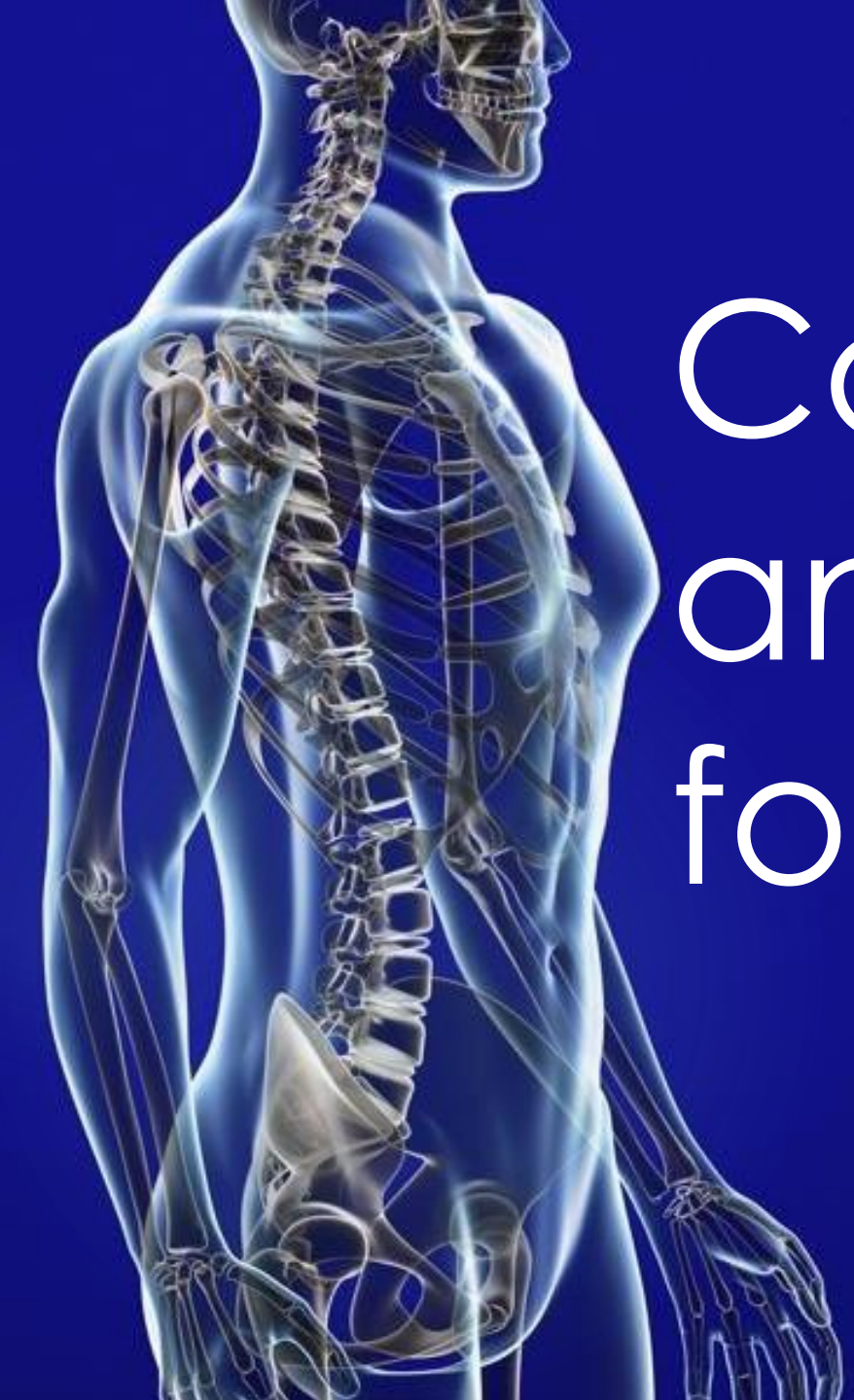


# Calcium, vitamin D and other nutrients for bone health

Dalitza M Alvarez Valentin, MD

Diabetes, Drug And Endocrinopathies Semianual Convention 2019

05/25/2019

# Disclaimers

- No conflict of Interest

# Objectives:

- The optimal nutrition to maximize bone gain, minimize bone loss, and reduce fragility fracture risk.
- Recognize the vitamins and major minerals involved in bone health.
- Understand the Functions of essential nutrients in the bone health

# Introduction:

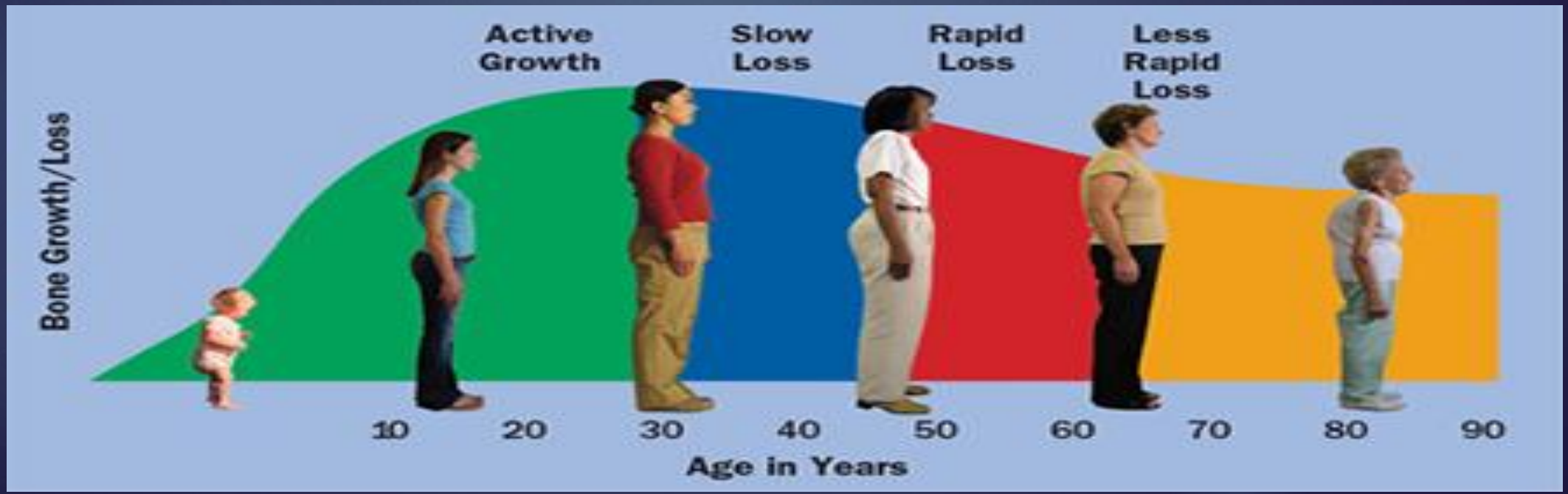
- Nutrition is an important modifiable factor that affects bone health. Diet is a complex mixture of nutrients and foods that interact with each other.
- The desire to maintain health, including bone health, into old age has led to almost one-half of the population and 70% of older adults in the United States and up to 26% in Europe using dietary supplements.

Current Evidence on the Association of Dietary Patterns and Bone Health: A Scoping Review[1,2,3]
Elham Z Movassaghand Hassan Vatanparast*

1. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003-2006. J Nutr. 2011;141:261-266. 2. Marques-Vidal P, Pécoud A, Hayoz D, et al. Prevalence and characteristics of vitamin or dietary supplement users in Lausanne, Switzerland: the CoLaus study. Eur J Clin Nutr. 2009;63:273-281. 3. Rovira MA, Grau M, Gostafer O, Covas MI, Schröder H. Dietary supplement use and health-related behaviors in a Mediterranean population. J Nutr Educ Behav. 2013;45:386-391.

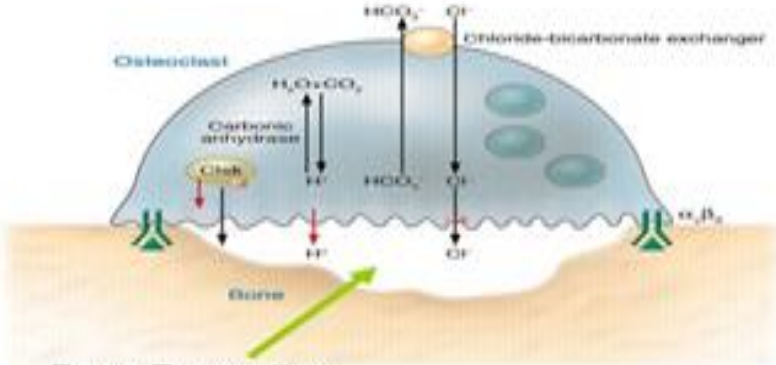
# SKELETAL HEALTH THROUGHOUT LIFE

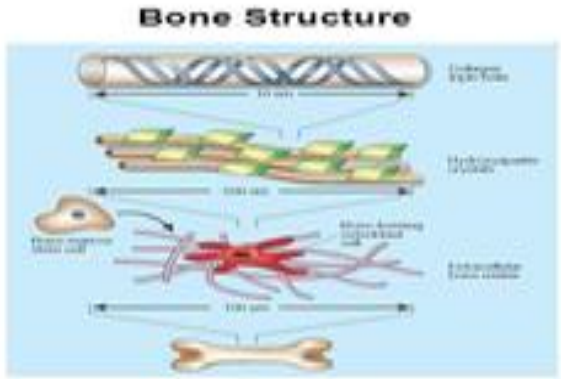
- Modifiable determinants of adult bone health, to include nutrition, influence accrual of peak bone mass and size.
- Bone growth generally tracks at a consistent trajectory during youth until puberty, when bone turnover and nutrient demand markedly increase. Depending on the skeletal site, peak bone mass occurs by the end of the second or early in the third decade of life. Supported by sufficient nutrition, bone mass and bone turnover remain relatively stable in midlife.
- Menopause-related estrogen deficiency leads to an increase in bone remodeling. The rate of bone resorption exceeds formation, leading to micro-architectural deterioration and loss of both cortical and trabecular bone.




THE USE OF VITAMINS AND MINERALS IN SKELETAL HEALTH: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT Daniel L. Hurley, MD, FACE1; Neil Binkley, MD, FACE2; Pauline M. Camacho, MD, FACE3; Dima L. Diab, MD, FACE, FACP, CCD4; Kurt A. Kennel, MD, FACE5; Alan Malabanan, MD, FACE, CCD6; Vin Tangpricha, MD, PhD, FACE7

# BONE HEALTH




Bone Resorption

Hydrochloric Acid = Dissolve Mineral

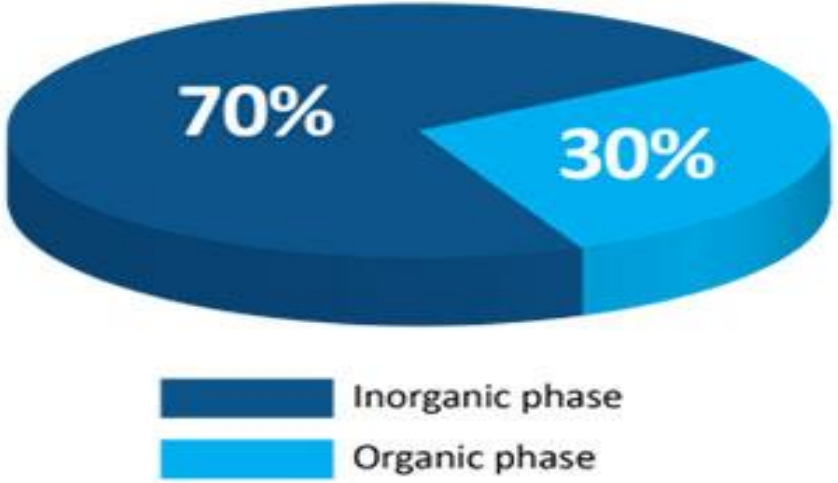
Hydroxyapatite ($Ca_5(PO_4)_3(OH)$) = Storage of Calcium in Bone

Acid Proteases (Enzymes) = Digest Bone Matrix Protiens (Collagen, etc)

## INORGANIC PHASE 70%

- **Hydroxyapatite 95%**
- **Other components 5%**

(Mg, Na, K, F, Zn, Sr and C)



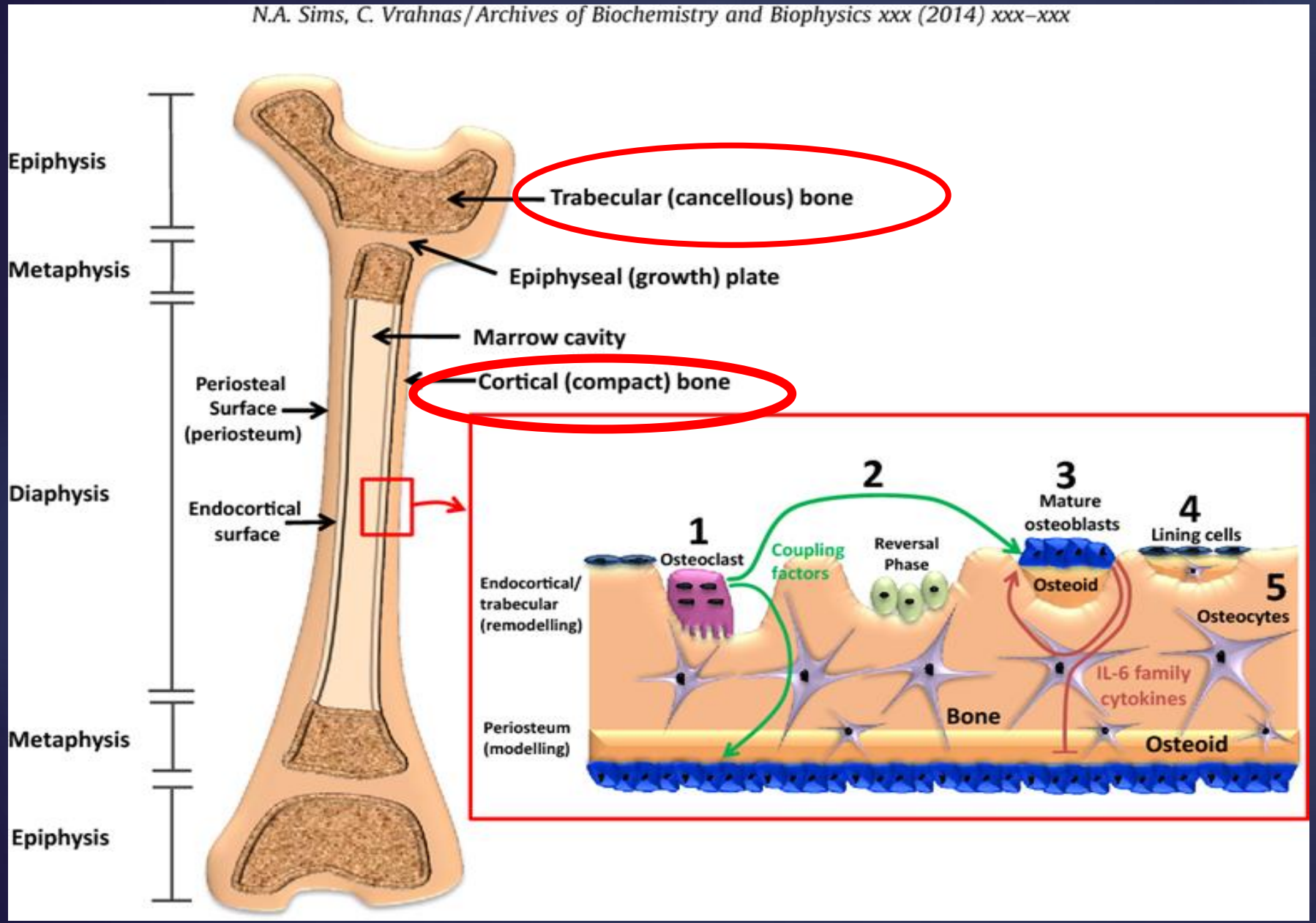

## ORGANIC PHASE 30%

- **Bone matrix 98%**

collagen type I 95%
non-collagenous proteins 5%
(BMPs, TGF – ß: 2% NCPs)

- **Bone cells 2%**

Osteoblasts
Osteocytes
Osteoclasts




- Bone is a mineralized connective tissue that exhibits two different types of bone:
- Cortical bone
  - The cortical bone has a predominantly structural function, since 80%–90% of its volume is calcified
- Trabecular bone
  - The role of the trabecular bone is regarded as metabolic and only 15%–25% calcified.

Calcium


Magnesium

Vitamin D


Vitamin k

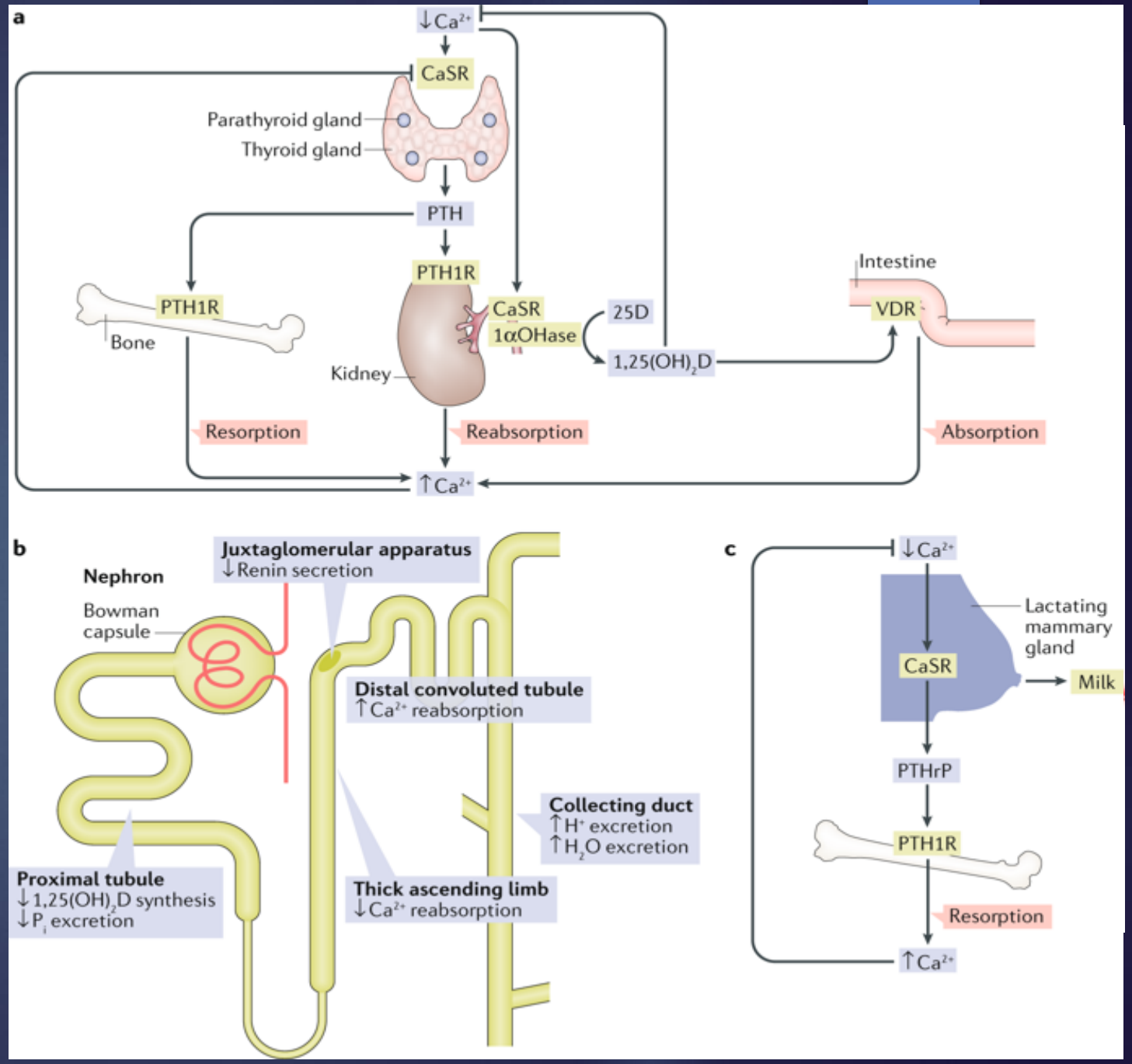

Zinc

Manganese


Boron

# Calcium

- Calcium is an essential element that plays numerous biological functions in the body, and one of the most important is the skeletal mineralization. Calcium is the major component of the bone, where it is present at more than 99% as calcium-phosphate complexes, and provides the skeleton strength and structure, making the bone a metabolic reservoir to maintain the intra- and extra-cellular calcium pool.
- The concentration of serum ionized calcium is tightly maintained at the physiological range in healthy subjects, by the action of calciotropic hormones:
  - Parathyroid hormone (PTH)
  - 1,25-dihydroxyvitamin D [1,25(OH)$_2$D],
  - Fibroblast Growth Factor 23 (FGF23),
  - Calcitonin.

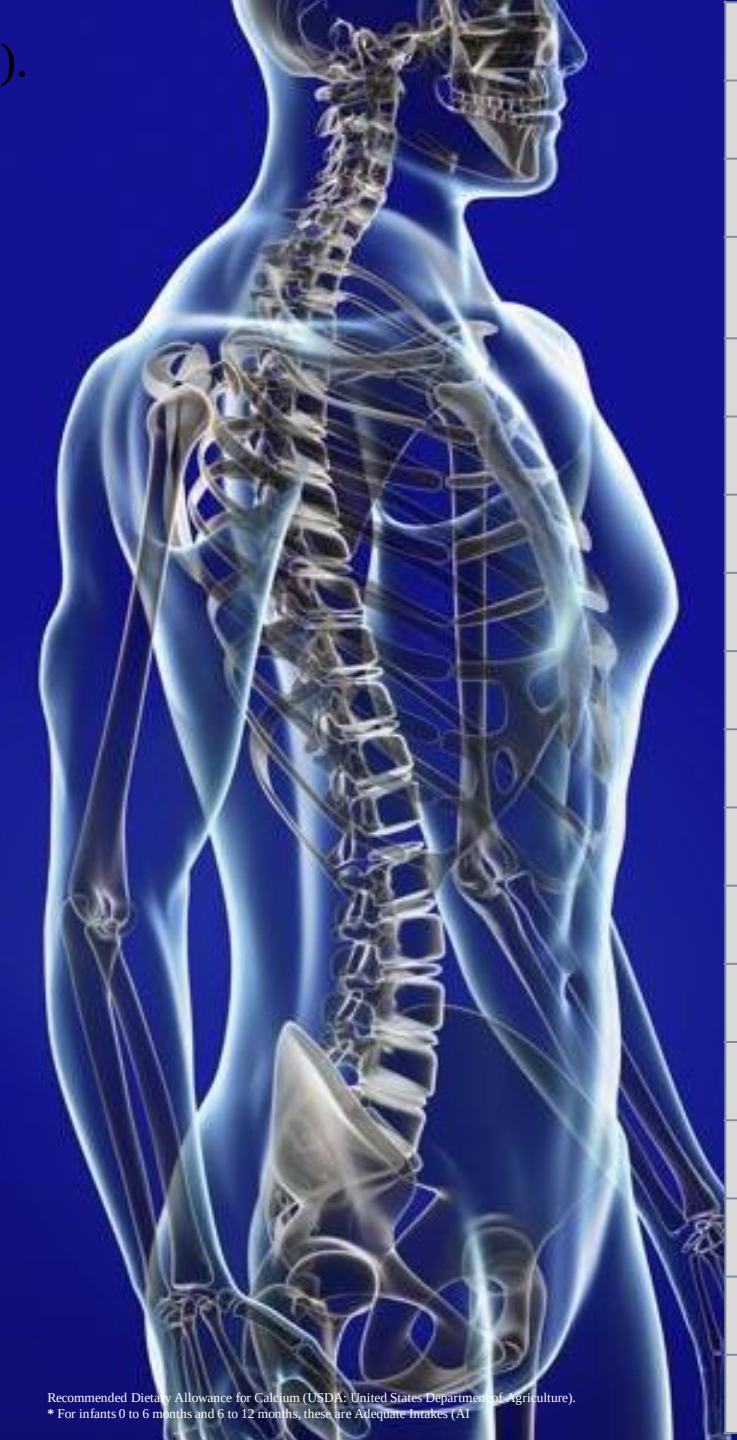


# CALCIUM

- Few clinical trials have assessed the effects of calcium supplementation on BMD and fracture risk independent of vitamin D administration.
- Two RCTs of calcium supplementation in elderly women reported **reduced bone turnover and decreased bone loss.**
- A Cochrane meta-analysis reported calcium alone was not superior to vitamin D alone in preventing fractures in postmenopausal women and older men.
- Several meta-analyses showed that calcium given with vitamin D reduces vertebral and nonvertebral fracture risk, consistent with vitamin D's action to improve gastrointestinal (GI) absorption of calcium and ensure adequate bone mineralization.

Avenell A, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. Cochrane Database Syst Rev. 2014;4:CD000227

).



| Life Stage Group | RDA/AI * (mg/day) |
|---|---|
| Infants | |
| 0 to 6 months | * 200 |
| 6 to 12 months | * 260 |
| Children | |
| 1–3 years | 700 |
| 4–8 years | 1000 |
| Males/Females | |
| 9–13 years | 1300 |
| 14–18 years | 1300 |
| 19–30 years | 1000 |
| 31–50 years | 1000 |
| 51–70 years (males) | 1000 |
| 51–70 years (females) | 1200 |
| >70 years | 1200 |
| Pregnancy/Breastfeeding | |
| 14–18 years | 1300 |
| 19–50 years | 1000 |

Recommended Dietary Allowance for Calcium (USDA: United States Department of Agriculture).
* For infants 0 to 6 months and 6 to 12 months, these are Adequate Intakes (AI

# Calcium

| Food | Calcium, milligrams |
|---|---|
| Milk (skim, 2 percent, or whole, 8 oz | 300 |
| Yogurt (6 oz) | 250 |
| Orange juice (with calcium, 8 oz | 300 |
| Tofu with calcium (1/2 cup | 435 |
| Cheese (1 oz) | 195 to 335 (hard cheese = higher calcium) |
| Cottage cheese (1/2 cup) | 130 |
| Ice cream or frozen yogurt (1/2 cup ) | 100 |
| Soy milk (8 oz ) | 300 |
| Beans (1/2 cup cooked ) | 60 to 80 |
| Dark, leafy green vegetables (1/2 cup cooked) | 50 to 135 |
| Almonds (24 whole) | 70 |
| Orange (1 medium) | 60 |

# Side Effects

- The total intake of calcium (diet plus supplements) should not routinely exceed 2000 mg/day, because of the possibility of adverse effects
- **Nephrolithiasis**
  - In randomized clinical trials, calcium supplements have been associated with an increased risk of kidney stones.
  - The Women's Health Initiative (WHI) trial reported an increased risk of kidney stones in postmenopausal women who were supplemented with calcium and vitamin D when compared with placebo.

Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Women's Health Initiative Investigators Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006;354(7):669

# Side Effects

- The effect of calcium supplementation on risk of CVD, particularly MI, is controversial. However, neither calcium supplements (up to 1000 mg daily), increased dietary intake of calcium, nor vitamin D supplements have been shown to increase all-cause or cardiovascular mortality.
- One meta-analysis of trials comparing vitamin D with or without calcium with no treatment or placebo, **calcium plus vitamin D was associated with reduced all-cause mortality in older adults** (hazard ratio [HR] 0.91, 95% CI 0.84-0.98.

Langsetmo L, Calcium and vitamin D intake and mortality: results from the Canadian Multicentre Osteoporosis Study Rejnmark L, Avenell A, Masud T, Anderson F, Meyer HE, Sanders KM, Salovaara K, Cooper C Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab. 2012 Aug;97(8):2670-81. Epub 2012 May 17.

- In the WHI trial, there was no effect of calcium and vitamin D supplementation on CVD.
  - 36,282 postmenopausal women ages 50 to 69 years were randomly assigned to calcium (1000 mg/day) plus vitamin D (400 IU/day) or placebo. After seven years, calcium plus vitamin D supplementation had no significant effect on the incidence of **MI** (confirmed in 411 and 390 women assigned to calcium/vitamin D and placebo, respectively; HR 1.05, 95% CI 0.91-1.20) or **stroke** (362 versus 377 strokes; HR 0.95, 95% CI 0.82-1.10).

Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M, Women's Health Initiative Investigators Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007;115(7):846

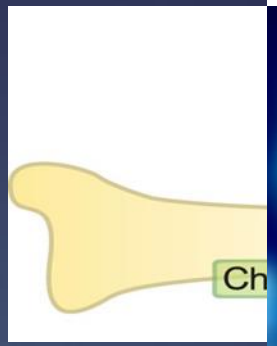
- Two meta-analyses evaluating calcium or calcium with or without vitamin D supplementation raised some concern about an increased risk of MI in patients randomly assigned to calcium versus placebo (**166 versus 130 MIs;** pooled relative risk [RR] 1.27, 95% CI 1.01-1.59) or calcium with or without vitamin D versus placebo (**374 versus 302 MIs;** RR 1.24, 95% CI 1.07-1.45). The meta-analyses had several limitations.
  - Not designed to explore cardiovascular
  - The baseline dietary calcium intake in the trials ranged from 750 to 1240 mg daily, and the addition of calcium supplements raised total intake over 1500 to 2000 mg daily in many patients, which is higher than recommended

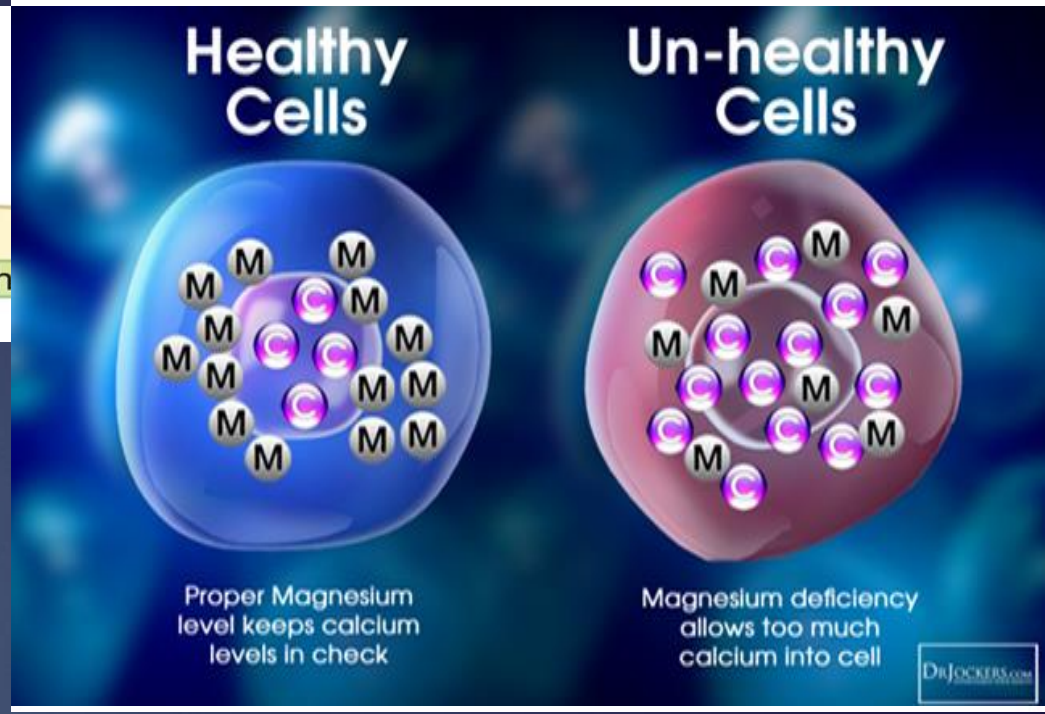
Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IEffect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ. 2010;341:c3691. Epub 2010 Jul 29,

# Recommendations:

- The National Osteoporosis Foundation and the American Society for Preventative Cardiology stated that calcium intake not exceeding 2,000 to 2,500 mg/day should be considered safe from CV risk.
- The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis recommend sufficiency of both calcium and vitamin D as part of the treatment regimen. A patient's total calcium intake should be assessed from both the diet and any supplement use, and the total daily amount of calcium should not exceed 1,200 to 1,500 mg.
- Studies suggest that it is most prudent to obtain calcium from food sources and to use supplements only as needed to reach the recommended total calcium intake

# Role of Magnesium

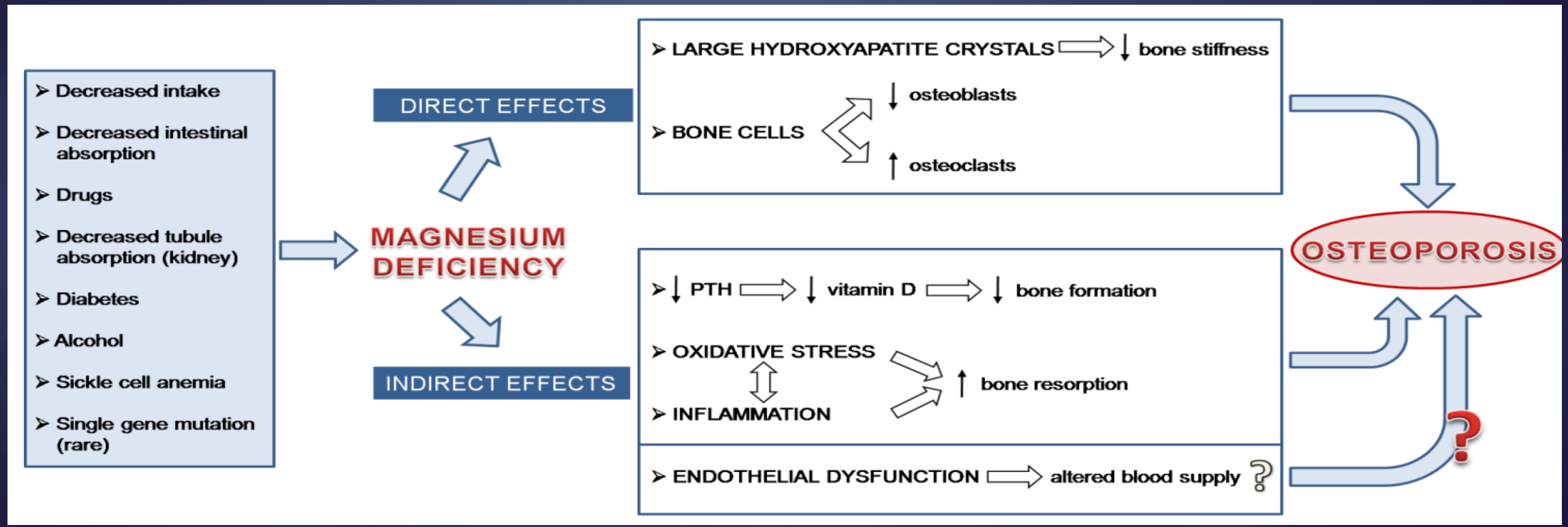


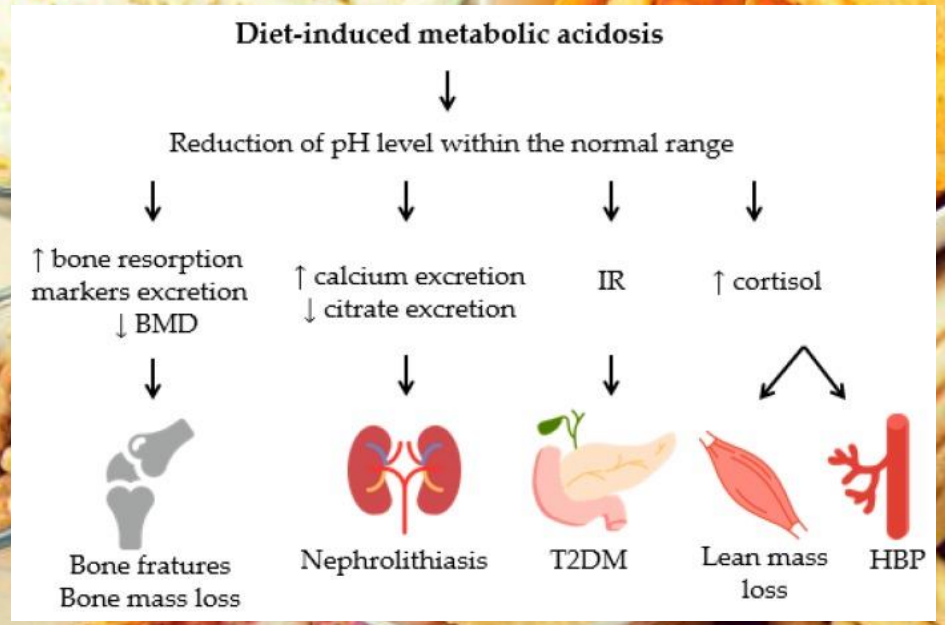

- About 60% of total Mg is stored in the bone.
- Mg is essential to all living cells, including osteoblasts and osteoclasts.
- Magnesium also has a role to play, together with the thyroid and parathyroid glands, in supporting bone health: stimulating the thyroid's production of calcitonin, which acts as a bone-preserving hormone, and regulating parathyroid hormone.
- Magnesium is an essential cofactor in 80% of all cellular enzymes. It is necessary for the conversion of vitamin D into its active form, and a deficiency of magnesium can lead to a syndrome known as vitamin D resistance.
- *Alkaline phosphatase*, also requires magnesium for activation, and if levels are low, abnormal bone crystal formation can result.
- Magnesium and calcium function together, so deficiency of one markedly affects the metabolism of the other. In fact, increasing calcium supplementation without increasing magnesium supplementation can actually *increase magnesium loss*. The use of calcium supplements in the face of a magnesium deficiency can lead to calcium deposition in the soft tissues, such as the joints, where it can promote arthritis, or in the kidney, contributing to kidney stones.

# Magnesium deficiency

- Hypomagnesmia exhibits other interesting phenomena, that of reducing the absorption of Ca, causing vitamin D to form hormonally inactive metabolites, and impairing the release of parathyroid hormone. both of which are involved in bone mineralization processes.

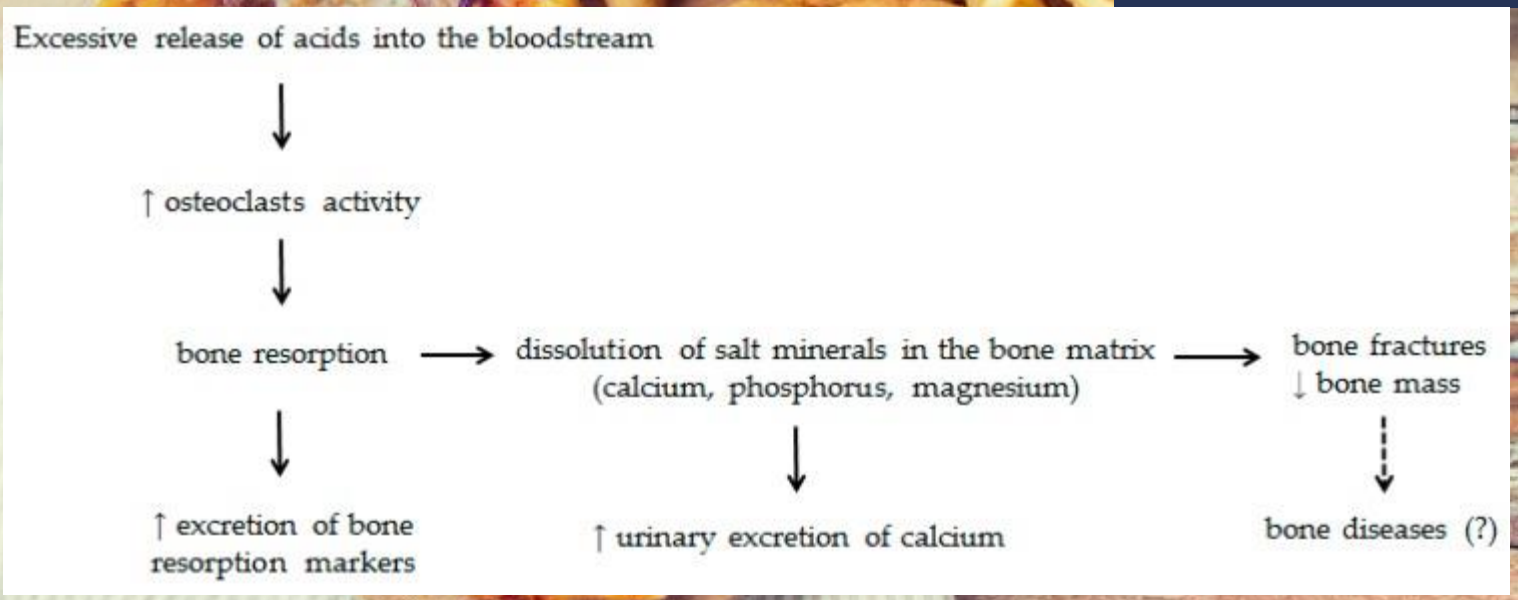



Mazur A., Maier J.A., Rock E., Gueux E., Nowacki W., Rayssiguier Y. Magnesium and the inflammatory response: Potential physiopathological implications. Arch. Biochem. Biophys. 2007;458:48–56. doi: 10.1016/j.abb.2006.03.03




A western diet develop a low-grade acidosis which is intensified by aging. Recently, the acid load imposed by this diet has been suggested to play a role in the pathophysiology of osteoporosis. Indeed, metabolic acidosis has been shown to lead to calcium loss from bone, to inhibit osteoblast function and stimulate osteoclast activity, and to impair bone mineralization.

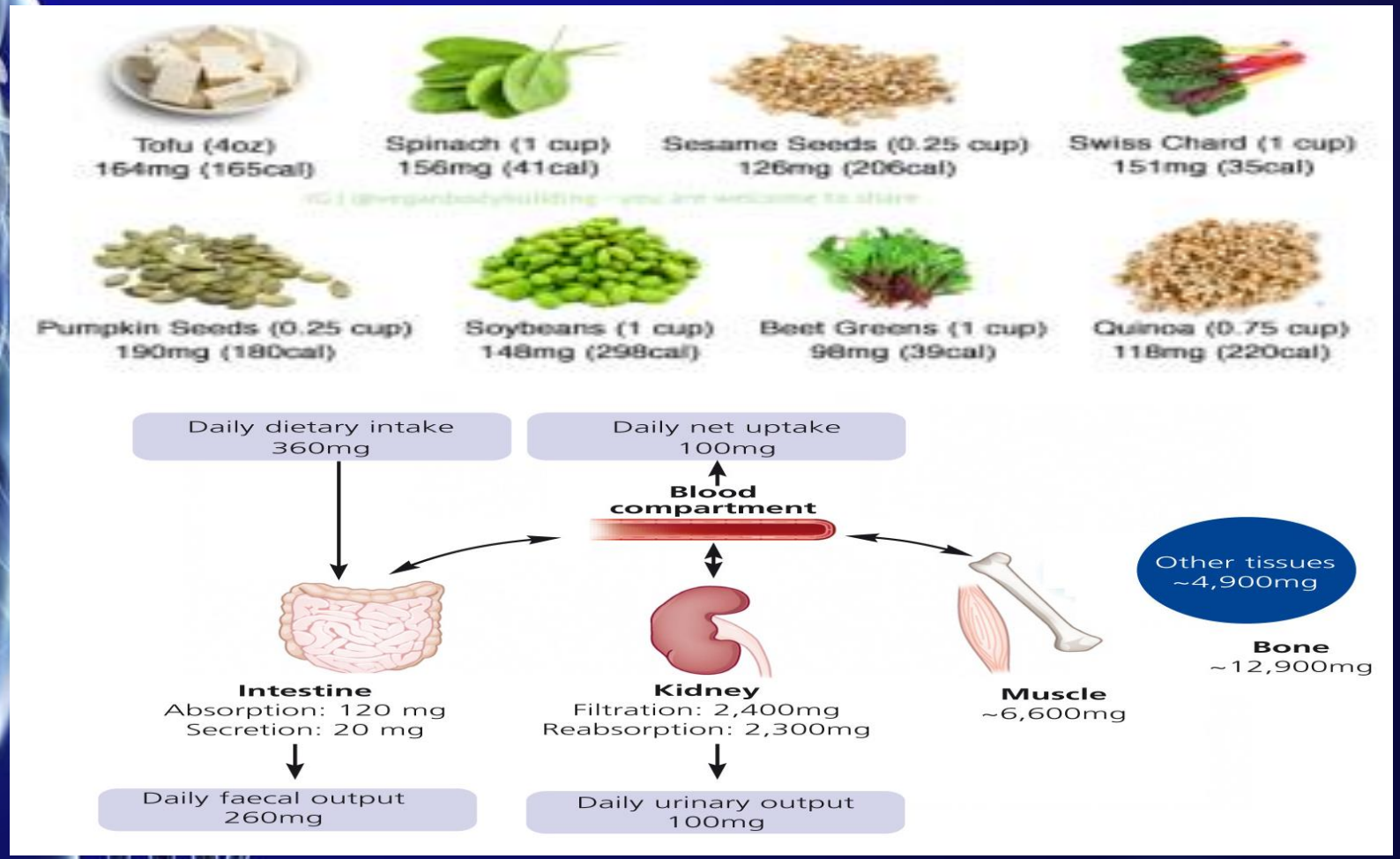
Accordingly, a neutralizing diet improves bone micro-architecture and bone mineral density . It is therefore feasible that part of the effects of Mg on the skeleton is due to its capability to act as a buffer for the acid produced by the typical western diet.




Diet-Induced Low-Grade Metabolic Acidosis and Clinical Outcomes: A Review
Renata Alves Carnauba[1,*] Ana Beatriz Baptistella,[1] Valéria Paschoal[1] and Gilberti Helena Hübscher[2]

# Magnesium Daily Recommendations:

- The average daily magnesium intake is 360 mg.

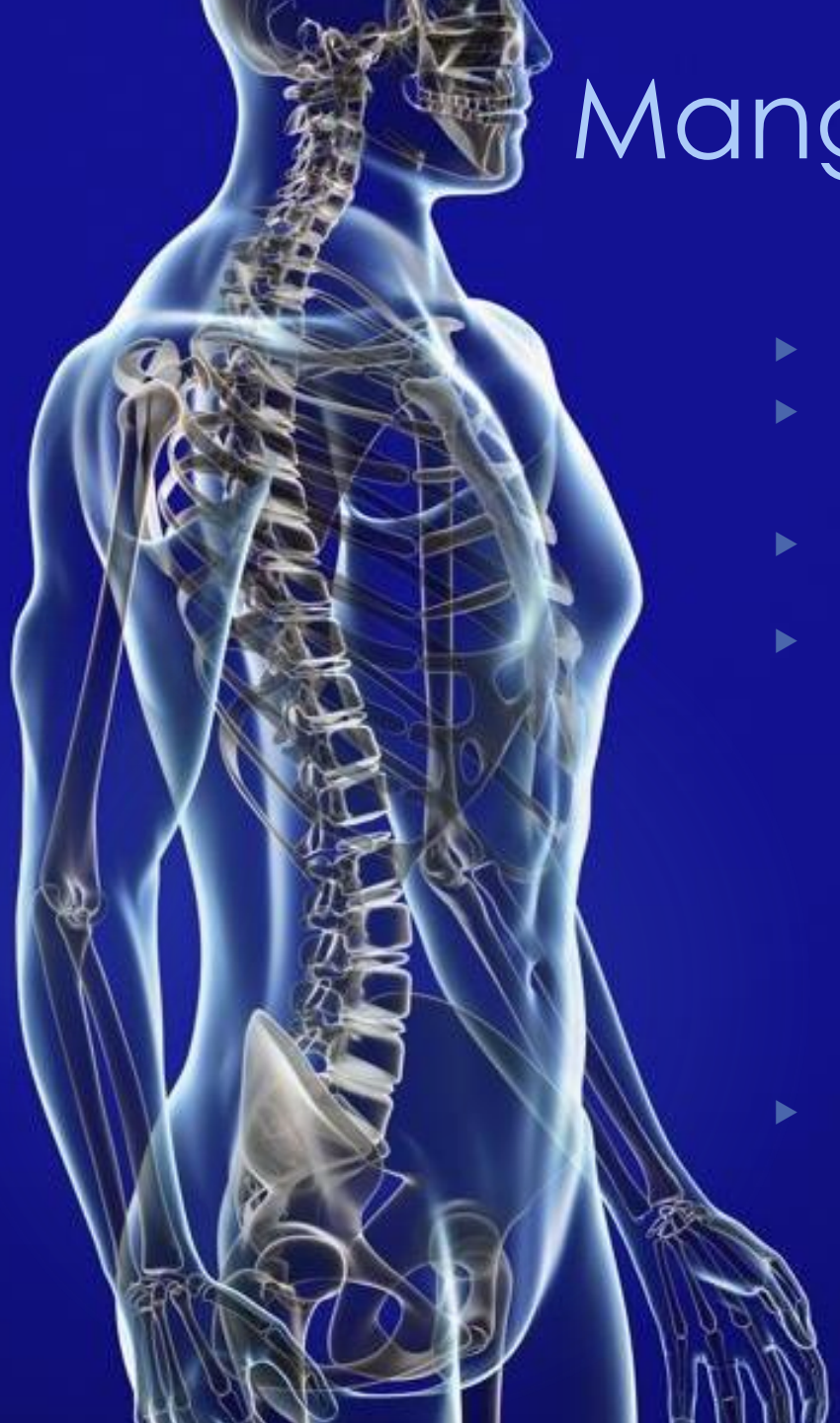


# Boron

- Boron found naturally in plants, and a diet consuming fruits, leafy vegetables, nuts, and legumes.
- Boron may stabilize and extended the half life of Vitamin D and estrogen and increase the renal retention of calcium and magnesium, but there are insufficient data to recommended supplementation for skeletal health.

Integr Med (Encinitas) 2015 Aug; 14(4): 35–48.
PMCID: PMC4718861PMID: 26770156
Nothing Boring About BoronLara Pizzorno MDiv, MA, LMT

Miljkovic D, Miljkovic N, McCarty MF. Up-regulatory impact of boron on vitamin D function—does it reflect inhibition of 24-hydroxylase? Med Hypotheses. 2004;63(6):1054–1056.
Nuklear. Estradiol Synthesis. Licensed under CC BY-SA 4.0 via Wikimedia Commons, work by Lara Pizzorno. [Accessed July 8, 2015].http://commons.wikimedia.org/wiki/File:Estradiol_synthesis.svg#mediaviewer/File:Estradiol_synthesis.svg



# Manganese

- Manganese is one of the 13 essential minerals to support healthy bones.
- Manganese produce a chemical called chondroitin sulfate. And chondroitin sulfate, along with osteocalcin, form the material in which the fibers and cells of connective tissue are embedded. This material helps to maintain healthy bones and joints.
- Manganese is also the co-factor for your bone-building osteoblast cells to produce a number of enzymes
- A study to demonstrate manganese's role in healthy bones. A 2.5-year placebo-controlled study enrolled 225 postmenopausal women from the San Diego greater metropolitan area. All of the women were over 50 and in good general health. The women were given either:
  - A placebo supplement
  - A calcium supplement providing a total of 1,000 mg of calcium per day (250 mg per tablet taken 4 times daily)
  - A trace mineral supplement containing copper (5 mg), manganese (2.5 mg) and zinc (15 mg), taken once daily
  - Or both the calcium and trace mineral supplements.
- The results The women who took the placebo supplement, the calcium supplement alone, or the trace mineral supplement alone all saw a drop in spine bone mineral density (BMD.) But the women who took both the calcium and trace mineral supplements saw an increase in their spinal BMDs

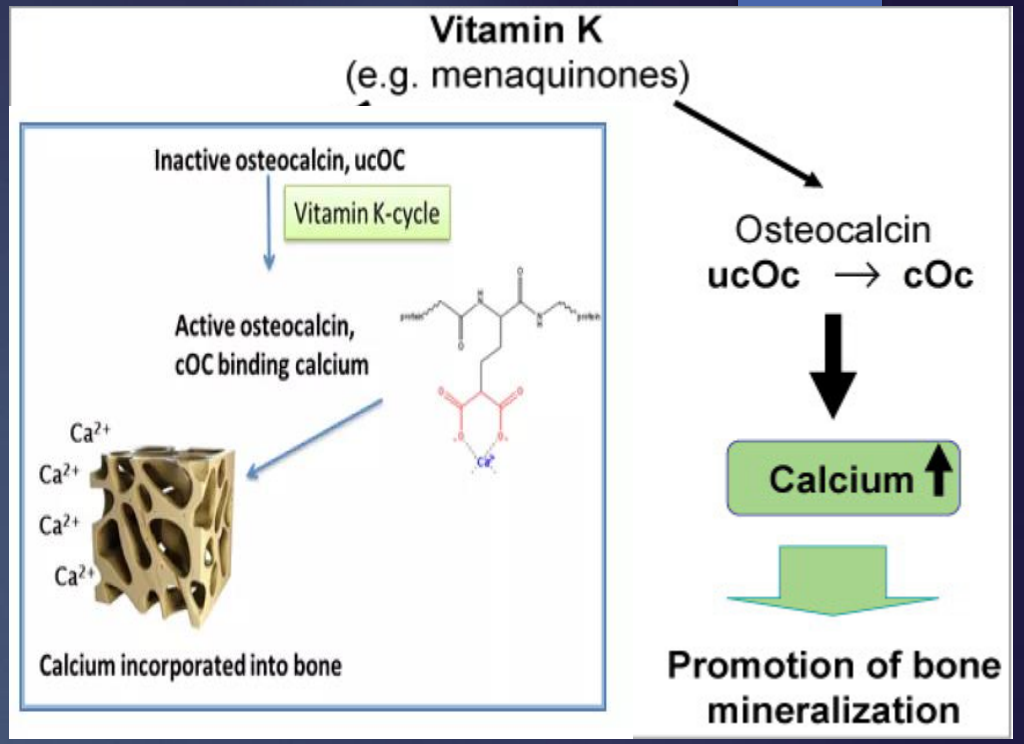
- 2.3 mg per day for men aged 19 and above
- 1.8 mg per day for women aged 19 and above
- 2 mg per day for pregnant women
- 2.6 mg per day for breastfeeding women

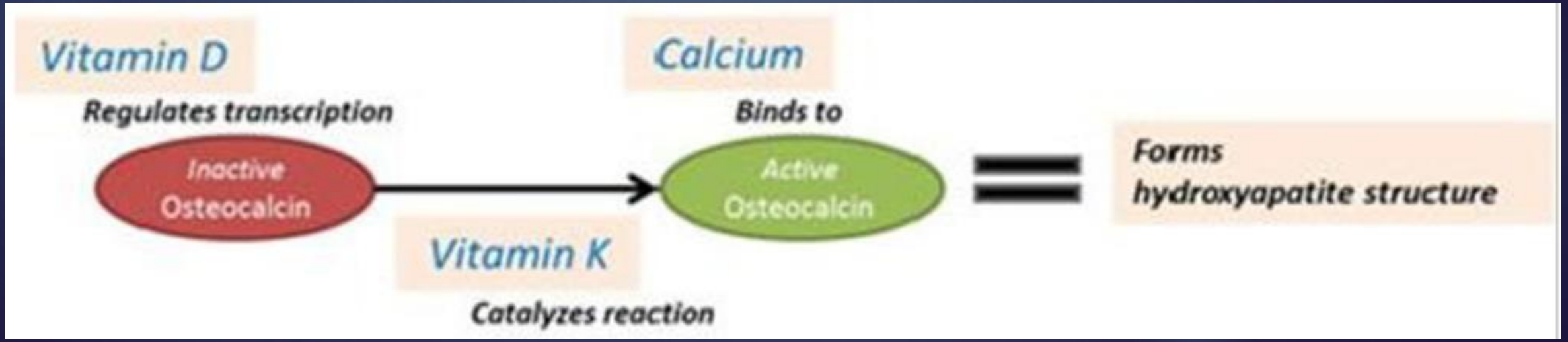
**Best Food Sources of Manganese**

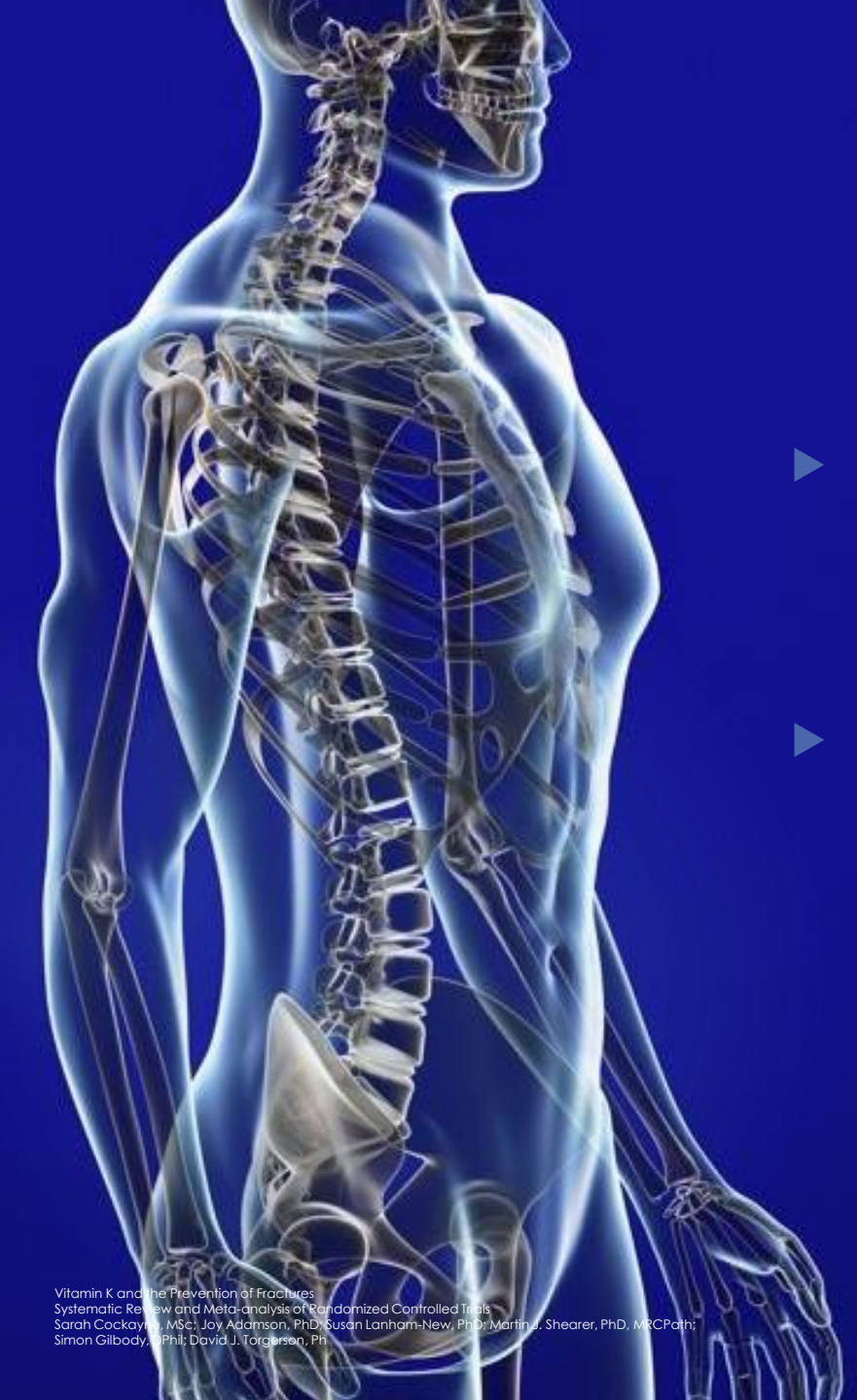
| Food | Serving Size | Amount in milligrams |
|---|---|---|
| Cloves | 1 teaspoon | 1.27 |
| *Oats, cooked | ½ cup | 3.84 |
| *Brown rice, cooked | 1 cup | 1.76 |
| *Garbanzo beans, cooked | 1 cup | 1.69 |
| Spinach | 1 cup | 1.68 |
| Pineapple | 1 cup | 1.53 |
| Pumpkin seeds | ¼ cup | 1.47 |
| Tempeh | 4 ounces | 1.46 |
| Tofu | 4 ounces | 1.34 |
| *Quinoa | 0.75 cup | 1.17 |
| Walnuts | ¼ cup | 1.02 |
| Sweet potato | 1 cup | 0.99 |
| *Lentils, cooked | 1 cup | 0.98 |
| *Lima beans, cooked | 1 cup | 0.97 |

# Vitamin k

- Osteocalcin is a protein produced by the osteoblasts, must be carboxylated before it can be effective. Vitamin K functions as a cofactor of γ-carboxylase and essential for γ-carboxylation of osteocalcin, a major noncollagenous bone matrix protein important in bone mineralization.
- Undercarboxylated osteocalcin, lacks structural integrity, and its ability to bind to hydroxyapatite is impared.



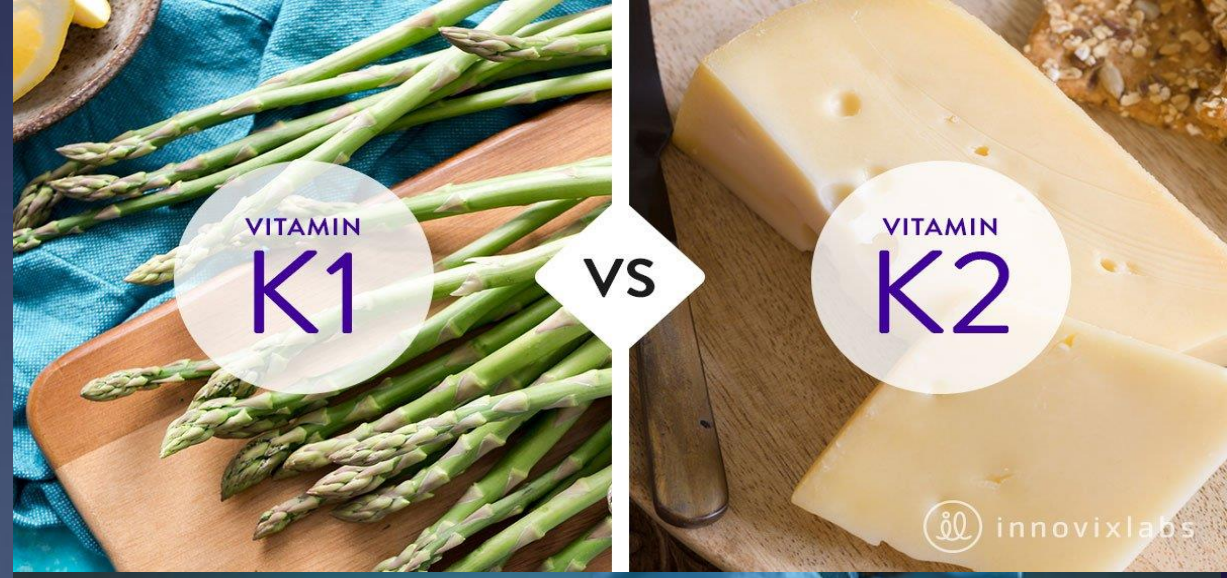


- RCT included postmenopausal women consuming calcium and vitamin D–fortified dairy with or without vitamin K. After 1 year, the vitamin K groups had significantly lower serum ucOC ratios.
- **Significant increases in total body BMD occurred in all treatment groups, with better increases in spine BMD observed only in the vitamin K groups after controlling for 25(OH)D levels and dietary calcium intake**.

Vitamin K and the Prevention of Fractures
Systematic Review and Meta-analysis of Randomized Controlled Trials
Sarah Cockayne, MSc; Joy Adamson, PhD; Susan Lanham-New, PhD; Martin J. Shearer, PhD, MRCPath; Simon Gilbody, DPhil; David J. Torgerson, Ph

# Vitamin K

- There are two naturally occurring vitamin K forms; phylloquinone (K1) is the major dietary form (especially in green leafy vegetables), whereas menaquinone (K2) is the main tissue form, to include bone. Vitamin K2 is synthesized by gut bacteria but also present in some foods (fermented soy beans, cheese, and curds).
- A review of eight small RCTs (n = 63 to 241 subjects) of 1 to 2 years in duration showed that a synthetic vitamin K2, decreased serum ucOC, increased spine BMD, and reduced the incidence of vertebral fractures.

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# Vitamin k Recomendations

**Table 1: Adequate Intakes (AIs) for Vitamin K [3]**

| Age | Male | Female | Pregnancy | Lactation |
|---|---|---|---|---|
| Birth to 6 months | 2.0 mcg | 2.0 mcg | | |
| 7–12 months | 2.5 mcg | 2.5 mcg | | |
| 1–3 years | 30 mcg | 30 mcg | | |
| 4–8 years | 55 mcg | 55 mcg | | |
| 9–13 years | 60 mcg | 60 mcg | | |
| 14–18 years | 75 mcg | 75 mcg | 75 mcg | 75 mcg |
| 19+ years | 120 mcg | 90 mcg | 90 mcg | 90 mcg |


| Food | Serving Size | Vitamin K (mcg |
|---|---|---|
| Kale, cooked | 1/2 cup | 531 |
| Spinach, cooked | 1/2 cup | 444 |
| Collards, cooked | 1/2 cup | 418 |
| Swiss chard, raw | 1 cup | 299 |
| Swiss chard, cooked | 1/2 cup | 287 |
| Mustard greens, raw | 1 cup | 279 |
| Turnip greens, cooked | 1/2 cup | 265 |
| Parsley, raw | 1/4 cup | 246 |
| Broccoli, cooked | 1 cup | 220 |
| Brussels sprouts, cooked | 1 cup | 219 |
| Mustard greens, cooked | 1/2 cup | 210 |
| Collards, raw | 1 cup | 184 |
| Spinach, raw | 1 cup | 145 |
| Turnip greens, raw | 1 cup | 138 |
| Endive, raw | 1 cup | 116 |
| Broccoli, raw | 1 cup | 89 |
| Cabbage, cooked | 1/2 cup | 82 |
| Green leaf lettuce | 1 cup | 71 |
| Prunes, stewed | 1 cup | 65 |
| Romaine lettuce, raw | 1 cup | 57 |
| Asparagus | 4 spears | 48 |
| Avocado | 1 cup (cube, slice, puree) | 30-48 |
| Tuna, canned in oil | 3 ounces | 37 |
| Blue/black-berries, raw | 1 cup | 29 |
| Peas, cooked | 1/2 cup | 21 |

* Food Values are from the U.S. Department of Agriculture, Agricultural Research Service. 2010. USDA National Nutrient Database for Standard Reference, Release 23. Nutrient Data Laboratory home page: http://www.ars.usda.gov/nutrientdata

# FLUORIDE

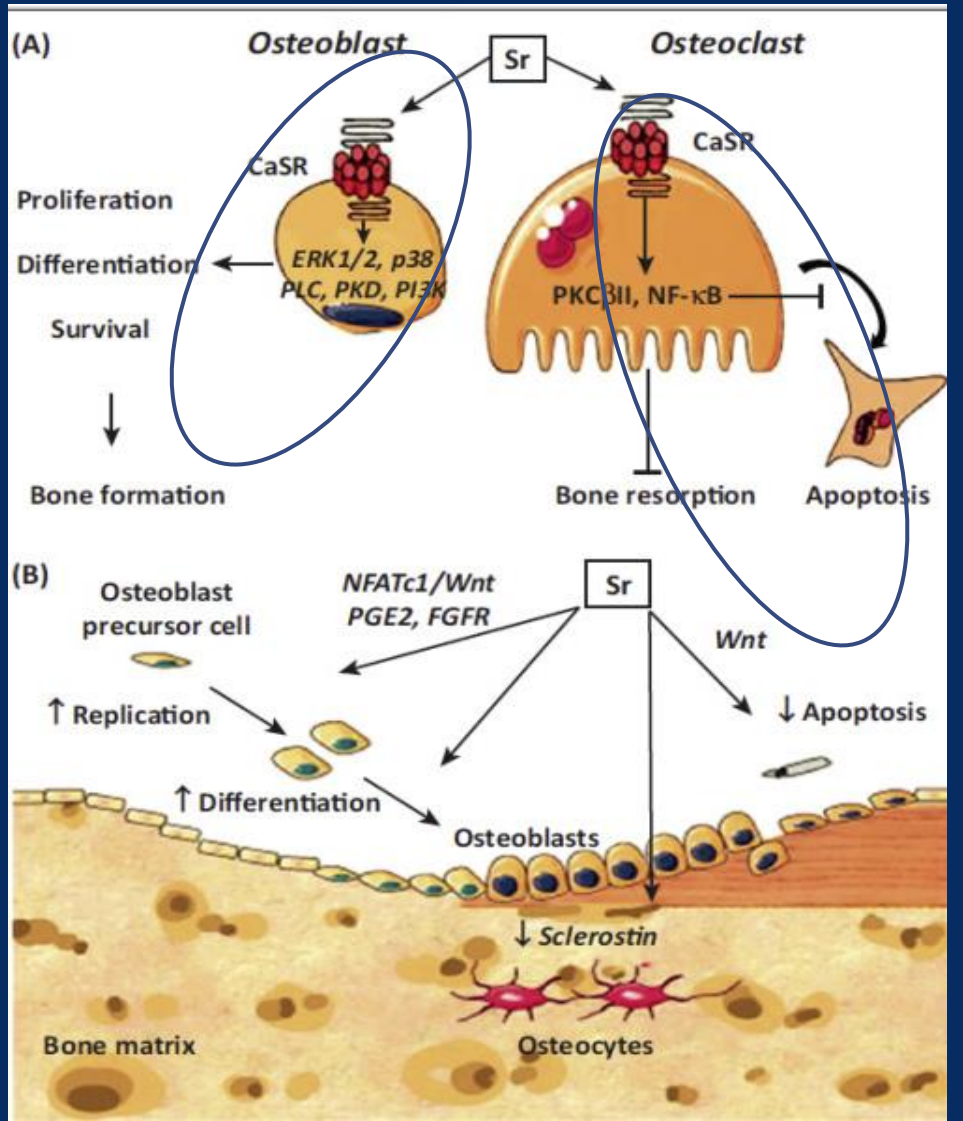
Fluoride supplementation is not recommended for skeletal health

- Fluoride is naturally present in soil and water and concentrates in the food chain. Fluoride absorption drops to 50 to 80% when complexes form with proteins, calcium, and other minerals.
- Approximately 95% of bodily fluoride is found in the bones and teeth.
- Fluoride stimulates bone formation at low doses, and although the mechanism is unclear, possible means include increasing osteoblast number and function.
- At a dose of 75 mg/day, bone may become abnormally mineralized and susceptible to fracture , and skeletal fluorosis has developed from excessive consumption of fluoride in tea.
- A meta-analysis reported no benefit for reducing vertebral fractures and an increased nonvertebral fracture risk after 4 years of treatment.

. Everett ET. Fluoride's effects on the formation of teeth and bones, and the influence of genetics. J Dent Res. 2011;90:552-560. 30. Riggs BL, O'Fallon WM, Lane A, et al. Clinical trial of fluoride therapy in postmenopausal osteoporotic women: extended observations and additional analysis. J Bone Miner Res. 1994;9: 265-275.

# Strontium supplementation is not recommended for skeletal health

- It is a naturally occurring mineral in soil and water.
- Strontium has chemical similarity to calcium but is found primarily on the surface of bone apatite crystals, and only a small amount replaces calcium within the crystal lattice.
- Strontium is rapidly incorporated into bone and reduces bone resorption while modestly stimulating bone formation.
- Strontium ranelate is approved outside the U.S. for the treatment of severe osteoporosis and reported to decrease the incidence of vertebral and nonvertebral fractures. However, due to lack of data on bone health and concerns of severe cutaneous drug reactions and increased CV events, strontium supplementation is not recommended for skeletal health.

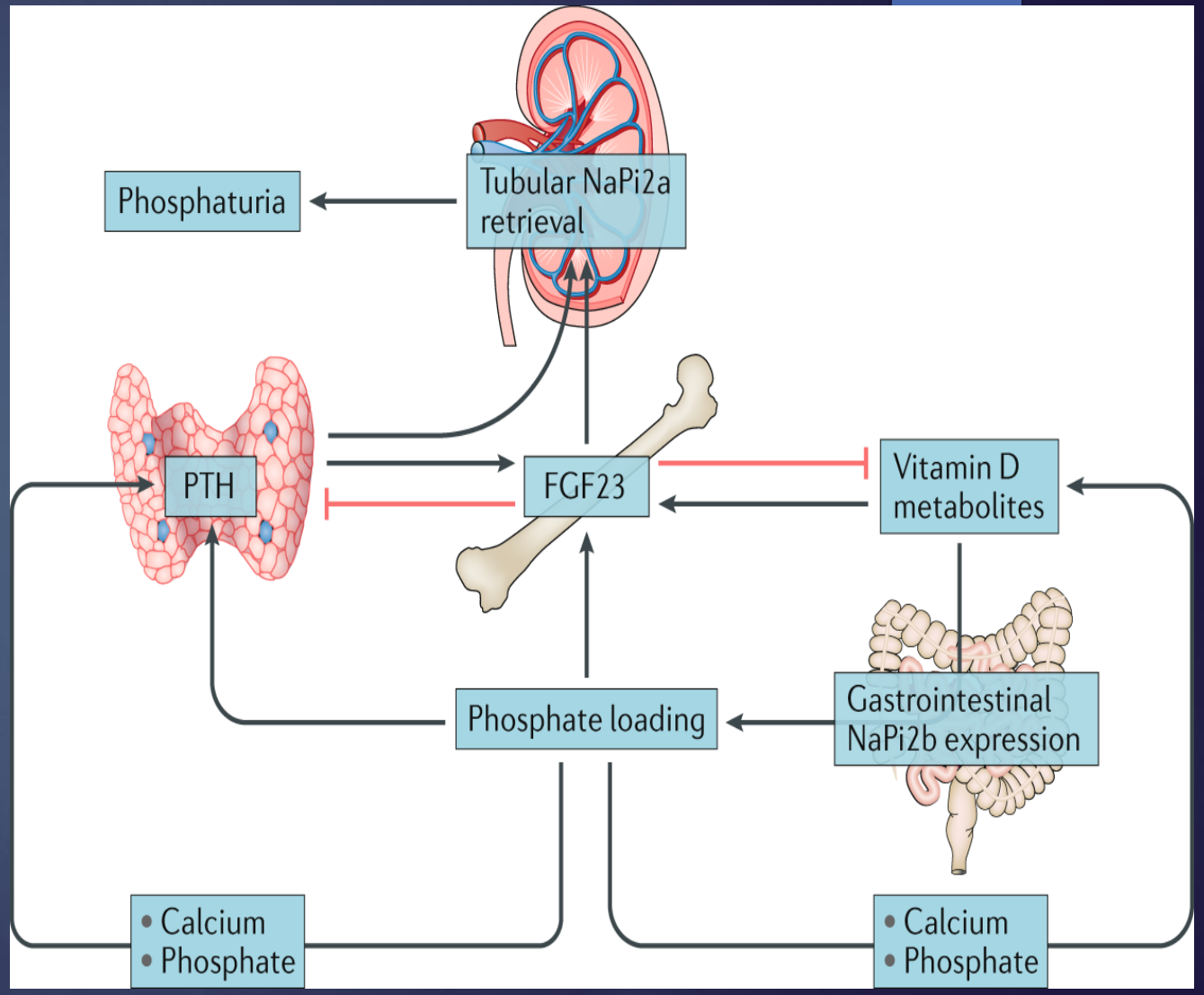



Neil Binkley, MD, FACE2; Pauline M. Camacho, MD, FACE3; Dima L. Diab, MD, FACE, FACP, CCD4; Kurt A. Kennel, MD, FACE5; Alan Malabanan, MD, FACE, CCD6; Vin Tangpricha, MD, PhD, FACE7
THE USE OF VITAMINS AND MINERALS IN SKELETAL HEALTH: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT

# Phosphate

Phosphate supplementation in otherwise healthy adults is not recommended and may be detrimental to bone, particularly in those with compromised renal function or low calcium intake

- Phosphate is readily absorbed in the gut, enhanced to some extent by 1,25-dihydroxyvitamin D.
- Insufficient phosphate intake can lead to impaired bone mineralization and rickets or osteomalacia, although inadequate intake is rarely a concern, except for persons experiencing starvation.
- Data suggest increased dietary phosphate intake is associated with increased PTH and FGF-23 levels and increased bone resorption. However, excessive phosphate consumption does not interfere with calcium absorption if there is adequate calcium intake and does not seem to be associated with a lower BMD.

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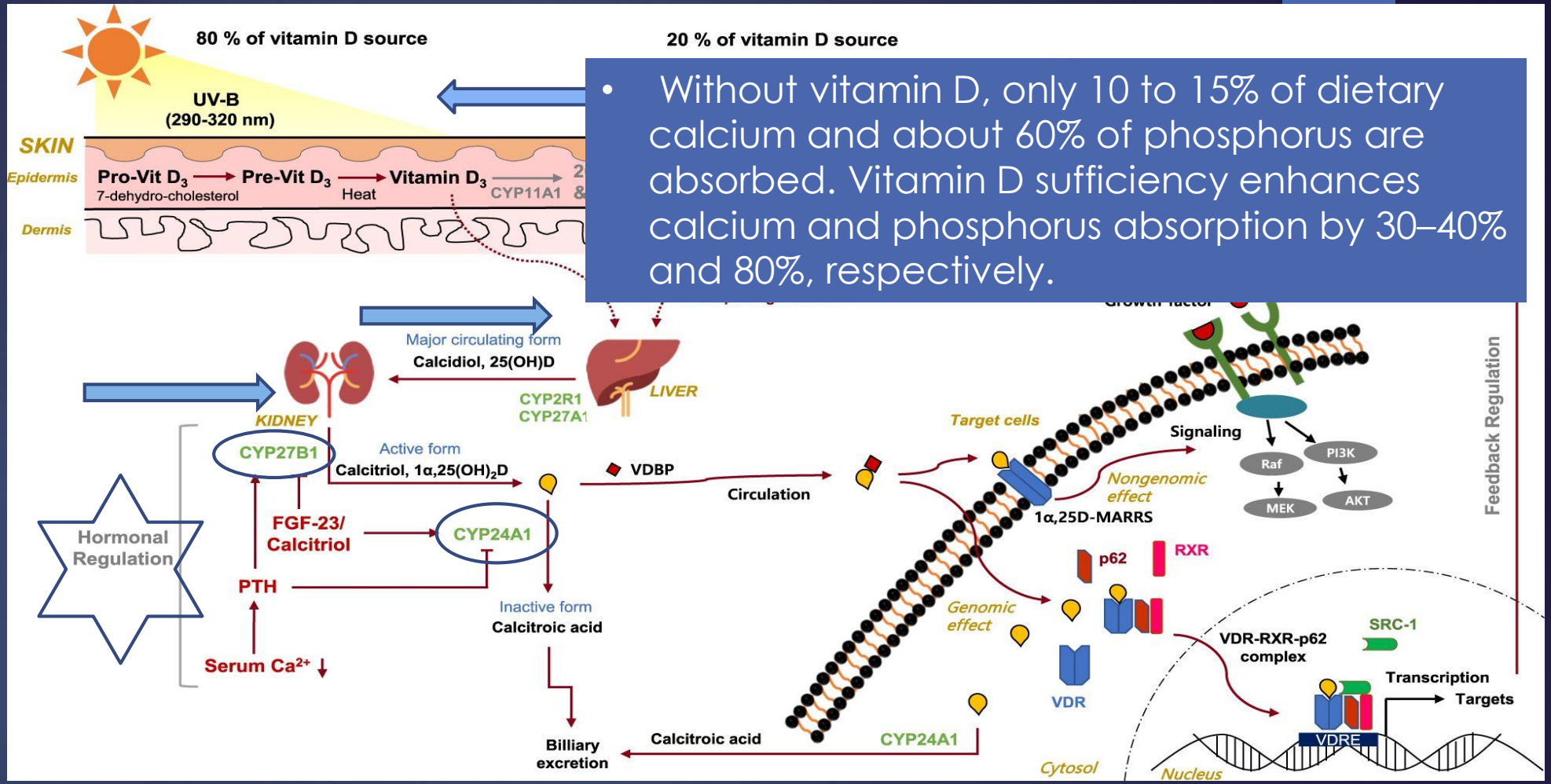
# Vitamin D- Metabolism

- **Hepatic** — The hepatic enzyme 25–hydroxylase places a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D (25[OH]D, calcidiol).
- **Renal** — In the renal tubule, entry of the filtered 25(OH)D-vitamin D-binding protein complex into the cells is facilitated by receptor-mediated endocytosis.
- Within the tubular cell, 25(OH)D is released from the binding protein. The renal tubular cells contain two enzymes, 1-alpha-hydroxylase (CYP27B1) and 24-alpha-hydroxylase (CYP24), that can further hydroxylate 25(OH)D, producing 1,25-dihydroxyvitamin D, the most active form of vitamin D, or 24,25-dihydroxyvitamin D, an inactive metabolite.




- Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D sufficiency enhances calcium and phosphorus absorption by 30–40% and 80%, respectively.

# Definitions of Vitamin D Deficiency

| The Endocrine Society | The Institute of Medicine (Health and Medicine Division of the National Academies) | The Mayo Clinic | The American Association of Clinical Endocrinologists |
|---|---|---|---|
| Deficiency: ≤ 20 ng/ml | Deficiency: < 12 ng/ml | Severe deficiency: < 30 ng/ml | Deficiency: < 30 ng/ml |
| Insufficiency: 21-29 ng/ml ng/ml | Insufficiency: 12-20 ng/ml | Mild to moderate Deficiency: 10-24 | Optimal: 30-50 ng/ml |
| Optimal: ≥ 30 ng/ml | Optimal: ≥ 20 ng/ml | Optimal: 25-80 ng/ml | |

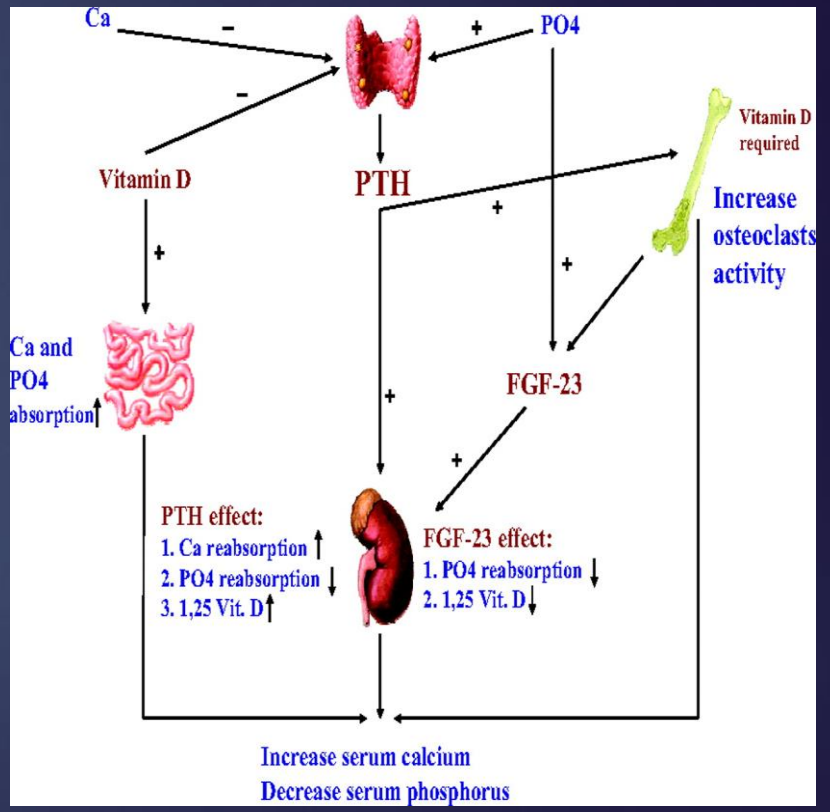
Kennel KA et al. Vitamin D deficiency in adults: When to test and how to treat. Mayo Clin Proc 2010; 85:752-758. IOM (Institute of Medicine). 2011 Dietary Reference Intakes for Calcium and Vitamin D. Washington DC: The National Academies Press. Holick MF et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96:1911-30 Camacho PM, Petak SM, Binkley N et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. Endocr Pract. 2016;22(Suppl 4):1-42.

# Cause Vitamin D deficiency

- Wearing a sunscreen with a sun protection factor of 30 reduces vitamin D synthesis in the skin by more than 95%.
- People with a naturally dark skin tone have natural sun protection and require at least three to five times longer exposure to make the same amount of vitamin D as a person with a white skin tone.
- There is an inverse association of serum 25(OH)D and body mass index (BMI) greater than 30 $kg/m^2$, and thus, obesity is associated with vitamin D deficiency.
- Patients with one of the fat malabsorption syndromes and bariatric patients are often unable to absorb the fat-soluble vitamin D, and patients with nephrotic syndrome lose 25(OH)D bound to the vitamin D-binding protein in the urine.
- Patients on a wide variety of medications, including anticonvulsants and medications to treat AIDS/HIV, are at risk because these drugs enhance the catabolism of 25(OH)D and $1,25(OH)_2D$.

# Consequences of Vitamin D Deficiency

- Secondary hyperparathyroidism maintains serum calcium in the normal range at the expense of mobilizing calcium from the skeleton and increasing phosphorus wasting in the kidneys. The PTH-mediated increase in osteoclastic activity creates local foci of bone weakness and causes a generalized decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis.
- Phosphaturia caused by secondary hyperparathyroidism results in a low normal or low serum phosphorus level. This results in an inadequate calcium-phosphorus product, causing a mineralization defect in the skeleton.
  - Rickets
  - Osteomalacia,
- Vitamin D deficiency also causes muscle weakness; affected children have difficulty standing and walking, whereas the elderly have increasing sway and more frequent falls, thereby increasing their risk of fracture



# Guideline Endocrine

- **Calcium and Vitamin D**
- In postmenopausal women with low BMD and at high risk of fractures with osteoporosis, we suggest that calcium and vitamin D be used as an adjunct to osteoporosis therapies.
- In postmenopausal women at high risk of fracture with osteoporosis who cannot tolerate bisphosphonates, estrogen, selective estrogen response modulators, denosumab, tibolone, teriparatide, and abaloparatide, we recommend daily calcium and vitamin D supplementation to prevent hip fractures.

# Treatment: Endocrine Society Recommendations

- Age 0-1
  - 2,000 IU per day Infants and Toddlers or 50,000 IU once weekly for 6 weeks to achieve a blood level 25(OH)D above 30 ng/ml. Followed by maintenance therapy of 400-1,000 IU/day.
- Children Age 1-18
  - 2,000 IU per day for at least 6 weeks or 50,000 IU once weekly for at least 6 weeks to achieve a blood level 25(OH)D above 30 ng/ml. Followed by maintenance therapy of 600- 1,000 IU/day.
- Adults
  - 6,000 IU per day or 50,000 IU per week for 8 weeks to achieve a blood level 25(OH)D above 30 ng/ml. Followed by maintenance therapy of 1,500-2,000 IU/day.
- Special Cases
  - Obese patients, those with malabsorption syndromes, and those on medications affecting vitamin D metabolism should receive a higher dose of 6,000 to 10,000 IU/day to achieve levels above 30 ng/ml. Followed by a maintenance dose of 3,000-6,000 IU/day.

Holick MF et al. Evalua7on, treatment, and preven7on of vitamin D deficiency: an Endocrine Society clinical prac7ce guideline. J Clin Endocrinol Metab 2011; 96:1911-30

# Prevention: Endocrine Society Recommendations

- The Endocrine Society recommends the following daily intakes of vitamin D to prevent deficiency and maximize bone health.
  - Children age 0-1: at least 400 IU/day. May require 1,000 IU/day to achieve > 30ng/ml •
  - Children age 1-18: at least 600 IU/day. May require 1,000 IU/day to achieve > 30ng/ml
  - Adults age 19-70: at least 600 IU/day. May require 1,500-2,000 IU/day to achieve > 30ng/ml
  - Adults older than 70: at least 800 IU/day. May require 1,500-2,000 IU/day to achieve > 30ng/ml
- Obese children and adults; those on anticonvulsant medications, glucocorticoids, and antifungals such as ketoconazole; and those taking medications for AIDS should be given at least two to three times more vitamin D for their age group to satesfy their body's requirement

Holick MF et al. Evalua7on, treatment, and preven7on of vitamin D deficiency: an Endocrine Society clinical prac7ce guideline. J Clin Endocrinol Metab 2011; 96:1911-30

# Prevention: AACE Recommendations

- Daily supplementation with vitamin D3 at a dose of 1,000 to 2,000 IU is typically needed to maintain an optimal serum 25(OH)D level.
- Higher doses may be necessary in the presence of certain factors including obesity, malabsorption, and certain ethnicities. Transplant patients and older individuals may also need higher doses.

Camacho PM, Petak SM, Binkley N et al. American Associa7on of Clinical Endocrinologists and American College of Endocrinology Clinical Prac7ce Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. Endocr Pract. 2016;22(Suppl 4):1-42.

# Vitamin D Toxicity

- Excess vitamin D supplementation can lead to hypercalcemia, but vitamin D toxicity is extremely rare. It generally occurs only after ingestion of large doses of vitamin D (>10,000 IU/day) for prolonged periods in patients with normal gut absorption or those ingesting excessive amounts of calcium.

**Do not administered yearly high-dose (eg, 500,000 international units) vitamin D.**

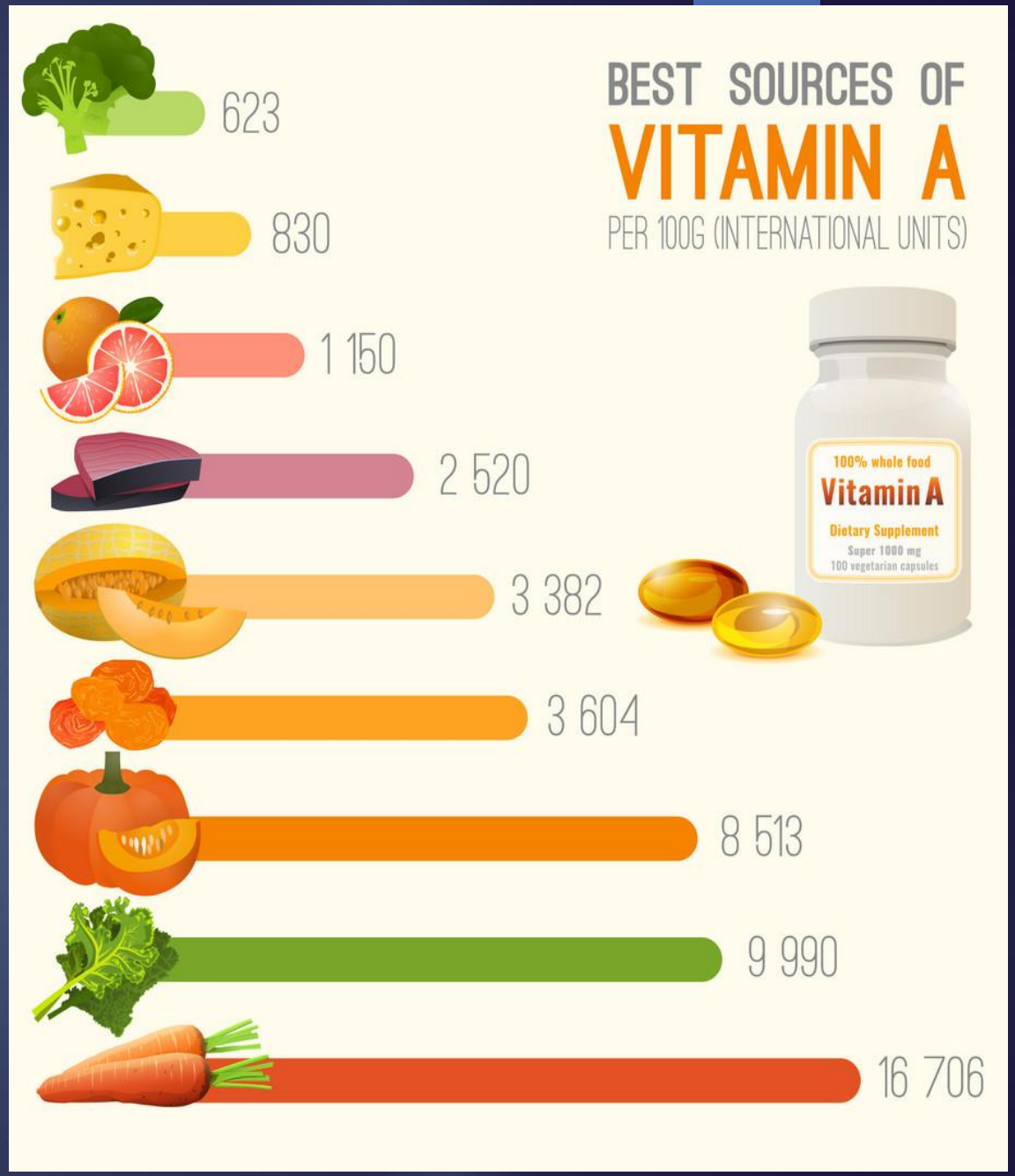
- hypercalcemia, including nausea, dehydration, and constipation, or symptoms of hypercalciuria such as polyuria and kidney stones.

# Vitamin D

| Food | Amount per serving IU |
|---|---|
| Cod liver oil, 1 tablespoon | 1360 |
| Salmon (sockeye), cooked, 3oz | 380 to 570* |
| Mushrooms that have been exposed to ultraviolet light to increase vitamin D, 3oz. | 889 |
| Mackerel, cooked, 3 oz. | 388 |
| Tuna fish, canned in water, drained, 3oz. | 40 to 68 |
| Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 8oz. | 100 |
| Orange juice fortified with vitamin D, 8oz. | 100 |
| Yogurt, fortified with vitamin D, 6oz. | 80 |

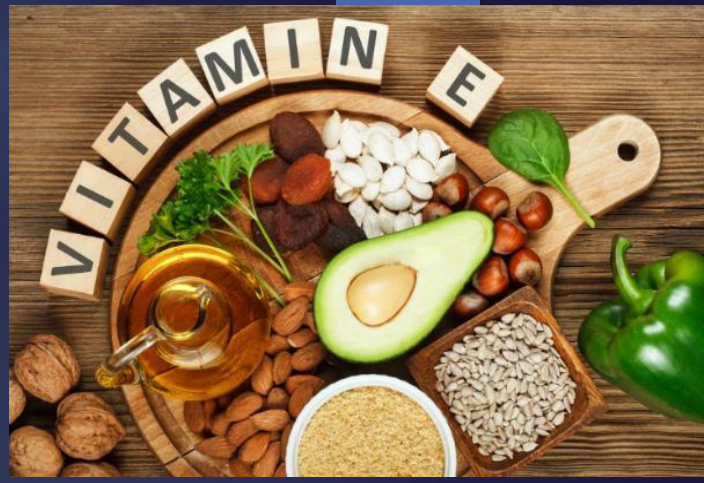
# Other Vitamins

- Vitamin A is known to influence bone content.
- Vitamin A is derived from retinol ingested as either retinyl esters (animal source foods) or carotenoids (fruits and vegetables) and metabolized to active compounds such as 11-cis-retinal, important for vision, and all-trans-retinoic acid, which is the primary mediator of the biologic actions of vitamin A.
- The role retinoids play in regulating osteoclastogenesis remains unclear.




THE USE OF VITAMINS AND MINERALS IN SKELETAL HEALTH: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT
Daniel L. Hurley, MD, FACE1; Neil Binkley, MD, FACE2; Pauline M. Camacho, MD, FACE3; Dima L. Diab, MD, FACE, FACP, CCD4; Kurt A. Kennel, MD, FACE5; Alan Malabanan, MD, FACE, CCD6; Vin Tangpricha, MD, PhD, FACE7

# Vitamin E




- There is conflicting evidence of the role of vitamin E on bone health. The most abundant vitamin E isomer present in food and most widely distributed in the body is α-tocopherol

No recommendation for vitamin E supplementation can be made for bone health.

- Supplementation generally shows positive effects in various animal models of osteoporosis, but high-dose αTF may be detrimental to bone.
  - Possible reasons αTF may be harmful to bone include interference with the effects of vitamin K on bone.

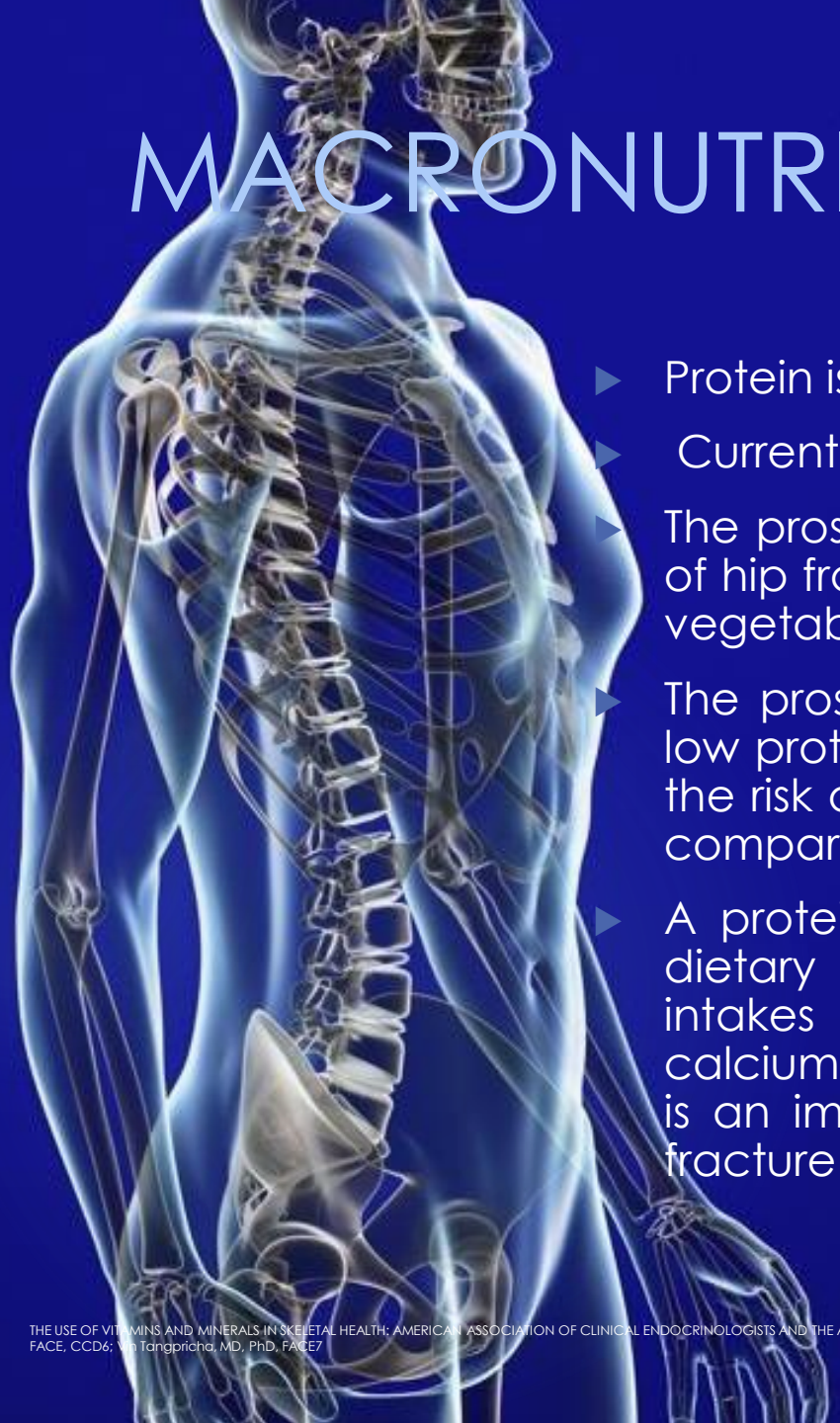
THE USE OF VITAMINS AND MINERALS IN SKELETAL HEALTH: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT Daniel L. Hurley, MD, FACE1; Neil Binkley, MD, FACE2; Pauline M. Camacho, MD, FACE3; Dima L. Diab, MD, FACE, FACP, CCD4; Kurt A. Kennel, MD, FACE5; Alan Malabanan, MD, FACE, CCD6; Vin Tangpricha, MD, PhD, FACE7

# Vitamin c


- Vitamin C is found naturally in fruits and vegetables, and it is a common fortification in cereals and juices due to its low toxicity.
- The prevalence of deficiency in the U.S. is reported as 6% . Human studies generally showed a positive relationship between vitamin C and bone health.
- The majority of studies have found either positive trends or significant effects of vitamin C on skeletal health. Vitamin C is known to play a role in collagen formation, bone matrix development, osteoblast differentiation, and in limiting bone resorption, but the exact effect that vitamin C may have on bone density is presently unknown.

THE USE OF VITAMINS AND MINERALS IN SKELETAL HEALTH: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT Daniel L. Hurley, MD, FACE1; Neil Binkley, MD, FACE2; Pauline M. Camacho, MD, FACE3; Dima L. Diab, MD, FACE, FACP, CCD4; Kurt A. Kennel, MD, FACE5; Alan Malabanan, MD, FACE, CCD6; Vin Tangpricha, MD, PhD, FACE7

# MACRONUTRIENTS



- Protein is a major nutrient essential for collagen synthesis in bone.
- Current IOM guidelines for dietary protein are 0.8 g/kg.
- The prospective Iowa Women's Health Study reported a decreased relative risk of hip fracture across increasing quartiles of animal protein intake, compared to vegetable protein, in postmenopausal women.
- The prospective 5-year Canadian Multicentre Osteoporosis study showed that low protein intakes (<12% of total calories) were associated with almost double the risk of fragility fracture in postmenopausal women and men aged ≥50 years compared to higher (≥15% of total calories) protein consumption.
- A protein and calcium interaction has been identified, suggesting increased dietary protein is associated with decreased fracture incidence with calcium intakes >800 mg/day, whereas the effect appears reversed during lower calcium intake. The balance of evidence suggests that adequate protein intake is an important modifiable risk factor associated with reduced risk of fragility fracture.

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| | Essential nutrient for growth and maintenance | Studies include RCTs | Effect on BCM | Effect on BMD | Effect on vertebral fractures | Effect on non-vertebral fractures | Recommended daily dose for bone health (adult RDA for 98% population health) |
|---|---|---|---|---|---|---|---|
| ***Minerals*** | | | | | | | |
| Calcium | Yes | Yes | + | + | + | + | 1,000-1,200mg/d |
| Phosphorus | Yes | | | | | | ? (700 mg) |
| Magnesium | Yes | | | 0/+ | | | ? (320-420mg) |
| Fluoride | Yes | Yes | + | 0/+ | 0/+ | -/0 | ? (3-4 mg) |
| Strontium | No | Yes | + | + | + | + | ?RDA |
| Boron | No | | | | | | ?RDA |
| ***Vitamins*** | | | | | | | |
| A | Yes | | | | | | ? (2,333-3,000 IU) |
| C | Yes | Yes | | 0/+ | 0/+ | 0/+ | ? (75-90 mg) |
| D | Yes | Yes | + | + | + | + | 1,000-2,000 IU/d (600 IU) |
| E | Yes | | | 0/+ | | | ? (15 mg = 22.5 IU) |
| K | Yes | | 0/+ | + | + | | ? (RDA not available; AI 90-120 µg/d) |
| | | | | | | | |

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# MUCHAS GRACIAS

# Prevalence of Vitamin D Insufficiency and Deficiency among Young Physicians at University District Hospital in San Juan, Puerto Rico. Ramírez-Vick, Hernández-Dávila, Rodríguez-Rivera N, López-Valentín, Haddock , Rodríguez-Martínez , González-Bossolo

- Vitamin D has been attracting increased attention because of higher prevalences of vitamin D insufficiency and deficiency than expected in areas with sufficient sun exposure. Even though sunlight exposure and diet are the main determinants of vitamin D status, other factors, such as age, race, the use (or not) of sunscreen, medications, and malabsorptive conditions, also affect vitamin D levels. Recent studies have found high prevalences of vitamin D deficiency and insufficiency in different populations. However, there are limited data regarding the prevalence of vitamin D deficiency and insufficiency in Puerto Rico. To shed more light on the subject, we evaluated a sample of 51 internal medicine residents and research fellows, aged from 25 to 39 years at the University District Hospital in San Juan, Puerto Rico, doing so by means of a questionnaire that explored basic socio demographic and lifestyle characteristics and collected anthropometric data; in addition, we obtained blood samples in order to determine 25-hydroxyvitamin D levels. The median 25-hydroxyvitamin D level was 21 ng/mL (range, 7-38 ng/mL). Forty-five participants (88.2%) had 25-hydroxyvitamin D concentrations of lower than 30 ng/mL. We found vitamin D deficiencies in 43.1% of the population and insufficiencies in 45.1%. Contributory factors to our findings include limited exposure to sunlight during periods of high sun intensity, increased body mass index, and a limited area of the body being exposed to sunlight. A relationship between reduced physical activity levels and hypovitaminosis D was also found. Both calcium intake and vitamin D intake, which were markedly below recommended daily allowances, were positively correlated with 25-hydroxy vitamin D levels, but with a weak association.