Female hormones & the impact on osteoporosis and bone health

Tanya Borowski

Major Functions of Bone

- Provide **structural** support for the body
- Provide **protection** of vital organs
- Provide an **environment for marrow**

(Red Cell formation)

- **Minerals homeostasis;**

As the main reservoir for minerals;

99% of the body's calcium

85% of its phosphate

50% of its magnesium

(Bartl and Bartl, 2017)

Bone Composition

An adaptable tissue with a protein 'matrix' that becomes strong with mineralization

- **30% organic matrix** (osteoid);

*- 90% type-I **collagen** fibres*

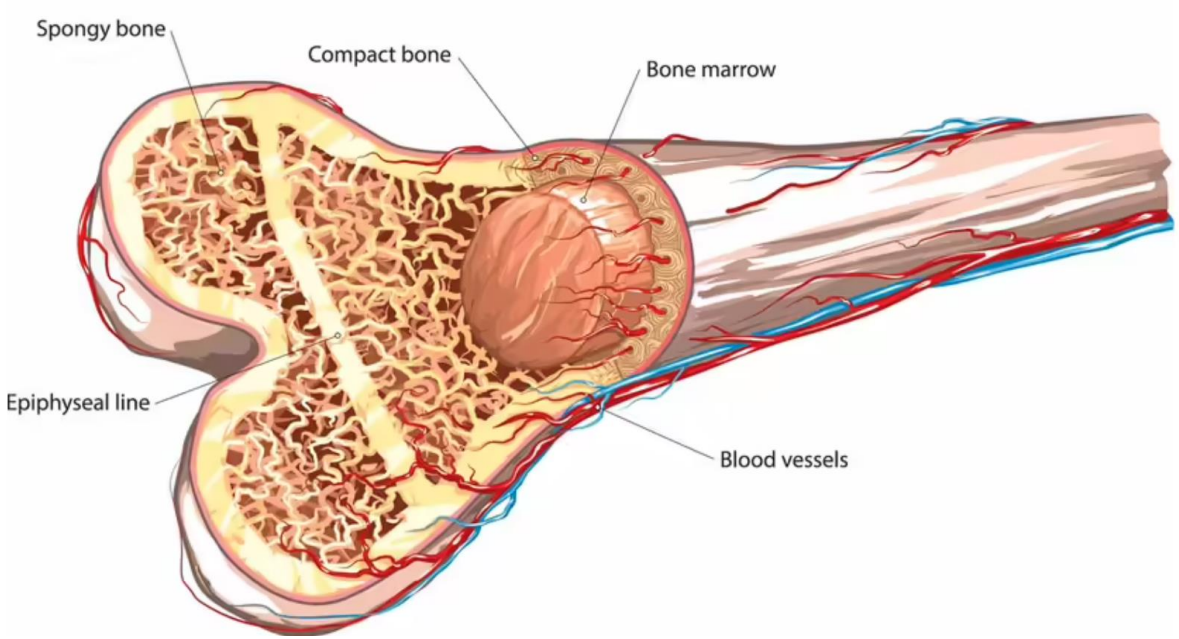
- ***70% inorganic mineral content***

-calcium ,phosphorous(hydroxyapatite);

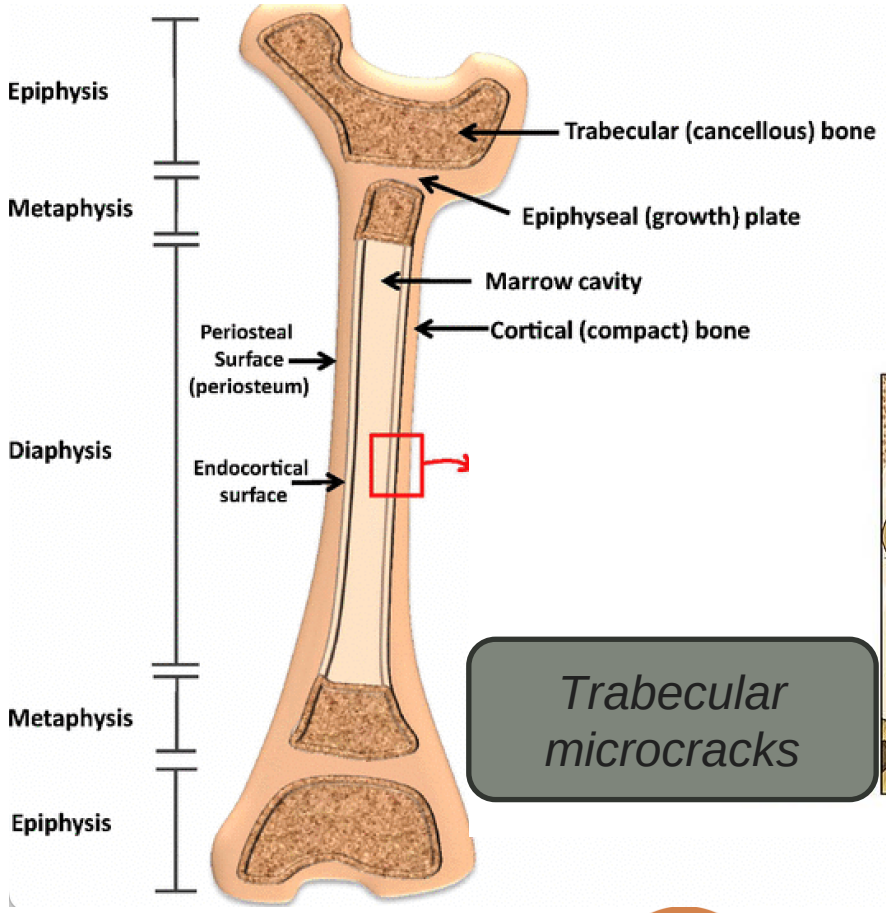
+ Na, Fl, Mg

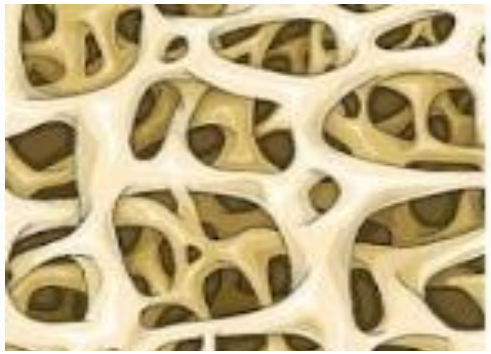
- Bone cells

- Blood supply

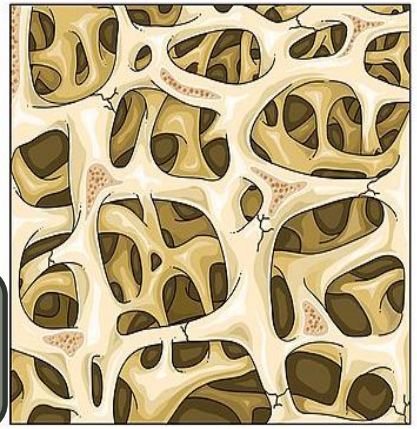


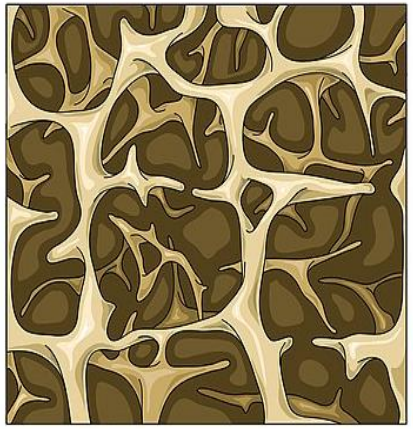
The Structure Bone





Trabecular microcracks





Osteoporotic trabecular Bone

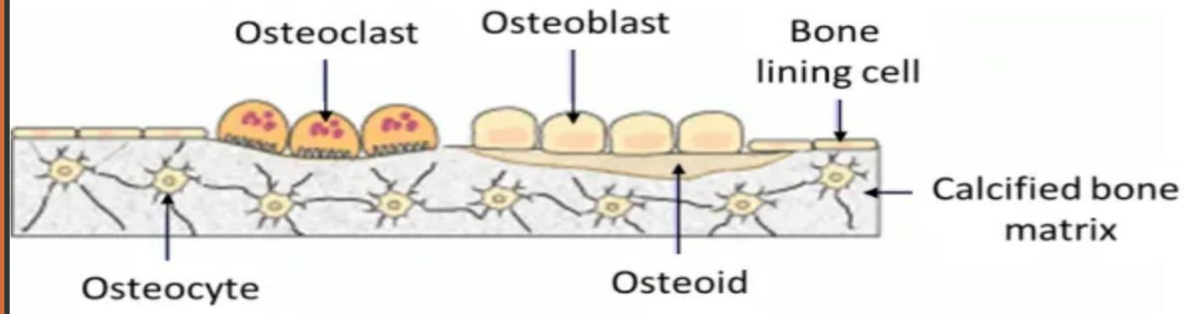
Specialized Bone cells

Osteoclasts- 1-2% of bone cells

Action; ***resorption*** *and* **remodeling mineralized tissue**

Derived; hematopoietic origin, **monocyte/macrophage lineage**

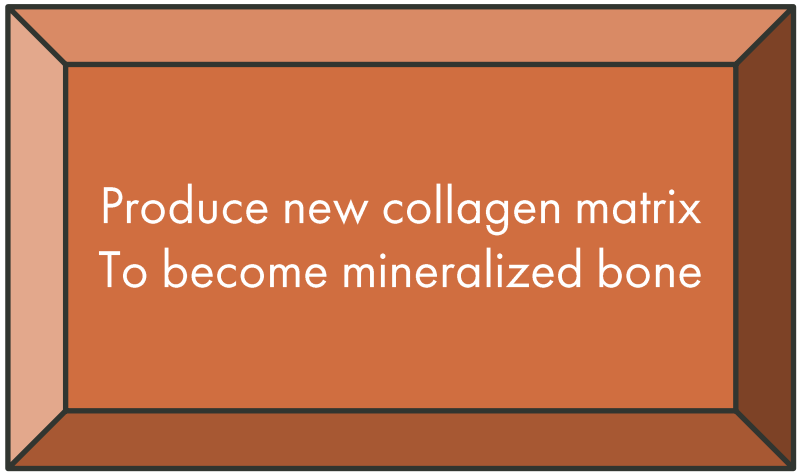
Their characteristic feature is a ruffled edge where active resorption takes place with the secretion of acid and bone-resorbing enzymes, which digest bone mineral and matrix.

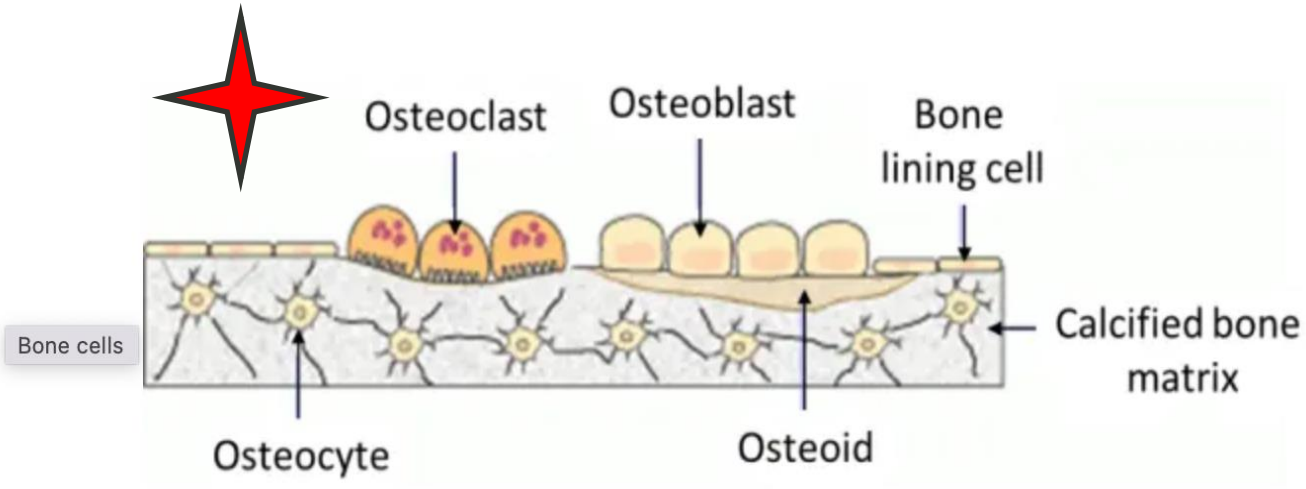


Specialized Bone cells

Osteoblasts- 5% of bone cells

- **Derived**; mesenchymal stem cells, differentiate to multiple cell lineages; ***osteoblasts***, *chondrocytes, myoblasts, adipocytes, and fibroblasts*





In the adult skeleton, the majority of bone surfaces that are not undergoing formation or resorption are lined by bone lining cells.

Specialized Bone cells

Osteocytes – 95% of bone cells

The master regulator, live up to 25 years

These cells are osteoblasts that become incorporated within the newly formed osteoid, which eventually becomes calcified bone.

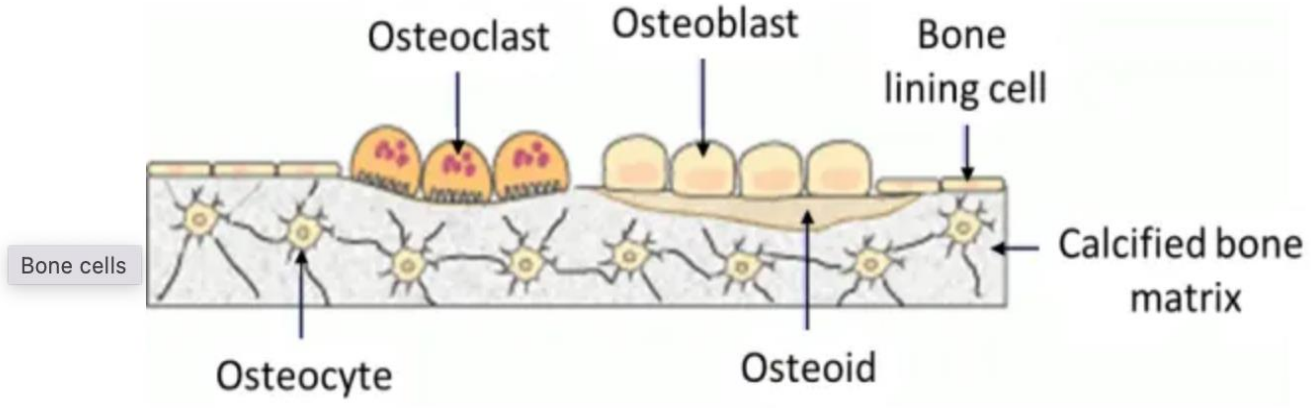
- Canaliculi, sense fluid waves from physical activity and microdamage

Release cytokines :

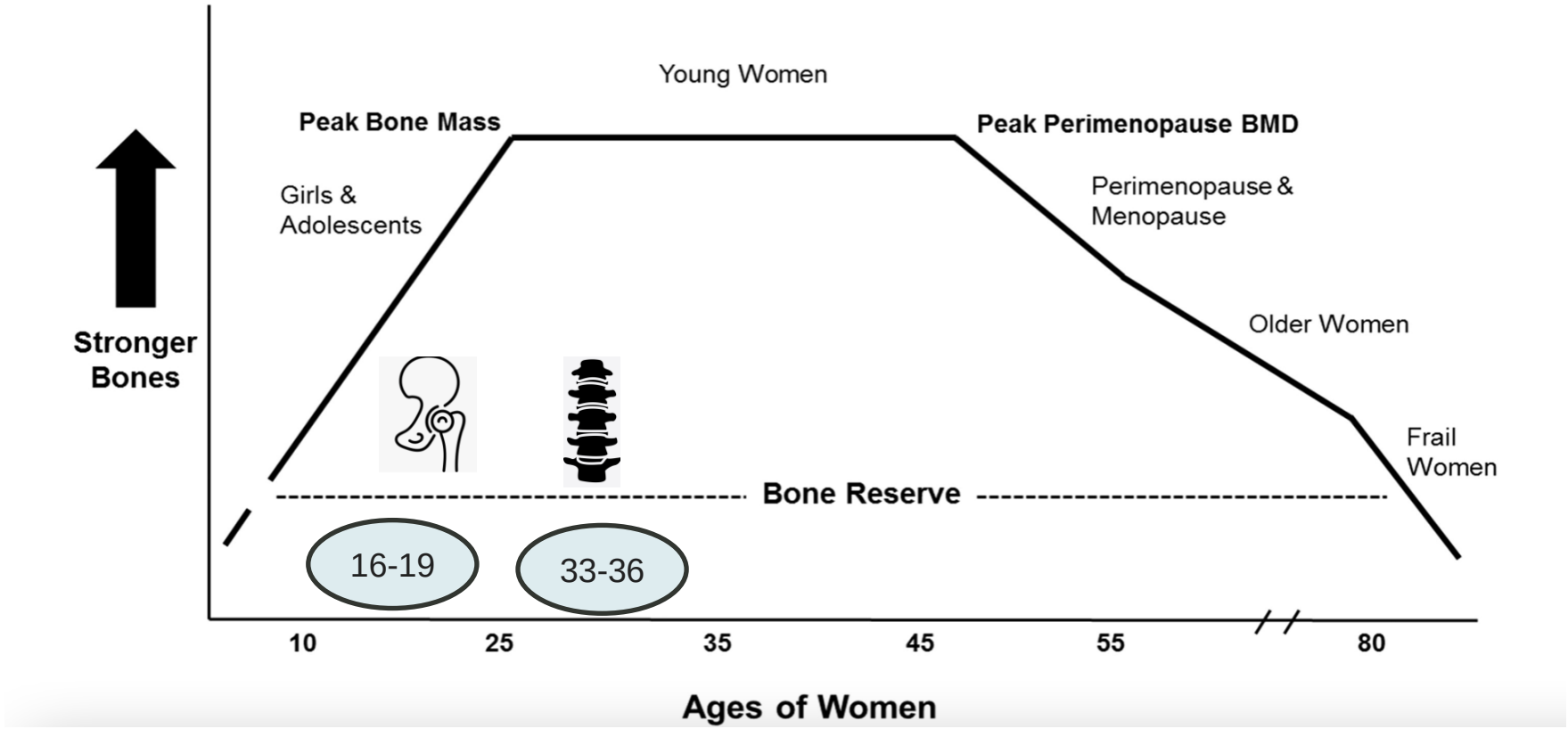
RANKL

Sclerostin

Dickkopf-related protein 1 (DDK1)

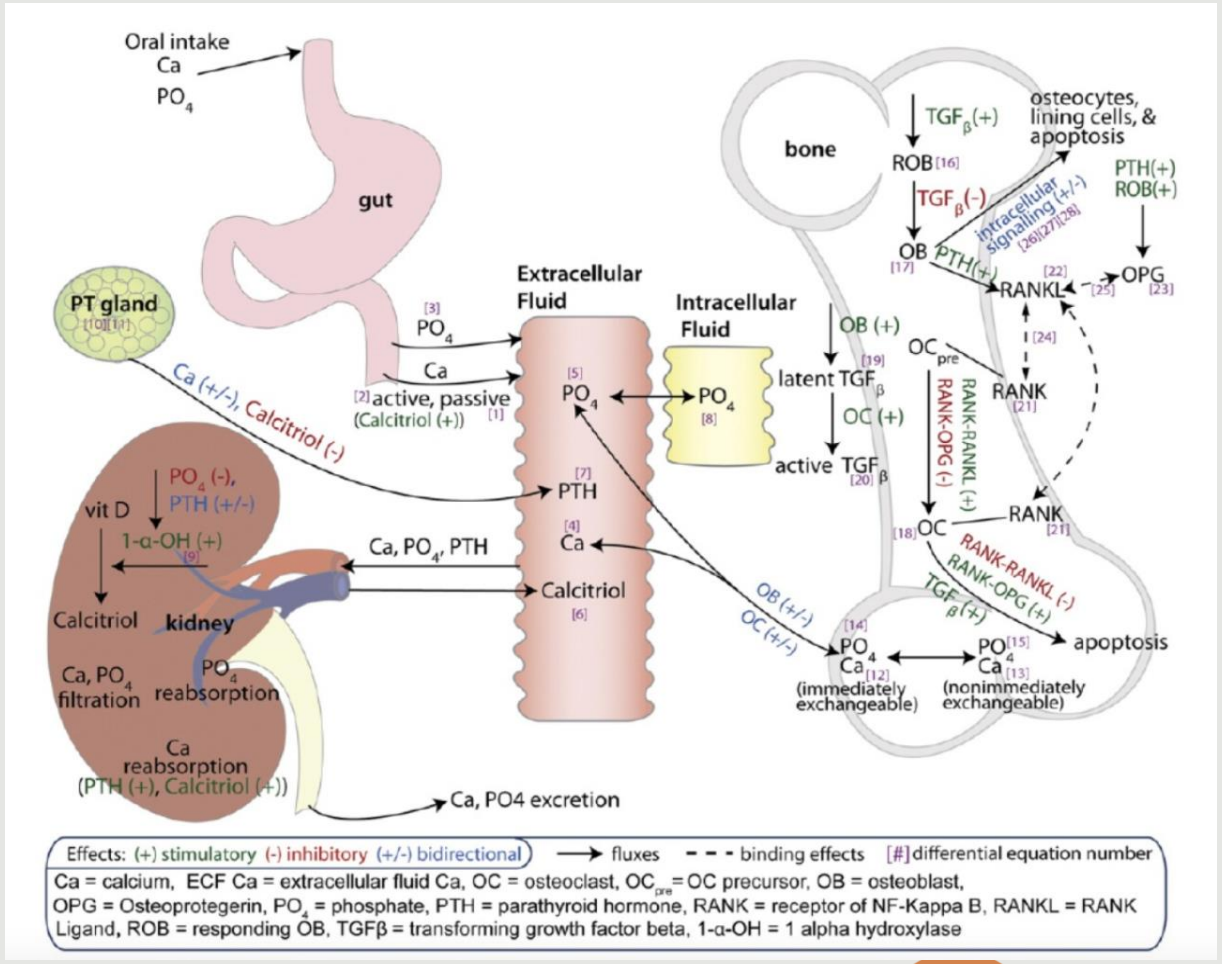


Modeling & Peak Bone Mineral Density



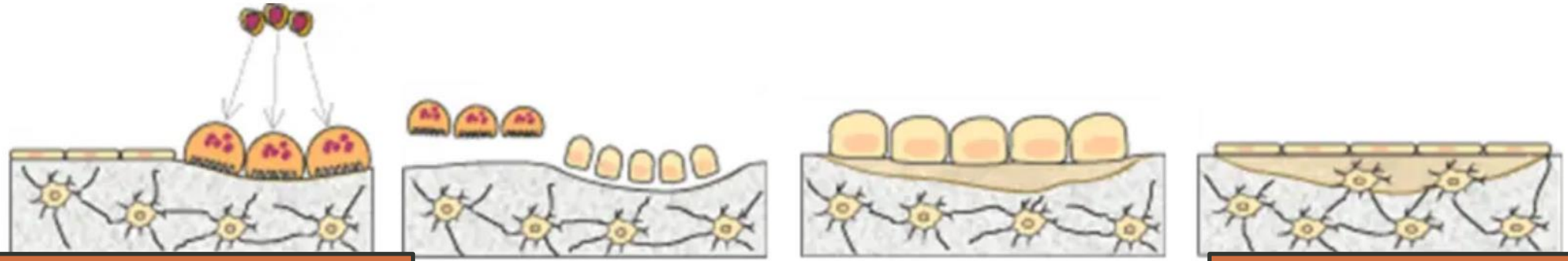
Once bone has formed and matured, it undergoes constant remodelling

Bone turnover is the balance between resorption & formation



Specialist Cells
Hormones
Enzymes
Chemical messengers
Nutrients

Five phases remodeling = coupling



Activation & resorption

Preosteoclasts stimulated & differentiate via cytokines & growth factors into mature active osteoclasts

Reversal
End of resorption

Formation
Osteoblasts synthesize new matrix

Quiescence
Osteoblasts become resting bone lining cells on newly formed bone surface

Wingless integrated – (**Wnt),**

Calcitonin, **RANKL**, Wingless/Integrated signalling pathway (Wnt), (IL)-1, IL-6, IL-11, macrophage colony-stimulating factor (M-CSF), and parathyroid hormone (PTH)

Cells and Signalling for remodelling

(RANK) - **osteoclasts**

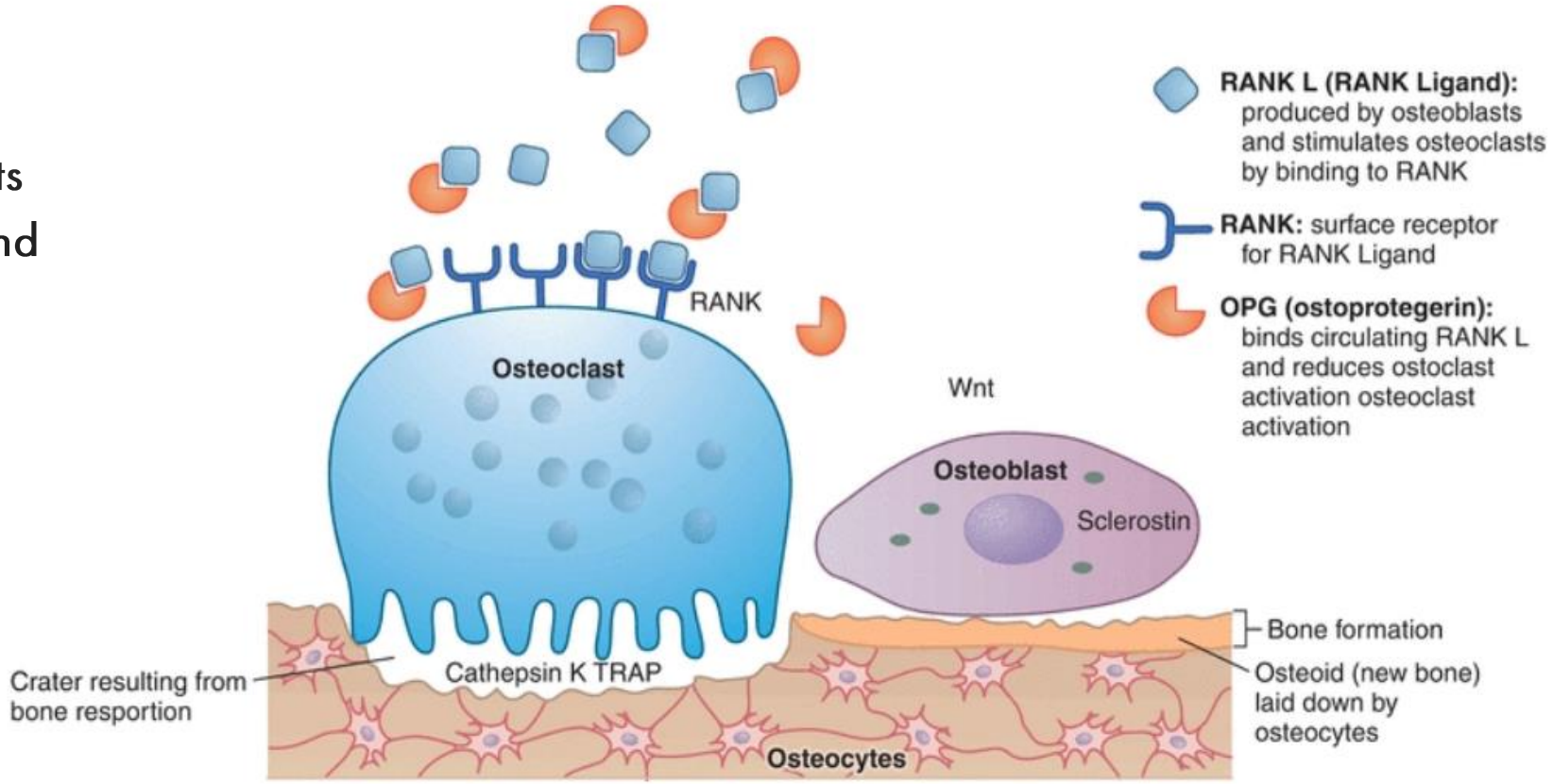
Receptor activator of NF-kB

(RANKL) – **Osteoblasts & 'clasts**

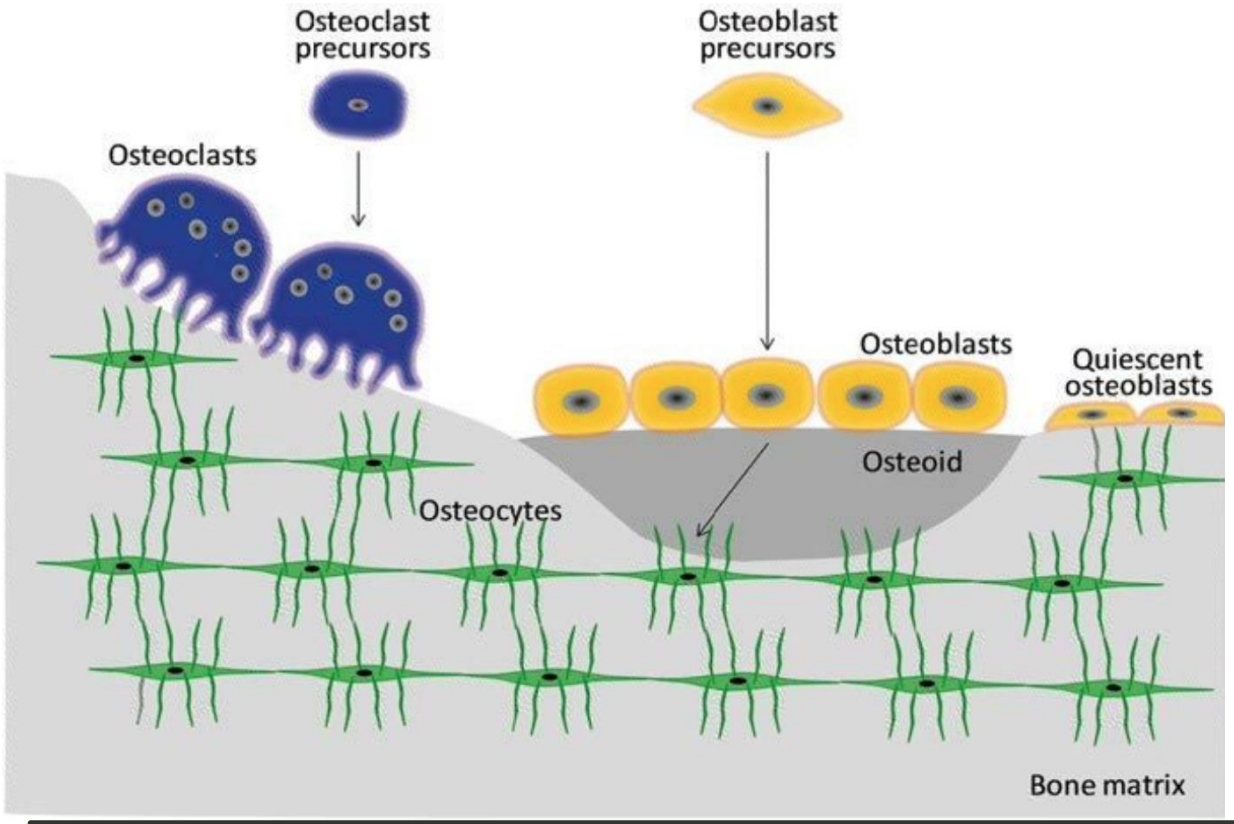
receptor activator of NF-kB **ligand**

(OPG)

osteoprotegerin – decoy



To Achieve Coupled Bone Remodeling



Resorption is quick (over 3 weeks)
Formation is slow (over 3–4 months)

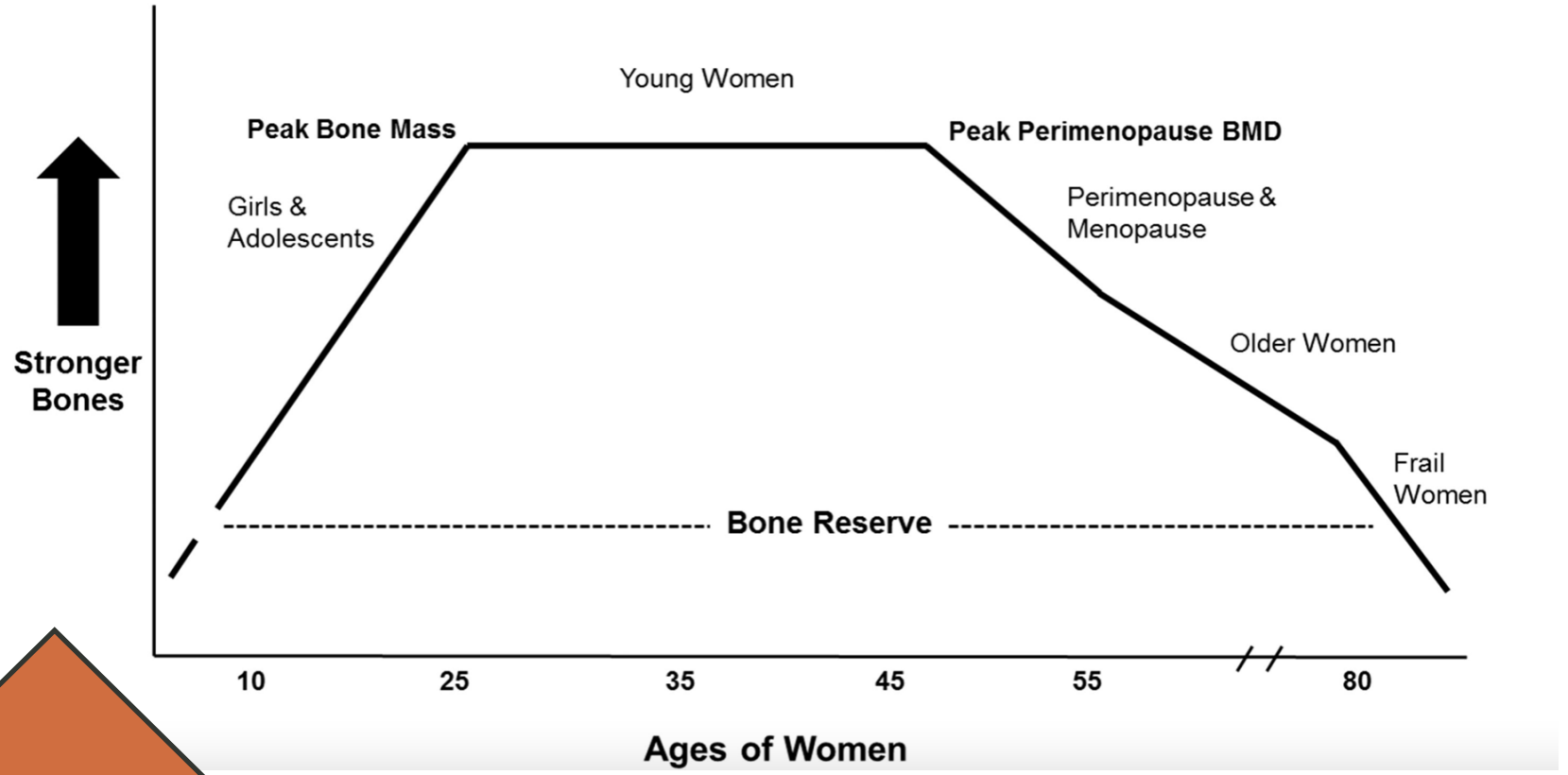
In general, trabecular bone resorption and formation occur 4 to 8 times as fast as cortical bone

The balance during the menstruating years likely determines lifelong bone health

E2
Slows
resorption

P4
stimulates
Formation

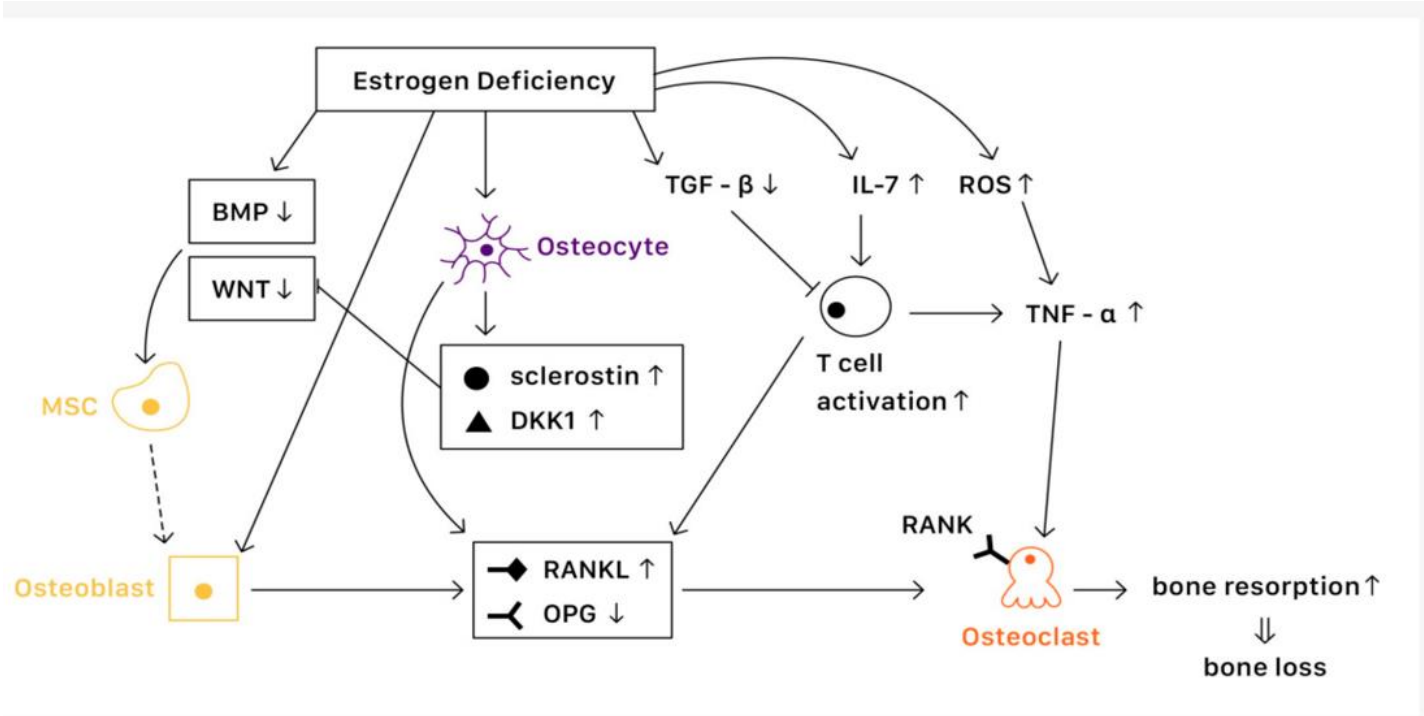
Puberty
IGF-1
GH



Hormonal roles on bone remodeling

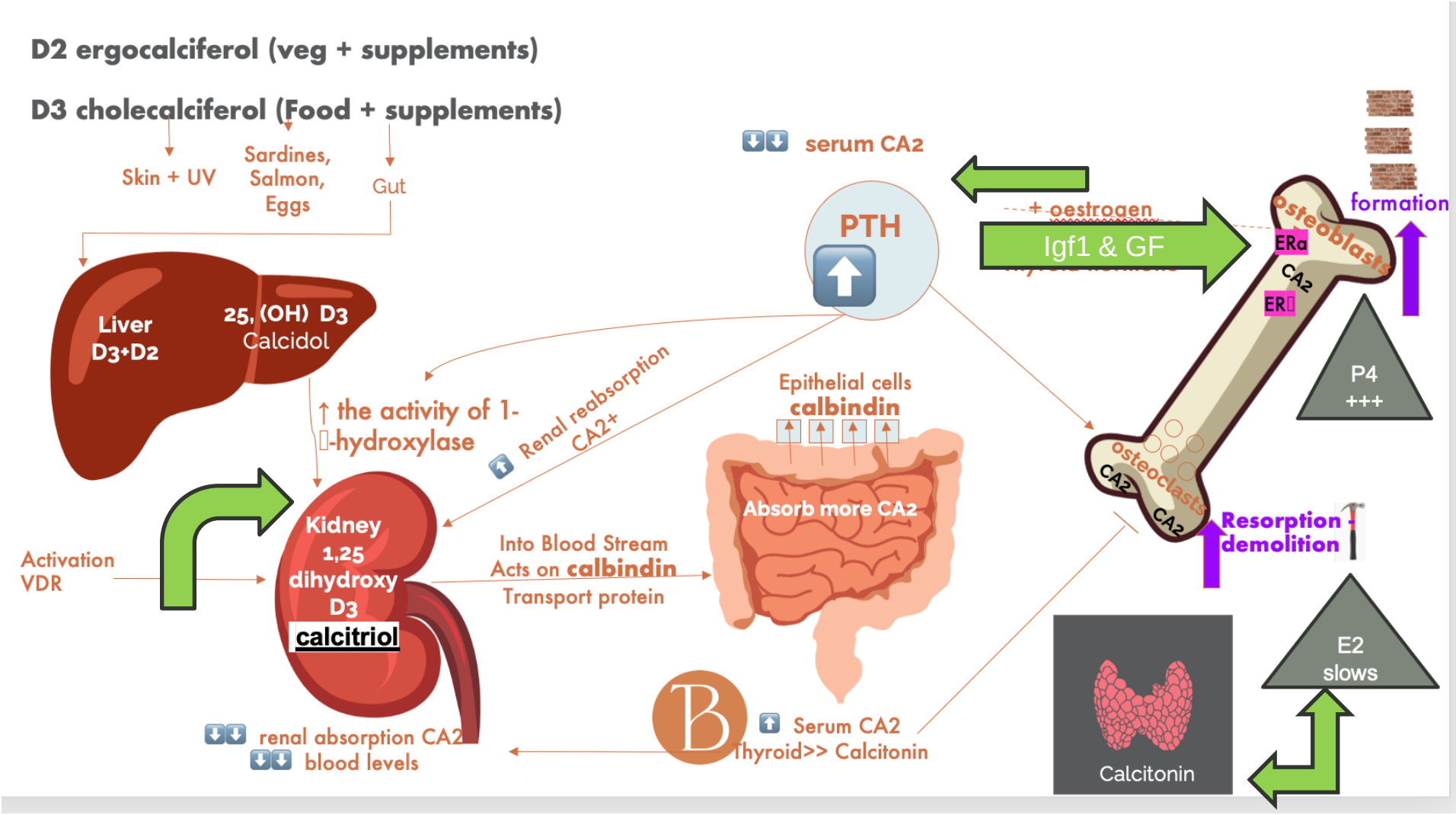
- E2 **most** important for bone, when in moderate or high physiological levels, its role to decrease resorption (via OPG & osteoblast production)
- P4 receptors osteoblasts , stimulates new osteoblast formation; create matrix

When E2 levels drop, this triggers a cascade of cytokines(RANK-L) stimulates a rapid increase in bone resorption.



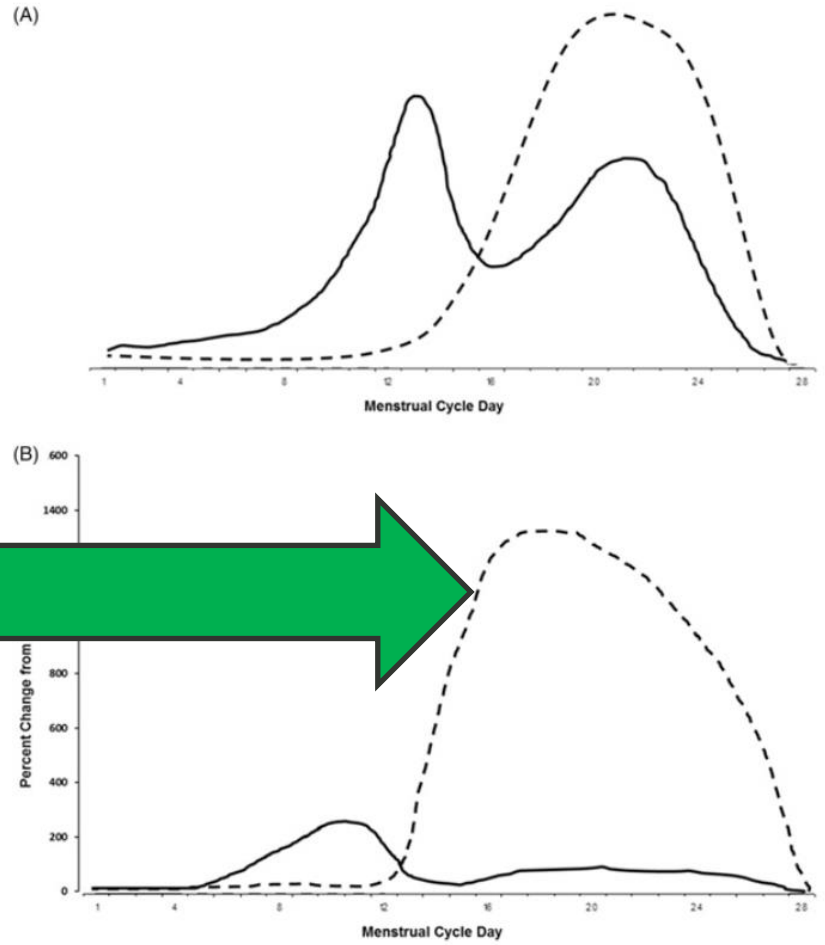
Int. J. Mol. Sci. **2022**, *23*(3), 1376; https://doi.org/10.3390/ijms23031376

- E2 **in addition** 1) lowering the sensitivity of bone mass to PTH, thus reducing bone resorption, 2) increasing the production of calcitonin, thus inhibiting bone resorption, 3) accelerating calcium resorption by the intestine, 4) reducing the calcium excretion from the kidney, and 5) direct effects in the bone via estrogen receptors a + b



Pre-menopause transition
Ovulatory Cycles = Bone Balance

- As E2 levels rise>*stimulate* Gh + IGF-1, bone resorptic inhibited
- P4 peak that stimulates bone formation.



Although the decreasing E2 levels from peak to menstrual flow trigger a small increase in bone resorption, P4's bone formation–stimulation counter-balances that to result in a net, stable BMD

E2 is in pmol/l and P4 in the 1000-fold higher nmol/l

Hormonal roles on bone remodeling

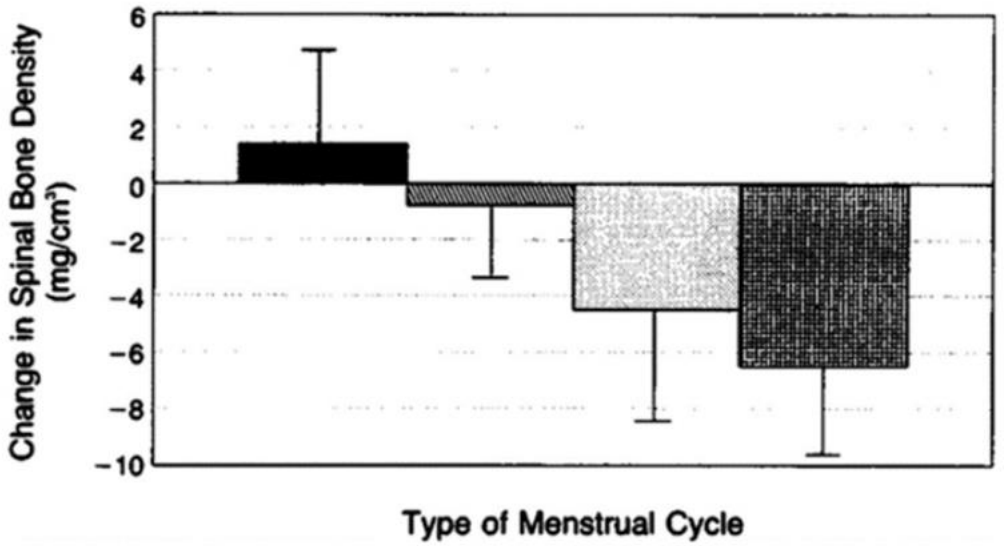
- Optimal P4 related bone formation requires luteal phase length 10-14 days

Prospective , observational study 1-year study 66 women

Those with ovulatory or experienced only one short luteal cycle per year maintained cancellous BMD.

Vs

Those with one or more short luteal phases or any anovulatory cycles significantly lost BMD at rates of 4–6%/year



Reprinted with permission from the New England Journal of Medicine

Hormonal roles on bone remodeling

A meta-analysis of spinal BMD change that monitored 436 women (18 - 46yrs) - 1 year for cycles and ovulation, showed that, within each study, *those with less than median proportion of normally ovulatory cycles*, were losing almost 1% (-0.86%) of spinal BMD/year.

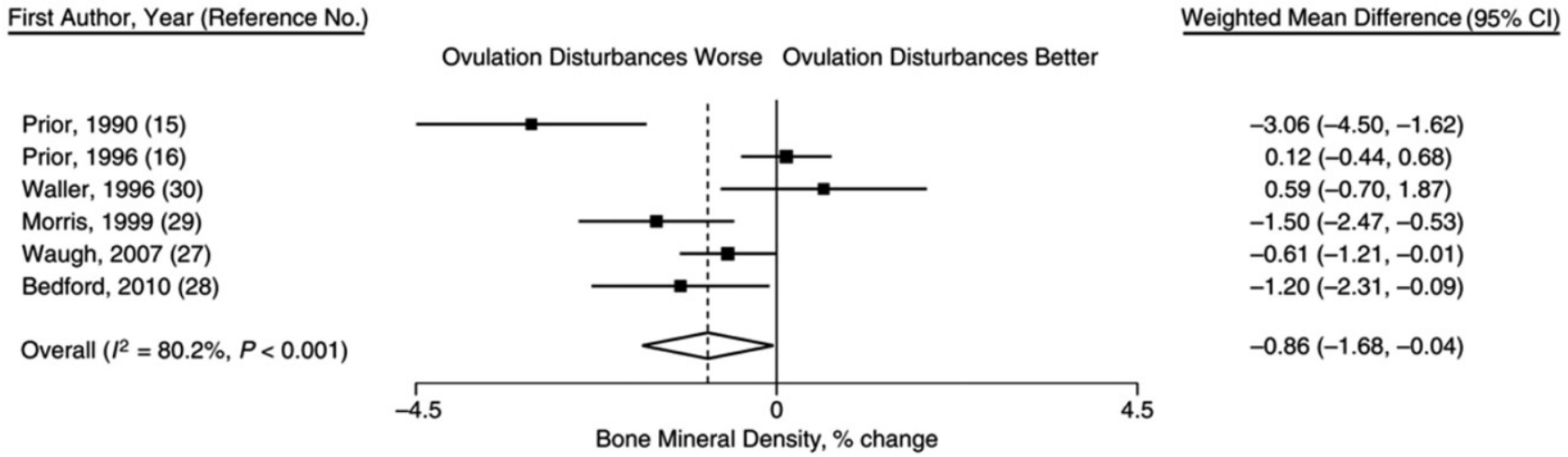


Figure 5. Forest plot from a meta-analysis of six prospective, observational studies in 436 premenopausal women tracking 1-year menstrual cycles, ovulatory characteristics and percentage changes in bone mineral density (BMD). Results show a highly heterogeneous ($I^2 = 80.2\%$) random effects model with -0.86%/year more spinal BMD loss in those with worse ovulatory disturbances[24]. Reprinted with permission of *Epidemiologic Reviews*[24].

Impacts COCP in Adolescence

Bone growth, modeling & remodeling modulated by E2, P4, androgens, GH, IGF-1

-Exogenous estradiol inhibits GH and IGF-1

-E2 increases stimulates osteocyte sensitivity to loading stimuli - impacting bone strength puberty

In contrast to observations from adult women, studies in teens indicate that COC use in adolescence can compromise bone mineral acquisition, especially in the first 3 years post menarche. Initial reports noted lower rates of bone mineral accrual in teens using low-dose (20 mcg ethinyl estradiol) COC formulations when compared with controls not taking hormonal contraceptives. A 1 year study found smaller mean gains in BMD in 79 teens (aged 12–18 years) taking a low-dose COC than in 107 non-user controls (19). Spine BMD increased by 2.3% (95% CI 1.49, 3.18) in users as compared with 3.8% (95% CI 3.11, 4.57) in controls ($P < 0.001$). Gains in femoral neck BMD were also significantly lower (0.3% vs. 2.3%, respectively, $p = 0.03$). A second study found significantly lower bone mineral acquisition in 67 adolescents (ages 12–19 years) using a low-dose COC as compared with non-users (20). These findings are consistent with those reported for young adult women (aged 19–22) taking low-dose COCs whose spine BMD was unchanged over 5 years while non-users gained 7.8% (21).

frontiers in Endocrinology

Hormonal Contraception and Bone Health in Adolescents

*Laura K. Bachrach**

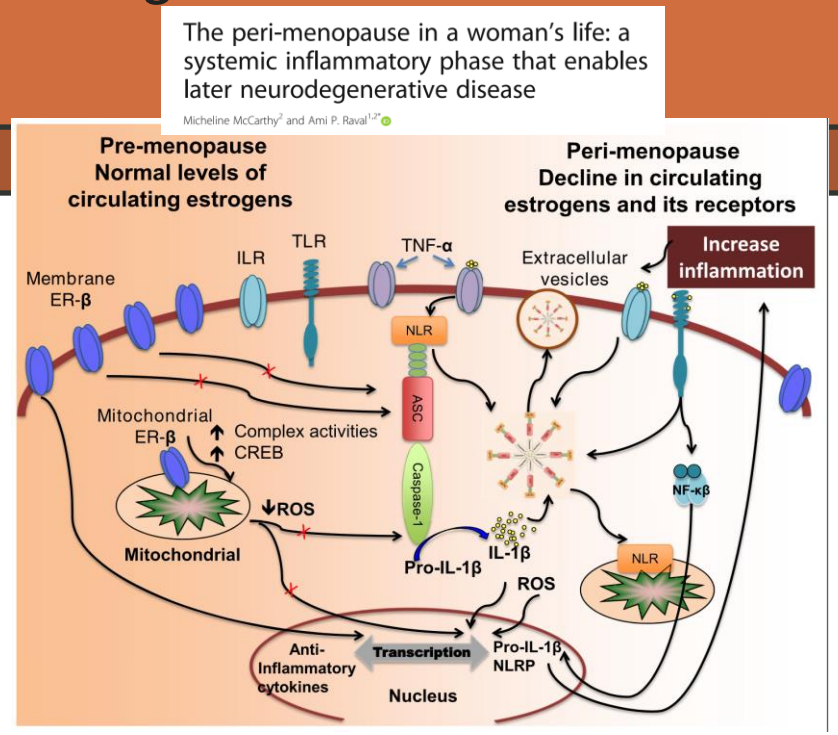
Intramuscular DMPA inhibits endogenous estrogen production resulting in lower estrogen concentrations and bone loss. This effect is dose-related, with decreases in BMD observed in adolescents (aged 12–21) given 150 mg or 104 mg every 12 weeks, but not when treated with 75 mg (30).

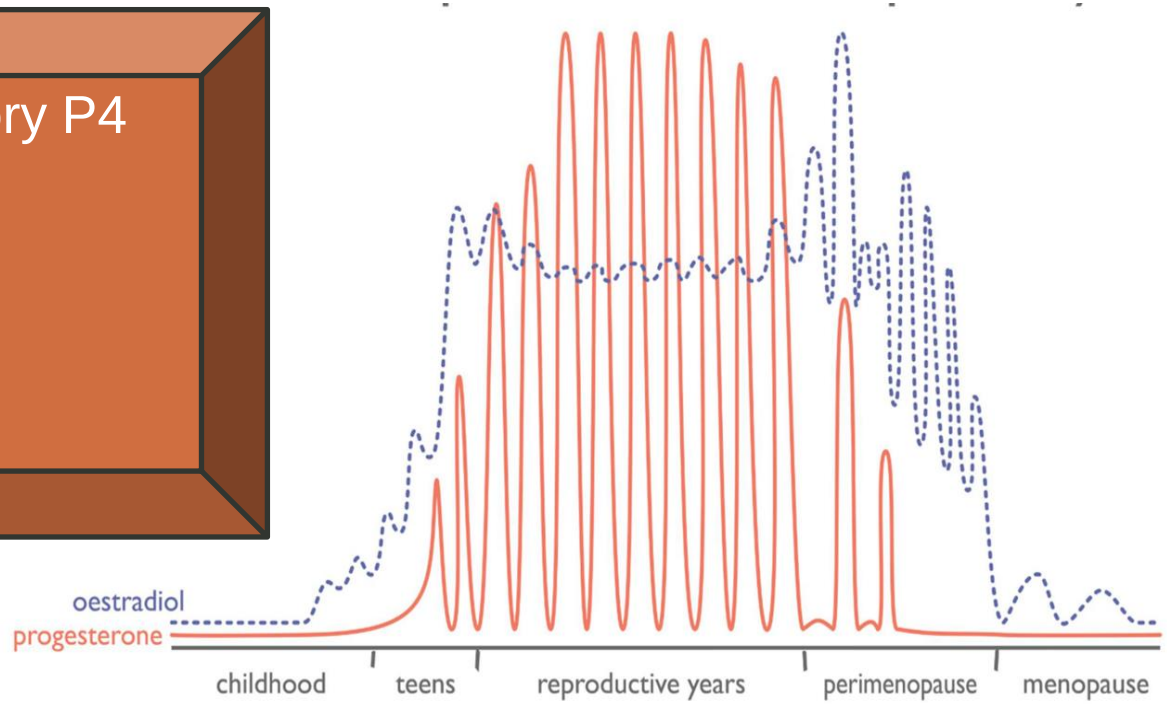
https://doi.org/10.3389/fendo.2020.00603

Perimenopause

1. Higher, erratic E2 and decreasing ovulatory P4
2. HPO feedback disturbances
3. Increased inflammation

Negative for bone balance



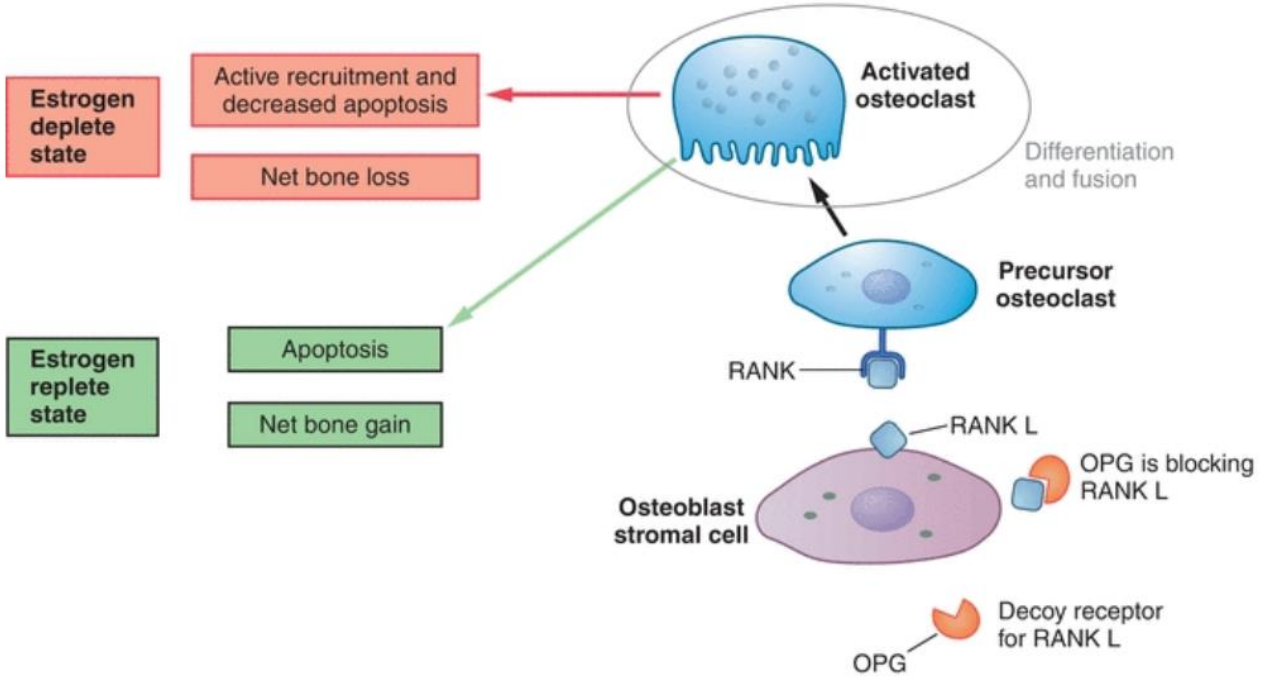


"ER-b has been shown to regulate a key component of the innate immune response known as the inflammasome…….. the ***menopausal transition as an inflammatory event***, plus regulation of the innate immune response"

The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. *J Neuroinflammation* **17**, 317 (2020). https://doi.org/10.1186/s12974-020-01998-9

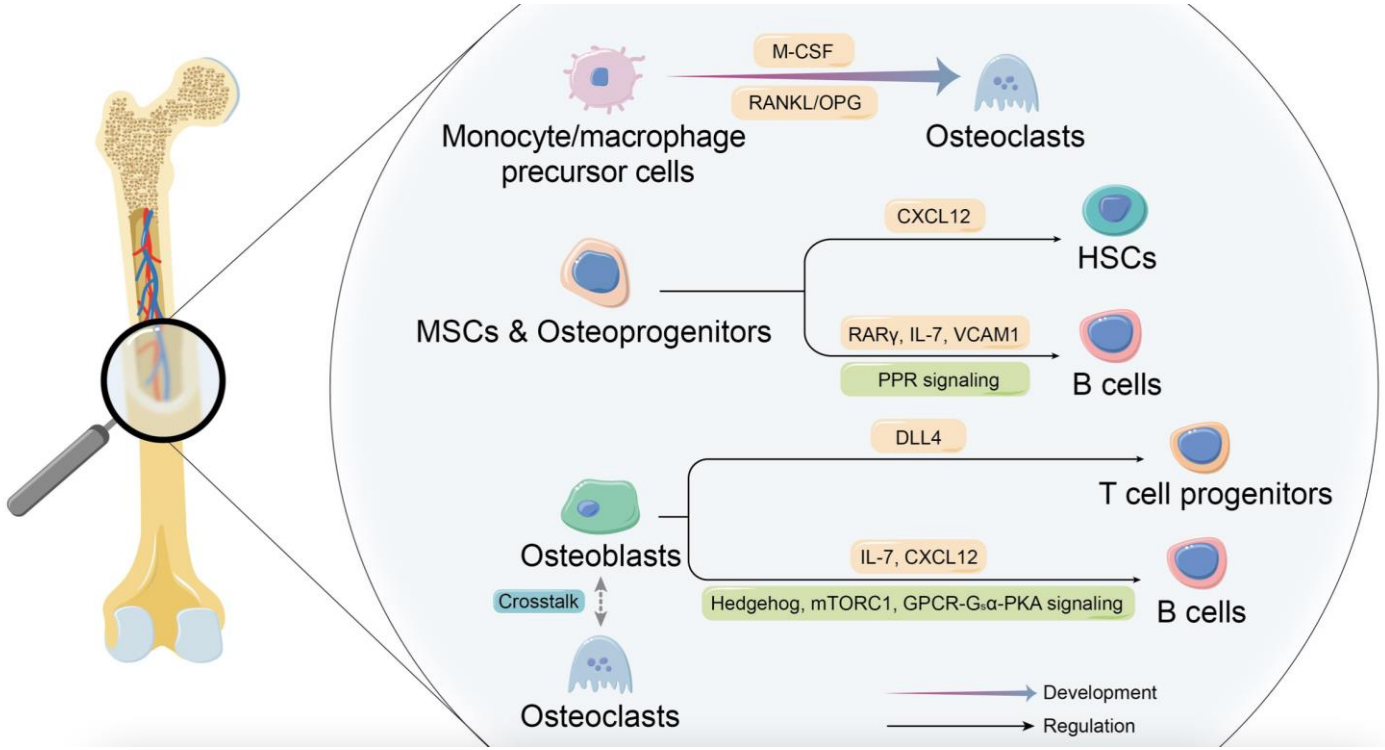
Menopause

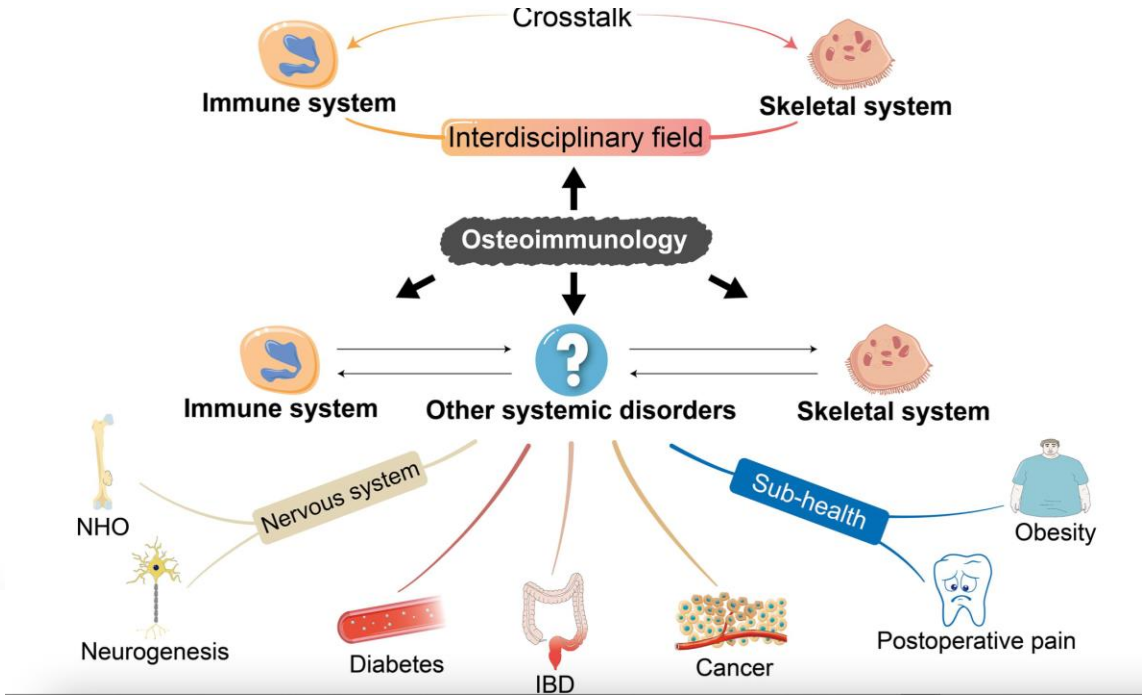
E2 exerts a tonic suppression of remodeling by directing **activated osteoclasts toward apoptosis**; in the absence of E2, osteoclastic activity predominates=net bone resorption.



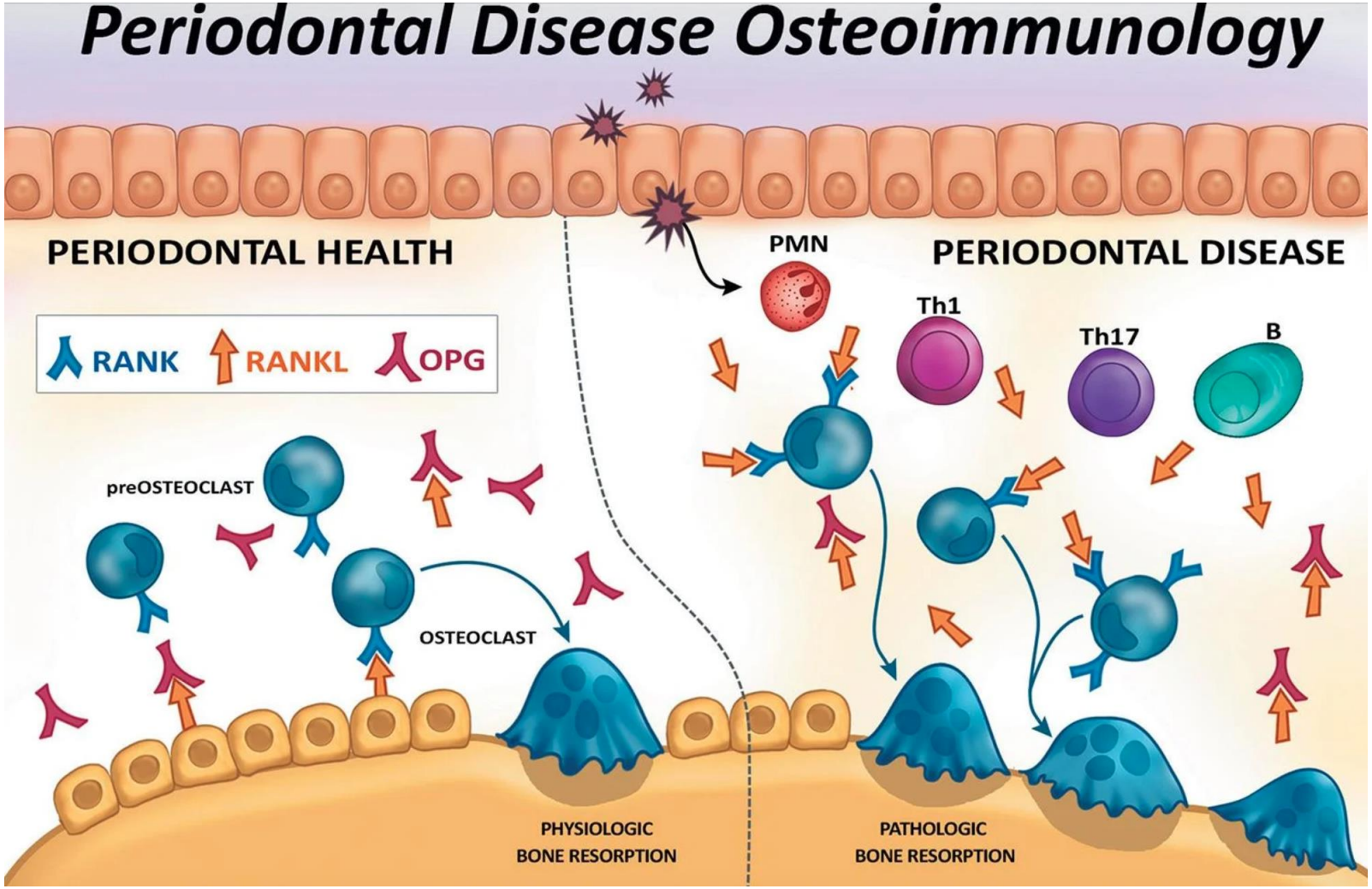
The enhanced expression of cytokines known to stimulate osteoclastogenesis, such as IL-1, IL-6, and TNF, RANKL also play an important role.

Osteoimmunology





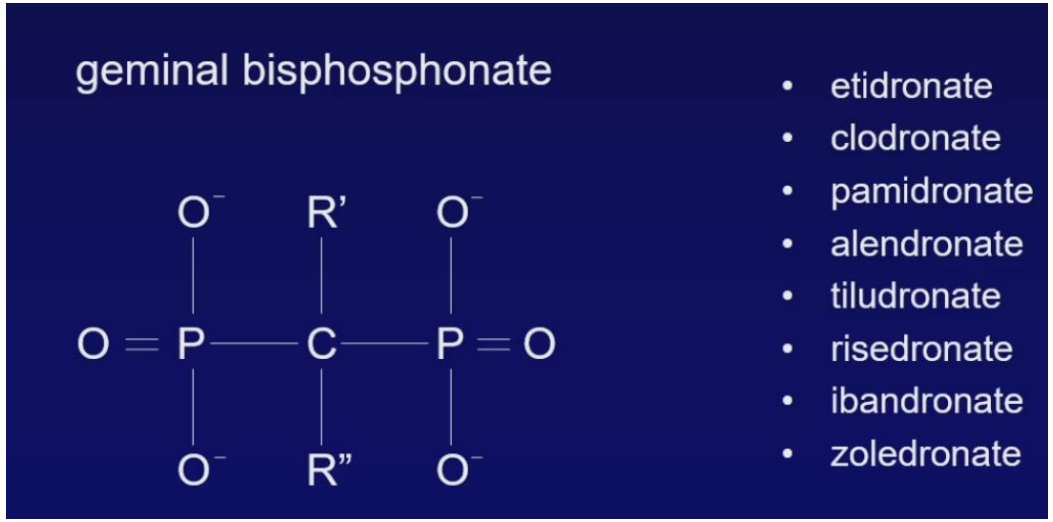
Messenger Proteins are release by immune cells in response to oral bacteria switching on T & B cells



Stimulated macrophages, DCs, and T cells promote the expression level of RANKL in periodontal ligament cells through their corresponding pro-inflammatory cytokines with OPG being degraded as well

Conventional treatment

Bisphosonates ; impair osteoclasts – increasing bone density, however not micro architecture or remodeling



- Gasto-intestinal side effects
- Atrial fibrillation
  - *more severe with IV bisphosphonates*
- Osteonecrosis of the jaw
  - more common with IV bisphosphonates
- Inflammatory eye disease
  - only with IV bisphosphonates
- Femoral stress fractures
  - long term use

Green et al. BMJ 2010;341:C4444
Sharma et al. N Engl J Med 2008; 359: 1410-11

Hormone Replacement

- Oestrogen therapy ; slows resorption , supports collagen and tensile bone strength (cannot measured by DEXA!)

> *Previously stated that an estradiol blood level of 146–220pmol/L required to protect against bone loss –current Estradiol levels as low as 75 pmol/L have a beneficial impact on bone density and fracture rates.*

- dose of estradiol as low as 0.25 mg/day produced an increase in bone density

- Progesterone , either as companion or alone (prior)

JAMA. 2003;290(8):1042-1048. doi:10.1001/jama.290.8.1042

Progesterone for the prevention and treatment of osteoporosis in women

J. C. Prior[a,b]

[a]Centre for Menstrual Cycle and Ovulation Research, Department of Medicine, Division of Endocrinology, University of British Columbia, Vancouver, BC, Canada; [b]School of Population and Public Health, University of British Columbia; BC Women's Health Research Network, Vancouver, BC, Canada

Progesterone has bone-forming activity by binding to receptors on the osteoblasts. This explains the decreases in spinal bone density seen in premenopausal women with low progesterone levels. In the Michigan Bone Health Study, those premenopausal women with the lowest bone mass had the highest rates of progesterone deficiency.

"The effects of progesterone and oestrogen on bone are synergistic and complementary to each other, and some clinical trials have found greater increases in spinal BMD when the progestin medroxyprogesterone acetate (MPA) is added to oestrogens than with oestrogens alone"

Strategies to reduce fracture risk vs improving Bone Density

- Reduce inflammation ; chronic inflammation = bone loss
- Medications that can contribute to bone loss ; corticoidsteroid, SSRIs, and PPI's
- Lifestyle factors; SAD diet, smoking , alcohol and early menopause all contribute heightened fracture risk
- Build muscle - the best way to prevent a fall , strengthens bone – remodeling , and improves insulin sensitivity *(Progressive muscle resistance training)*

Benefits Exercise

Hypertrophy
- AB crunch 3x 12-15
Leg curl 1 x 8-10 1 x 12-15
Leg press 1 x 8-12 1 x 12-20
Lateral raise 2 x 10-12 1 x 12-15
Single arm high row 1 x8-12
1x 12-15
Barbell row 1x 10 1 x 10-15

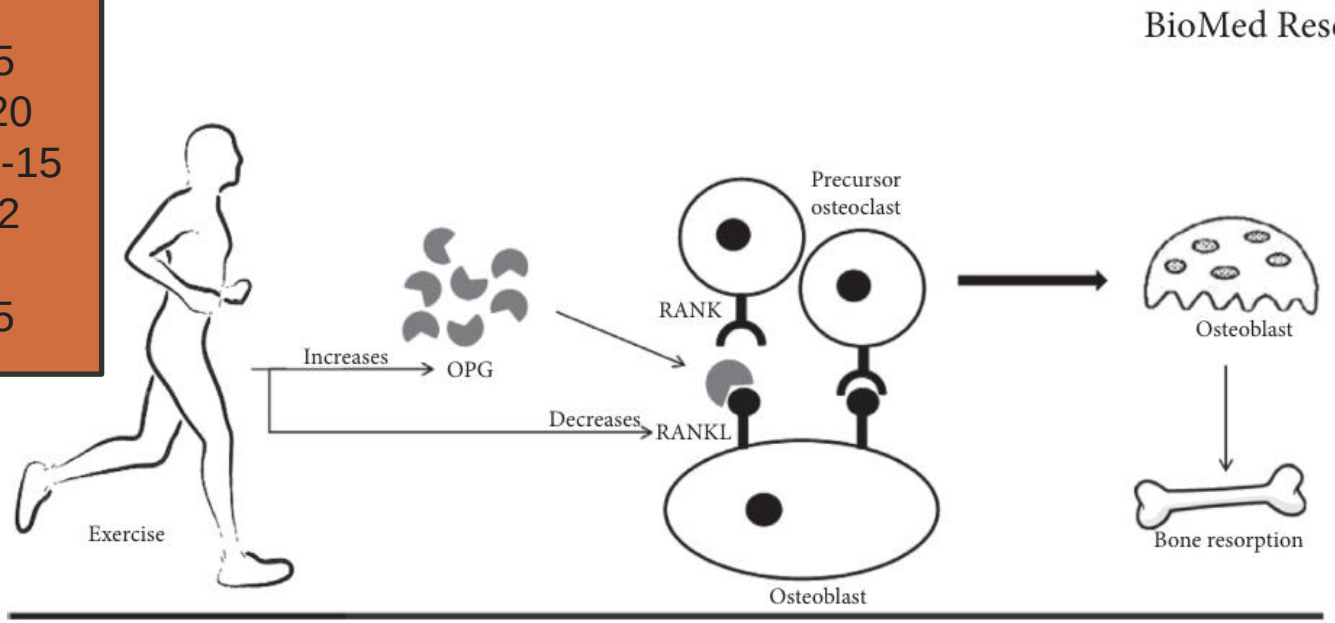


FIGURE 1: Interaction of exercise and RANKL/RANK/OPG biomolecular pathway. OPG: osteoprotegerin; RANK: receptor activator of nuclear factor κB; RANKL: receptor activator of NF-kB ligand.

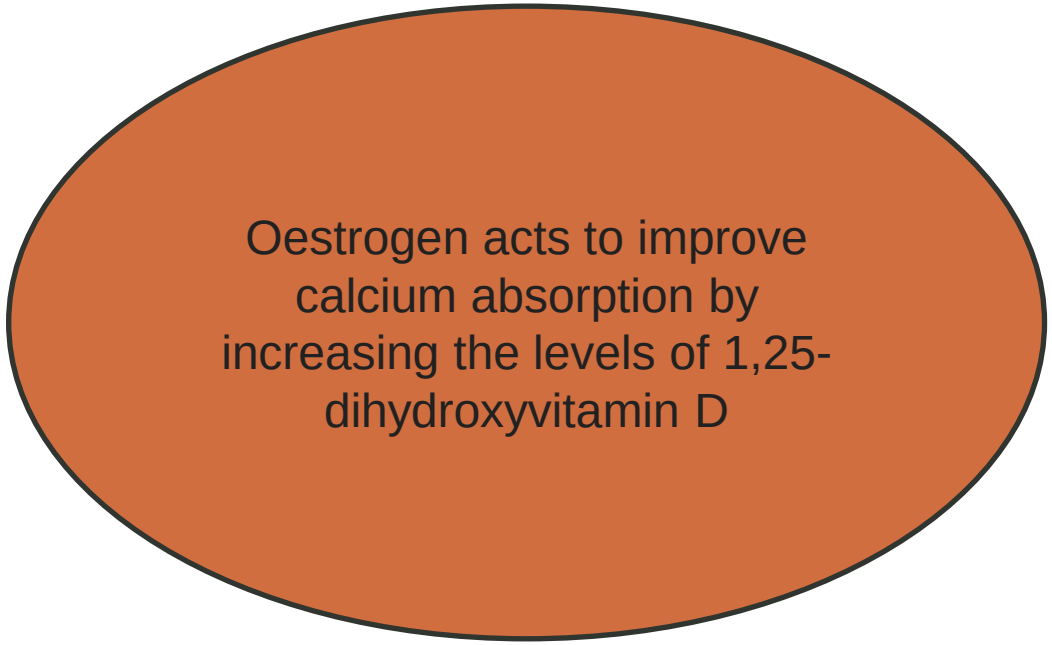
Strength
Deadlift 3 x 5-10
Lat pulldown 3 x 10-12
Lat raise 1 x 10-12
Bench press 3 x5
Leg curl 1 x 12-15
Squat 3 x 5

Feeding Bone

It's best you aim to get all the calcium you need from your food, The daily recommended intake is 700 mg a day- 1000mg if dx osteoporosis

There are plenty of foods you can eat to get calcium through your diet. Foods rich in calcium include:

- dairy products, like milk and cheese
- green leafy vegetables
- almonds
- sesame seeds and tahini
- Sardines
- pulses
- tofu



Royal Osteoporosis Society

Foods providing around 300mg of calcium per average portion

- Edam or gouda - 1 portion (40g)
- Paneer cheese - 1 serving (60g)
- Parmesan cheese - 1 serving (30g)
- Cheese omelette - 1 serving (120g)

Foods providing around 200mg of calcium per average portion

- Milk or milk drink e.g. hot chocolate (skimmed/semi-skimmed/whole) - 1 tumbler or mug (200ml)
- Calcium fortified soya milk - 1 tumbler or mug (200ml)
- Cheddar cheese & low fat hard cheese - Small matchbox size (30g)
- Yoghurt (low fat fruit, plain & calcium boosted soya) - 1 pot (125g)
- Porridge (made with semi-skimmed milk) - 1 bowl (160g - weight with milk)
- Halloumi - 1/2 serving (35g)
- Cauliflower cheese - 1 serving (200g)
- 12" pizza (cheese & tomato, vegetarian or meat topping) - 1/4 of a pizza
- Steamed or fried tofu - 1 serving (120g)
- Canned sardines - 1 serving for a sandwich (50g)

Foods providing around 100mg of calcium per average portion

- Cottage cheese - 2 tbsp (80g)
- Camembert - 1 portion (1/6 round, 40g)
- White pitta bread - 1 small (75g)
- Plain naan bread - 1/3 (43g)
- Baked beans - 1 small tin (200g)
- Cornish pasty - 1 medium size (155g)
- Sausages (pork or vegetarian) - 2 (40g)
- Tahini (sesame paste) - 1 heaped tsp (19g)
- Sesame seeds - 1 tbsp (12g)
- Tinned pink salmon - 1 small tin (105g)
- Grilled herring - 1 (119g)
- Ready made custard - 1 serving (120g)
- Dried figs - 2 (40g)

https://theros.org.uk/information-and-support/bone-health/nutrition-for-bones/calcium/calcium-rich-food-chooser/

Feeding Bone

Protein

50-80 grams pure protein a day, dependent on weight .

AA's most important for bone:- alaline, glycine and lysine

- bone broths; best for glycine
- red meat, chicken, salmon, tuna and dairy best for lysine

Vegetables to alkalinize & support microbiome
Optimize digestive surroundings
Reduce free radical exposure (AGEs)

Many nutrients provide anti-inflammatory and antioxidant benefits that may also play a role in downregulating cytokine production, RANKL production and dampening the immune response to preserve and build bone.

Nutrients

Cells. 2021 Jan; 10(1): 89.
Published online 2021 Jan 7. doi: 10.3390/cells10010089
PMCID: PMC7825801
PMID: 33430327

Regulation of Osteoclast Differentiation and Activity by Lipid Metabolism

Positive correlation between the intake of omega-3 fatty acids and bone mineral density in postmenopausal women. Recent research has pointed to eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids to reduce the number of osteoclasts and activity by suppressing RANK and RANKL expression along with other potent cytokines TNFa, IL-6 and PGE2. lipid mediators from omega-3 fatty acids have also shown bone preservation effects by modulating RANKL and OPG expression.

https://doi.org/10.1155/2013/589641

The Journal of Nutrition
Volume 144, Issue 3, March 2014, Pages 289-296

N-Acetylcysteine Supplementation Decreases Osteoclast Differentiation

N-acetyl cysteine (NAC) is a powerful antioxidant that has shown reduce oxidative stress, boost glutathione synthesis and reduce inflammation. In a postmenopausal osteoporosis animal model, NAC was found to prevent estrogen-deficient mice from bone loss by inhibiting oxidative stress, DNA damage and cellular senescence.

https://doi.org/10.3945/jn.113.185397

nutrients MDPI

Nutrients. 2013 Jan; 5(1): 97–110.
Published online 2013 Jan 10. doi: 10.3390/nu5010097

PMCID: PMC3571640
PMID: 23306191

Selenium in Bone Health: Roles in Antioxidant Protection and Cell Proliferation

Selenium is an essential trace element that has shown to improve bone health, immune surveillance, protect cell growth and acts as a potent antioxidant. Excessive intracellular reactive oxygen species (ROS) contribute to the development of osteoporosis by blocking osteoblasts developing from stem cells. Selenium increases the production of glutathione peroxidases, thioredoxin reductases and selenoproteins, which play key roles in reducing intracellular ROS and protecting osteoblasts

PMID: 37842299

Oxid Med Cell Longev. 2020; 2020: 6080597.
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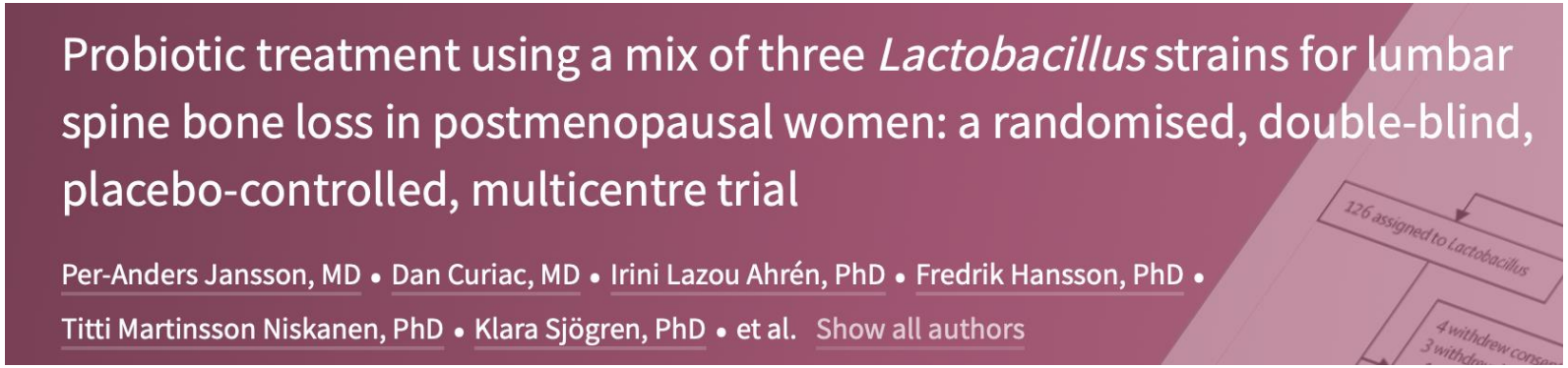
Oral Administration of Quercetin or Its Derivatives Inhibit Bone Loss in Animal Model of Osteoporosis

Yue-Yue Huang, [1] Zi-Hao Wang, [2] Li-Hui Deng, [2] Hong Wang,[2] and Qun Zheng[2]

Quercetin is a major dietary flavonoid found in onions and other vegetables that has shown benefits for many diseases and recently for bone loss. An animal model of postmenopausal osteoporosis showed that were given quercetin in their diet improved higher BMD in the lumbar spine and femur. Scientists also performed in vitro experiments and found a dose-dependent reduction of RANK/RANKL-stimulated expression of osteoclasts, building a strong case for quercetin as a potent inhibitor of osteoclastogenesis, and possible selective estrogen receptor modulator.

Gut microbiome & Osteoporosis

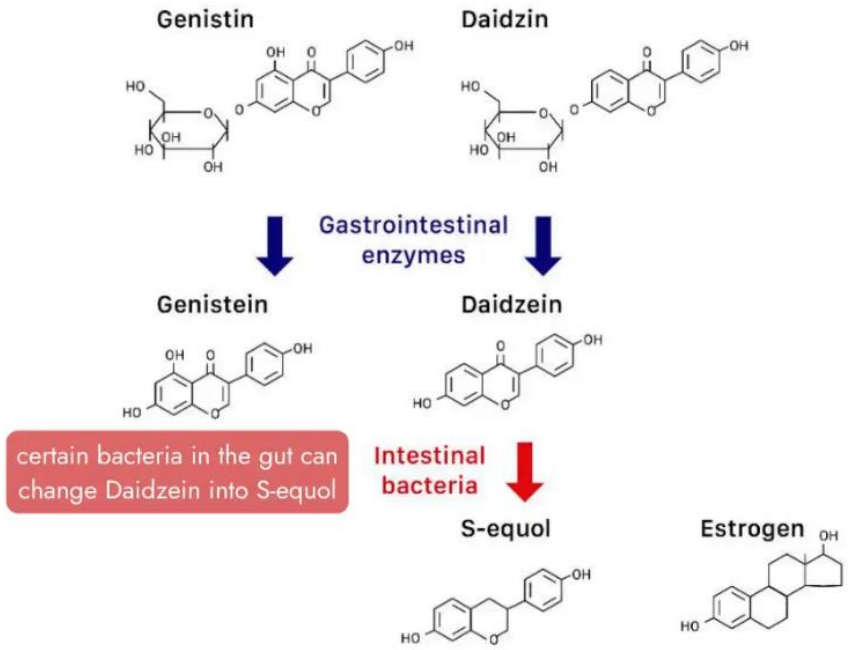
low oestrogen levels of menopause reduce gut microbial abundance and diversity



studies showed that the novel three-strain probiotic combination of Lactobacillus paracasei 8700:2 (DSM 13434), Lactobacillus plantarum HEAL9 (DSM 15312) and Lactobacillus plantarum HEAL19 (DSM 15313) suppressed the expression of proinflammatory cytokines (TNF-a and IL-6) and increased the expression of osteoprotegerin, reducing osteoclast-mediated bone resorption (Ohlsson et al, 2014)

Next Generation

DESIGNER OESTROGEN



PhytoSERM to Prevent Menopause Associated Decline in Brain Metabolism and Cognition

ClinicalTrials.gov ID NCT05664477

Sponsor Roberta Brinton

PhytoSERM 50mg tablet composed of the phytoestrogens daidzein, genistein and S-equol, administered orally every day for 24 weeks.	PhytoSERM is a dietary supplement containing equal amounts of genistein (16.7 mg ± 10%), daidzein (16.7 mg ± 10%) and S-equol (16.7 mg ± 10%).
Placebo Comparator: Placebo group Placebo product with identical shape, size and color with absence of daidzein, genistein, and S-equol. Administered orally every day for 24 weeks.	Drug: Placebo Placebo product with identical shape, size and color will be produced with absence of S-equol, daidzein and genistein. Ingredients include calcium carbonate, comprecel M102, croscarmellose sodium, stearic acid, Zeofree 5162, magnesium stearate, carnauba wax, coating cellulose clear (PEG), coating white (PEG), water.

PhytoSERM

Tofupill/Femarelle (DT56a): a new phyto-selective estrogen receptor modulator-like substance for the treatment of postmenopausal bone loss

Israel Yoles [1], Yariv Yogev, Yair Frenkel, Ravit Nahum, Michael Hirsch, Boris Kaplan

To evaluate the efficacy of Tofupill/Femarelle (DT56a), a novel phyto-selective estrogen receptor modulator (SERM), in preserving bone mineral density (BMD) in postmenopausal women.

The study sample consisted of 98 healthy, postmenopausal women who were randomly allocated, on a double-blind basis, to receive either 644 mg/d DT56a (study group) or 344 mg/d DT56a supplemented with calcium (low-dose group) for 12 months.

After 12 months of treatment, **BMD had increased in the study group by 3.6% in the lumbar spine (*P* = 0.039) and by 2.0% in the femoral neck (**NS). In the low-dose group, BMD had decreased in the lumbar spine by 0.6% (NS) and by 0.6% in the femoral neck (NS).

Osteogenesis and aging: lessons from mesenchymal stem cells

Arantza Infante [1], Clara I Rodríguez [2]

Affiliations + expand

PMID: 30257716 PMCID: PMC6158877 DOI: 10.1186/s13287-018-0995-x

A group of scientists documented menopausal women released far fewer stem cells in response to bone fracture, further delaying bone repair. Another study on osteoporosis reported that releasing one's own stem cells can in fact help maintain bone density.

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