapy

- Benefits are likely to outweigh risks for symptomatic women who initiate hormone therapy aged younger than 60 years or within 10 years of menopause onset (Level I)

The experts agree about who should not use hormone therapy

- For women who initiate hormone therapy more than 10 or 20 years from menopause onset or aged 60 years and older, the benefit-risk ratio appears less favorable than for younger women
- Greater absolute risks
  - Coronary heart disease
  - Stroke
  - Venous thromboembolism
  - Dementia

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Menopause and Osteoporosis

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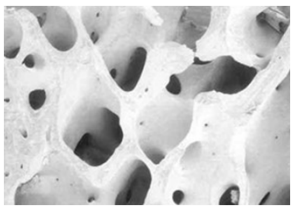
Resources:

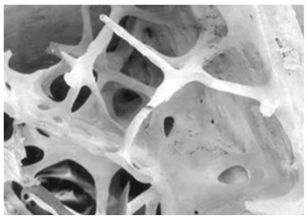
- National Osteoporosis Foundation
  - Cosman, F, de Beur, SJ, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int.* 2014;25:2359-2381
- American Association of Clinical Endocrinologists (AACE/ACE)
  - Camacho PM, Petak SM, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis, 2020 Update. *Endocr Pract.* 2020;26(Suppl 1). 1-46
- North American Menopause Society
  - Blake J, Lewiecki EM, et al. Management of osteoporosis in postmenopausal women: the 2021 position statement of the North American Menopause Society. *Menopause*. 2021;28(9)973-997

What is osteoporosis?

Normal bone



Osteoporotic bone

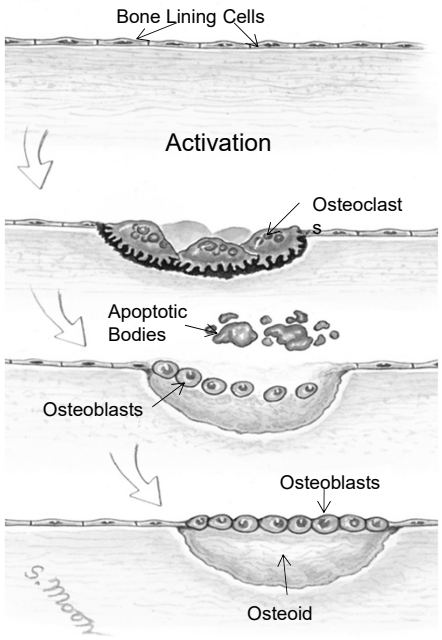


David Dempster, PhD. 2005, images used with permission

"Osteoporosis is a defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture"

NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. *JAMA*.2001;285:785-795

The Life Cycle of Bone



Resting

Resorption

Reversal

Formation ------ Mineralization

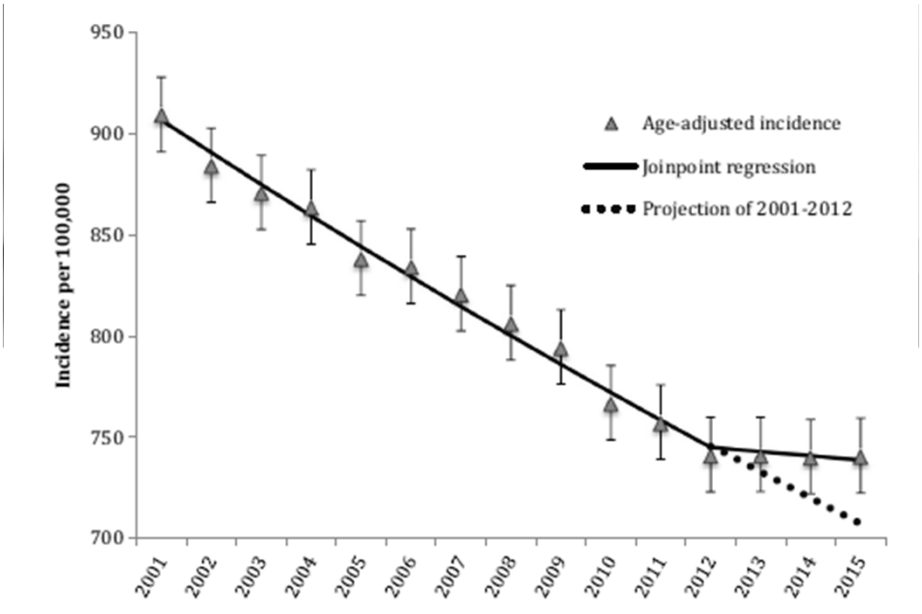
Steve Moon, MS,, Professor, School of Allied Medical Professions, OSU COM, Atwell Hall
Used with permission

When should we start thinking about bone health?

Hip Fractures

- Result in excess mortality of 10-20% within the first year
- *15% of women aged ≥ 80 will have a hip fracture*
- 20% of patients with hip fracture require long-term nursing home care
  - Decreased independence, depression, loss of quality of life
- Only 40% regain full independence follow hip fracture
- Account for 14% of all fractures but 72% of cost
  - In 2005 accounted for over 400,000 hospital stays
  - $12.5 billion annually
  - Estimated to exceed $25 billion in 2025

Camacho PM, Petak SM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis, Endocrine Practice September 2016, 22(4)



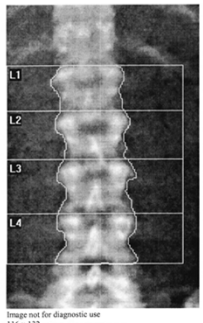
Used with permission

ASBMR Secondary Fracture Prevention Initiative Coalition, 2017 www.secondaryfractures.org

Lewiecki EM, et al. Hip fracture trends in the United States. Osteoporos Int (2018) 29:717-722

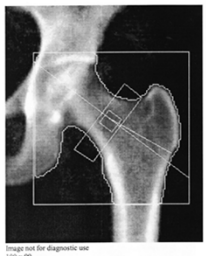
Screening Guidelines

- DXA
  - Women ≥ 65yo
  - Men ≥70
  - Postmenopausal women and men aged 50-69 based on risk factor profile
  - Postmenopausal women and men over age 50 who have had a fragility fracture
  - Screening of premenopausal women decided individually
  - Only to be done at facilities using accepted QA



DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
L1	12.83	13.95	1.087	1.5	117	1.7	121
L2	13.71	16.36	1.193	1.5	116	1.8	120
L3	16.37	19.97	1.220	1.2	113	1.5	116
L4	16.36	21.10	1.289	1.6	116	1.9	119
Total	**59.28**	**71.38**	**1.204**	**1.4**	**115**	**1.7**	**119**



DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
Neck	5.40	4.74	0.879	0.3	104	0.6	108
Total	32.50	34.76	1.070	1.0	114	1.2	117

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased

www.nof.org; Clinician's Guide to the Prevention and Treatment of Osteoporosis, updated 4/2014
Camacho PM, Petak SM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis, Endocrine Practice, May 2020

Newly menopausal women and bone health

- Age, weight, ethnicity
- Good height measurement
- Exam: goiter? Kyphosis?
- *History: FRACTURES?*
  - Steroids
  - Malignancy
  - Stones
  - Falls
  - **Physical assistance**
  - Occupation
  - Diet and supplements
  - Smoking
  - exercise

In the 1-2 years before menopause for a total of 8-10 years, see a 2% decline in bone density annually
- *This then slows to 0.5 – 1%*

Best determination of fractures to come: previous fractures

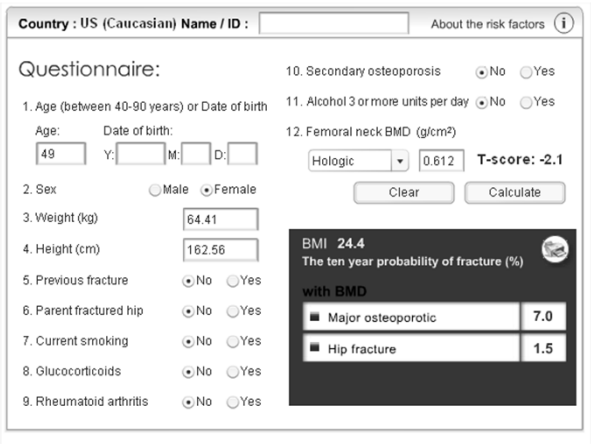
Family history is extremely important

You decide DXA testing is indicated:

- Diagnosis: T-score
  - Normal: ≥ -1.0
  - Osteopenia: <-1 - >-2.5
  - Osteoporosis: ≤-2.5

Also consider vertebral imaging?

- Osteopenia –

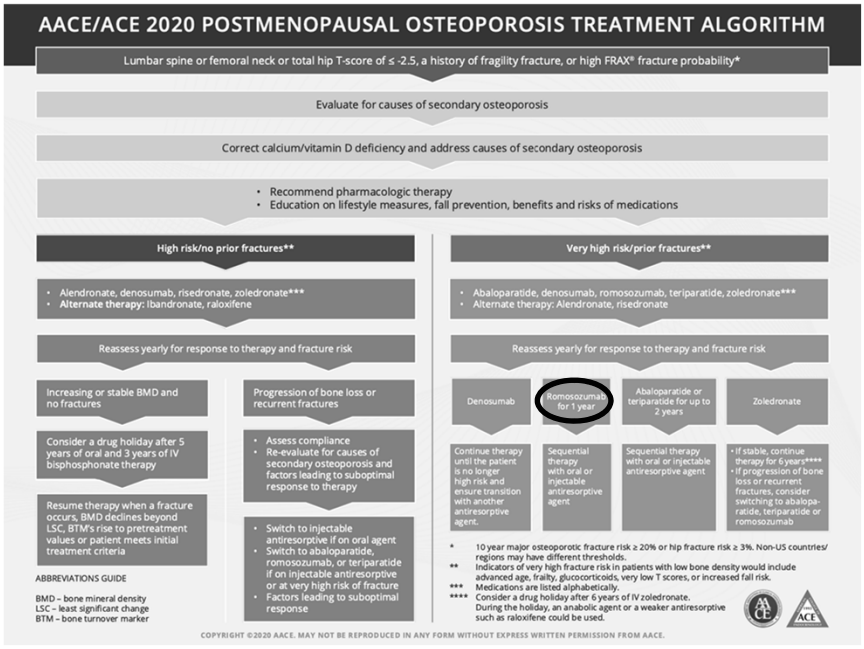


http://www.shef.ac.uk/FRAX/tool.jsp

NOF Treatment Recommendations

- Therapy is indicated in those with hip or vertebral (clinical or morphometric) fracture
  - NOF now recommends baseline plain X-rays or VFA of spine
- Treatment is indicated for those with T-score ≤-2.5
  - FRAX is recommended for T-score <-1.0 to >-2.5
- Diagnosis should be made using T-score from total hip, femoral neck or lumbar spine
  - Not forearm, though this is a valuable tool in certain groups
- The NOF currently *does not necessarily recommend bisphosphonates as first-line therapy*
  - Therapy should be based on efficacy, cost, safety, convenience – this usually is an oral bisphosphonate for first line therapy
- No pharmacologic therapy should be considered indefinite

Cosman F, de Beur SJ, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. August 2014



*Used with permission

Camacho PM, Petak SM, et al. *Endocr Pract* 2020: 26(Suppl 1)

Evaluation of Osteoporosis

- Basic look for 2^0 causes:
  - TSH
  - Calcium, phos, Mg
    - Albumin, for correction
  - PTH
  - 25(OH) vit D
  - Creatinine
- Other considerations:
  - Men: Testosterone
  - CBC
  - Serum immunofixation, free light chains
  - TTg, IgA, IgG
  - 24 hour urine calcium
  - 24 urine cortisol level
  - $1,25(OH)_2D$
  - Markers of bone turnover
    - BSAP, C-Tx

Calcium and vitamin D

- NOF and IOM Recs:
  - Calcium:
  - Men 50-70: 1000mg cal/d
  - Women ≥50, men ≥70 consume 1000 – 1200mg calcium/d
  - Increasing dietary calcium is preferred over calcium supplements
  - Vitamin D recommendations:
    - NOF: adults ≥ 50: 800-1000u/d
    - IOM: <70, 600 units/day; ≥70 800 units/day
    - Safe upper limit: 4000 units/day
    - Goal: ≥ 30ng/mL serum level

Milk 8 oz: 300mg

Yogurt 6oz: 250mg

Cheese 1": 150mg

www.nof.org: Clinician's Guide to Prevention and Treatment of Osteoporosis, updated 8/2014

www.ncbi.nlm.nih.gov Reference intakes for calcium and vitamin D

Giustina A, et al. Controversies in vitamin D: Summary Statement. J Clin Endocrinol Metab (2019) 104(2):234-240

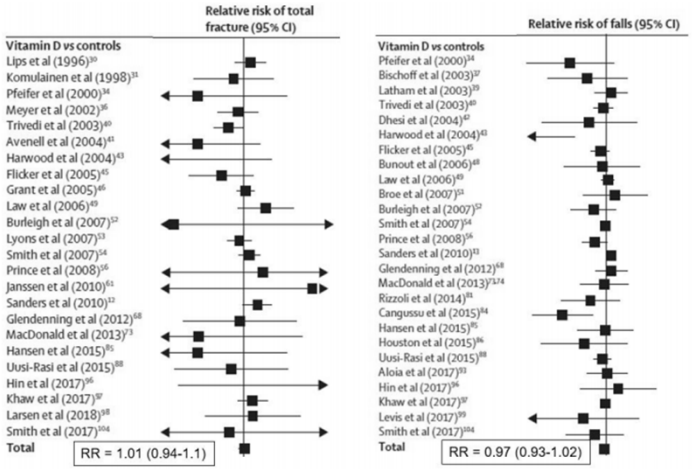
Calcium and vitamin d

- Calcium
  - Better to get from the diet
  - Average 'ambient' calcium in diet is 500mg
  - The gut cannot absorb more than 500mg of calcium at a time
  - Taking more than 1500mg of calcium does not improve calcium balance
    but taking more than 2000mg of calcium increases kidney stones by 17%
  - Carbonate vs. citrate?
- Vitamin D
  - Only one study (WHI) showed a *trend* toward reduction in hip fracture, and only in those with starting vitamin D of <18ng/mL
  - Our "normal" reference range for 25(OH)D is **wrong** (30-100)
  - Vitamin D levels consistently >60 can increase the risk of stones
  - Over the counter, daily vitamin D of 1000 units per day is felt superior to high-dose Rx ergocalciferol

Jackson RD, LaCroix AZ, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669-683

Hansen KE, John RE, et al. Treatment of vitamin D insufficiency in postmenopausal women: a Randomized clinical trial. *JAMA Intern Med*. 2015;175:1612-1621

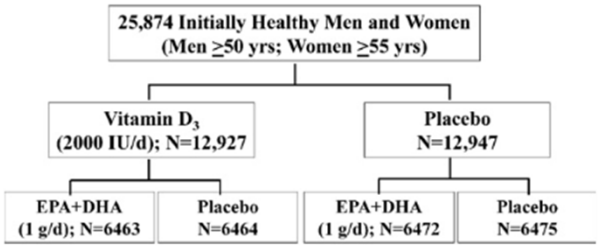
Meta-analysis of trials supplementing vitamin D on total fracture and risk of falls



Boland, et al. *Lancet Diabetes Endocrinol* 2018, 6: 847-858

Vitamin D supplementation

- USPSTF: does not support use of Cal or vitamin D in otherwise health community-dwelling adults
- IOF: calcium supplementation, with vitamin D, is supported for patients at high risk of Cal and Vitamin D deficiency and osteoporosis



Mean Treatment Period = 5.0 years
Blood collection in 16,956, follow-up samples in ~6000
Primary Outcomes: Cancer (total) and CVD (MI, stroke, CVD death)

VITaminD and OmegA-3 TriaL (VITAL)

Bassuk SS, Manson JE, *NEJM* 2019, 380:1, 33-44

Moyer, VA, et al. *Ann Intern Med* 2013, 158:691-696
Harvey, NC, Biver E, et al. *Osteoporos Int* 2017, 28:447-462

Exercise: "The perception that exercise can reverse osteoporosis in postmenopausal women by inducing new bone formation is unfounded".

- Impact-loading exercise programs may induce small gains in BMD
- *Goal is to reduce falls, improve balance*
- Core strength and good body mechanics should also be emphasized

Blake J, Cosman F, et al. NAMS Position Statement. *Menopause* 2021;28(9):973-997

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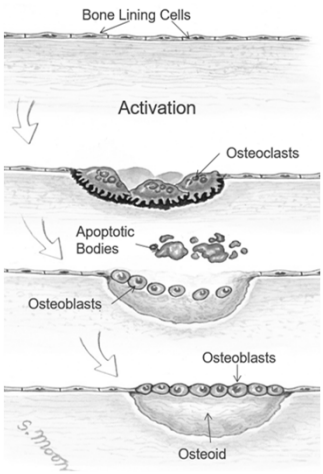
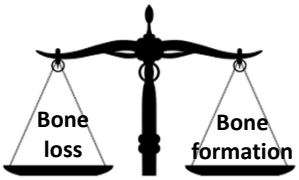
Other, non-pharmacologic approaches:

- Vitamin K: no evidence that vitamin K affects bone density or vertebral fracture risk
- Magnesium: WHI study (the only non-observational study of magnesium) showed no reduction in fracture risk
- Strontium: recently taken off of the market in Europe as was causing strokes
- Soda – two per day is OK; caffeine: two servings per day is OK
- Prunes?

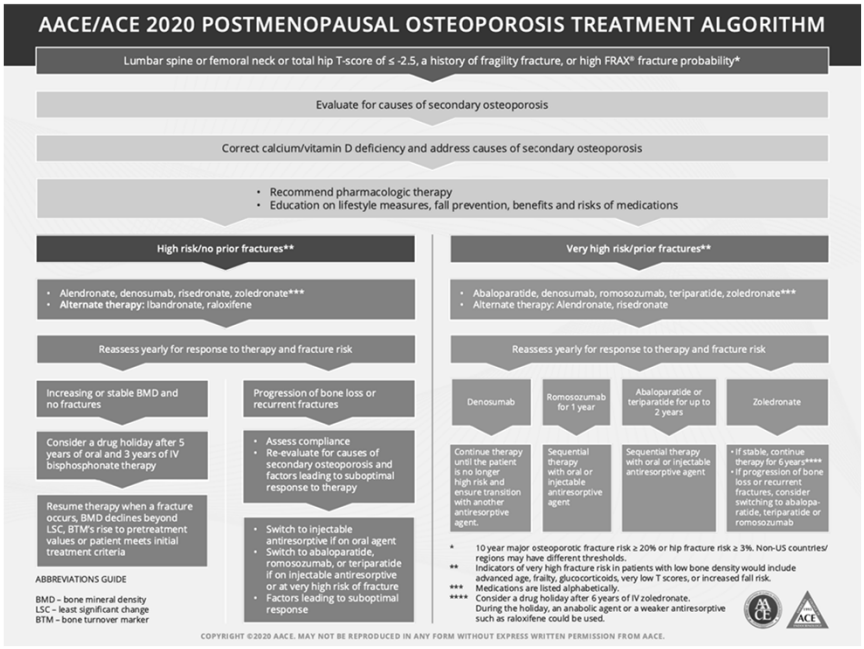
Therapy Considerations:



With estrogen:



Without estrogen:

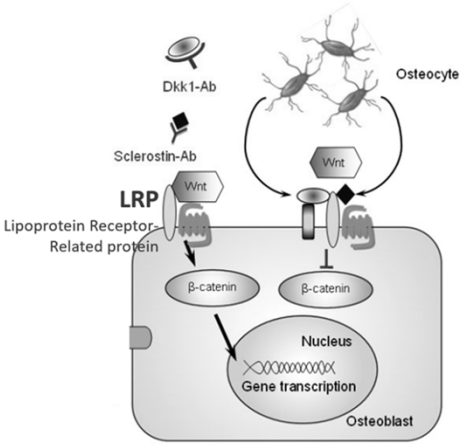


*Used with permission

Camacho PM, Petak SM, et al. *Endocr Pract* 2020: 26(Suppl 1)

Newest FDA approved therapy for osteoporosis:

Romosozumab: Anti-sclerostin antibody



- The binding of Wnt to its receptors induces association with LRP, β–catenin is stabilized and target genes are activated, resulting in *osteoblastic formation*
- **Sclerostin is a circulating inhibitor of the Wnt-signaling pathway, which binds to LRP 5 and 6**
- **High bone density was seen in nature with an inactivating mutation in the SOST gene which causes formation of sclerostin by osteocytes**

McClung MR. Endocrinology and Metabolism, Sept 2015(30): 429-435
Ng KW, Martin TJ. ASBMR Primer on Metabolic Bone Disease, 8th Ed, Ch 56, 461-467

"Don't miss the forest for the trees":