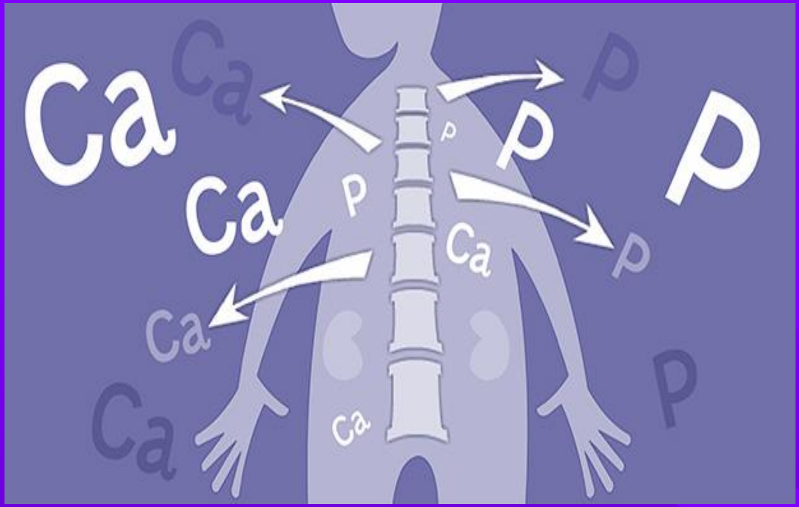

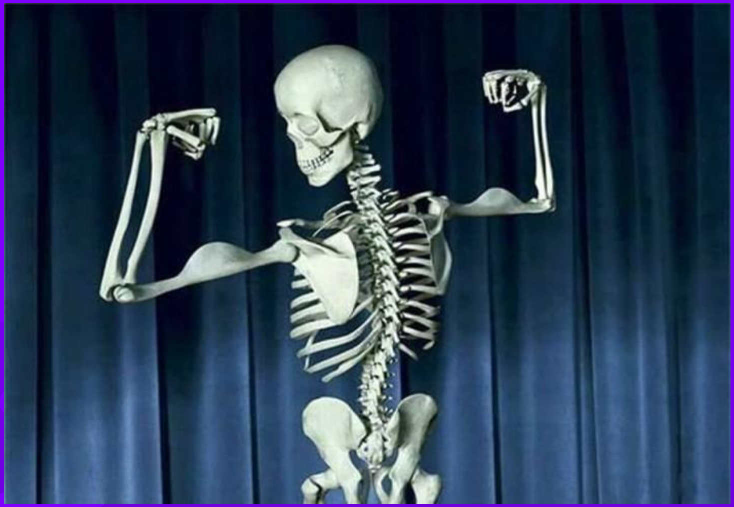

CALCIUM METABOLISM AND HOMEOSTASIS-CALCIOTROPIC HORMONES-METABOLIC ACTIONS. RECEPTORS AND SIGNALING

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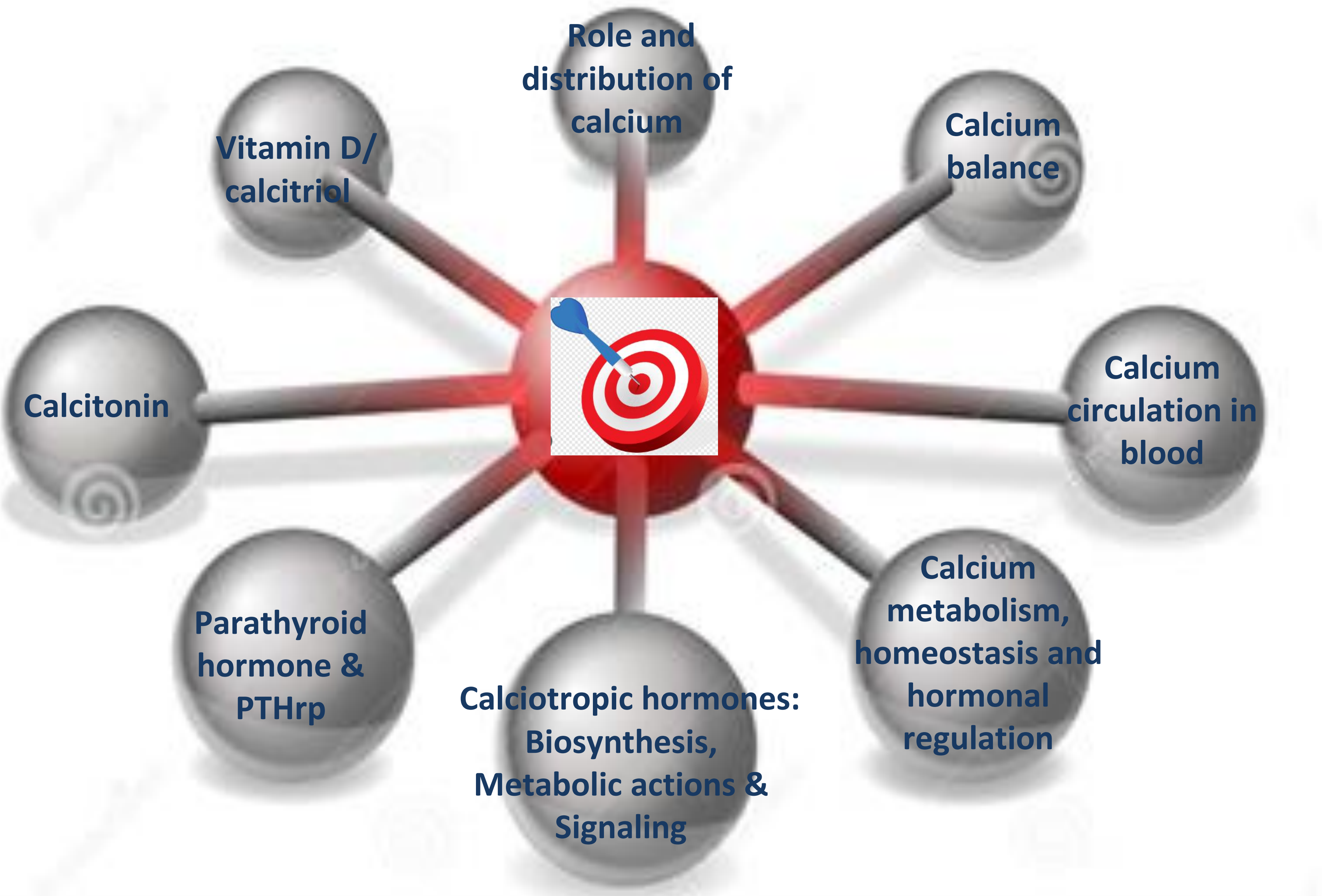
EDUCATIONAL AIMS



1. HOW CALCIUM IS DISTRIBUTED IN OUR ORGANISM?

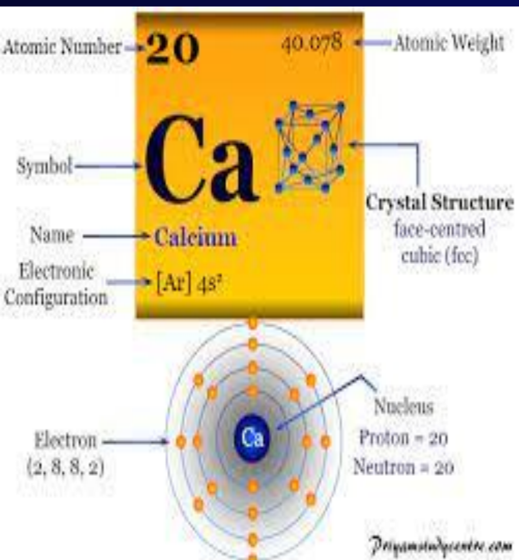
2 % body weight → 1,400 gr

1. Bones and teeth 99%
2. Extracellular fluid
3. Intracellular space

(2 and 3: < 1%)

> 99% of total body calcium is in bone and not easily accessible. Less than 1% is in the extracellular fluid and intracellular space (~20-30mmol total)

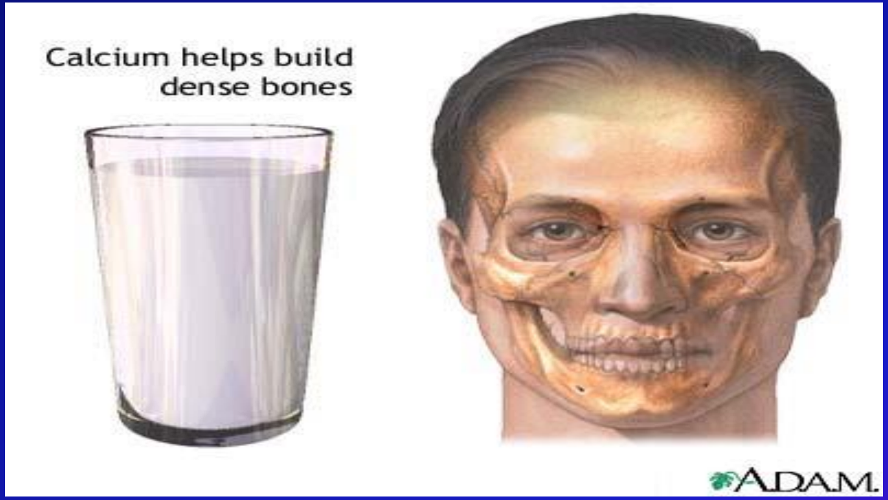
2. WHAT IS THE ROLE OF CALCIUM?



Calcium plays an important role in:

- Cell signaling and 2nd messenger
- Neurotransmission and hormone release
- Exocytosis of proteins
- Muscle contraction
- Blood clotting
- Biomineralization

3. WHAT ARE THE FOOD SOURCES FOR CALCIUM?



Dairy (cow, goat, sheep) and fortified plant-based milks (almond, soy, rice)

Cheese.

Yogurt.

Calcium-fortified orange juice.

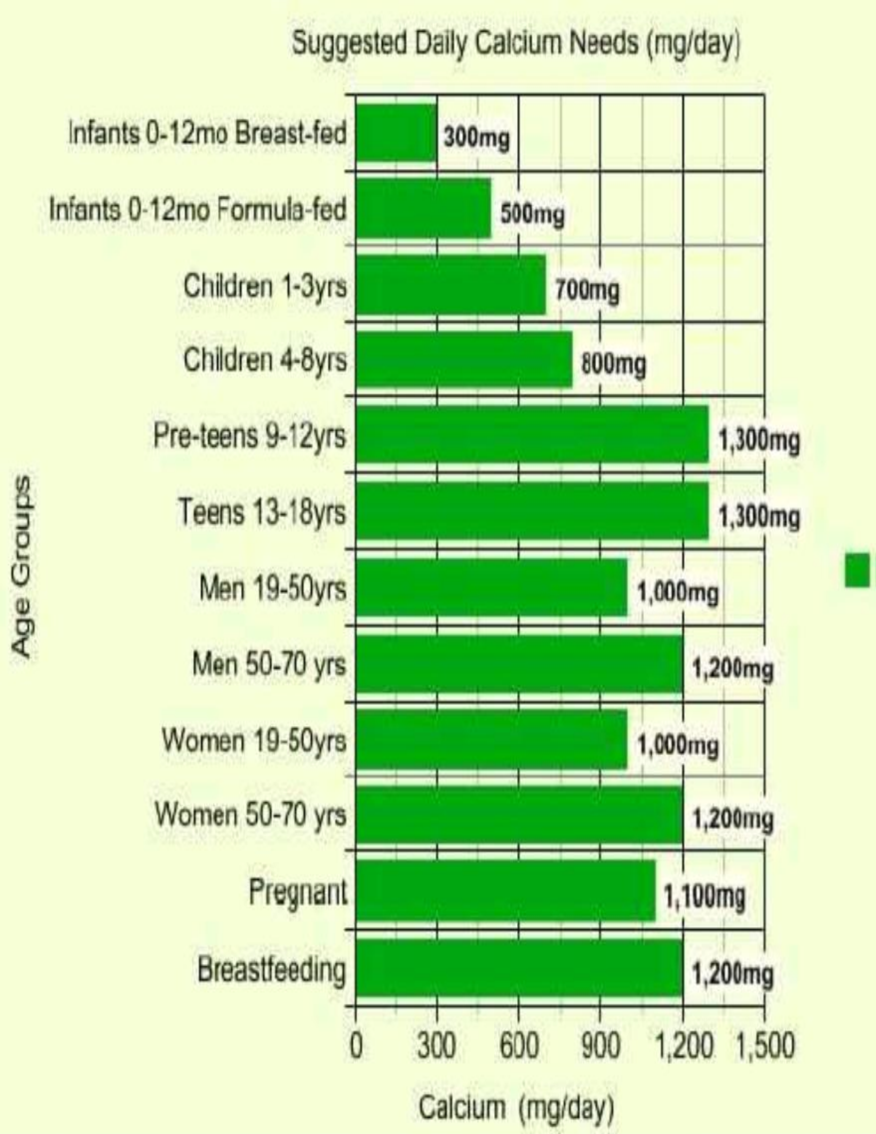
Winter squash.

Edamame (young green soybeans); Tofu, made with calcium sulfate.

Canned sardines, salmon (with bones)

Almonds.

4. WHAT ARE THE SUGGESTED DAILY CALCIUM NEEDS?



National Health and Medical Research Council. (2006) Executive Summary of Nutrient Reference Values f
Australia and New Zealand Including Recommended Dietary Intakes.

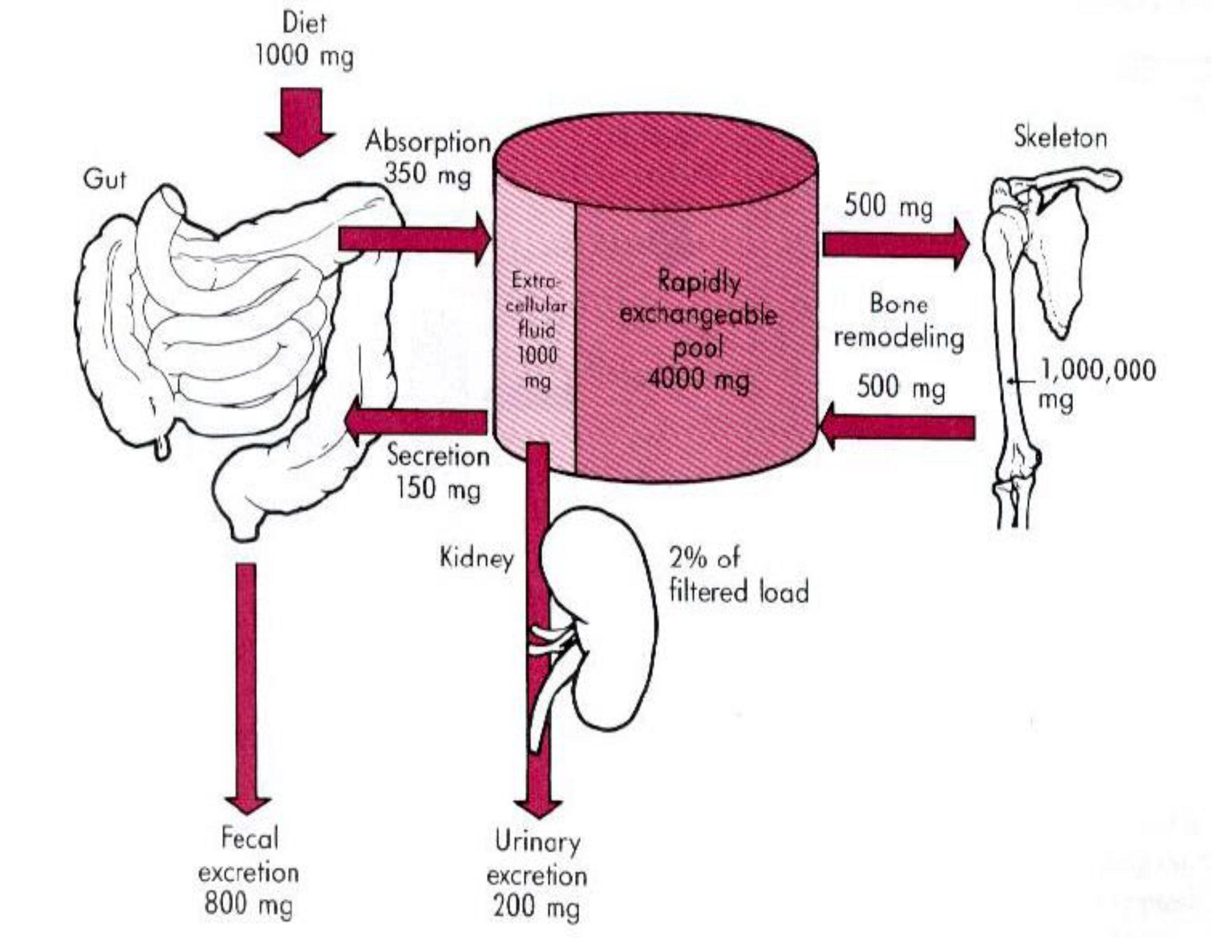
What is the food highest in calcium?

A Guide to Calcium-Rich Foods

Produce	Serving Size	Estimated Calcium*
Milk, skim, low-fat, whole	8 oz	300 mg
Yogurt with fruit, low-fat	6 oz	260 mg
Mozzarella, part-skim	1 oz	210 mg
Cheddar	1 oz	205 mg

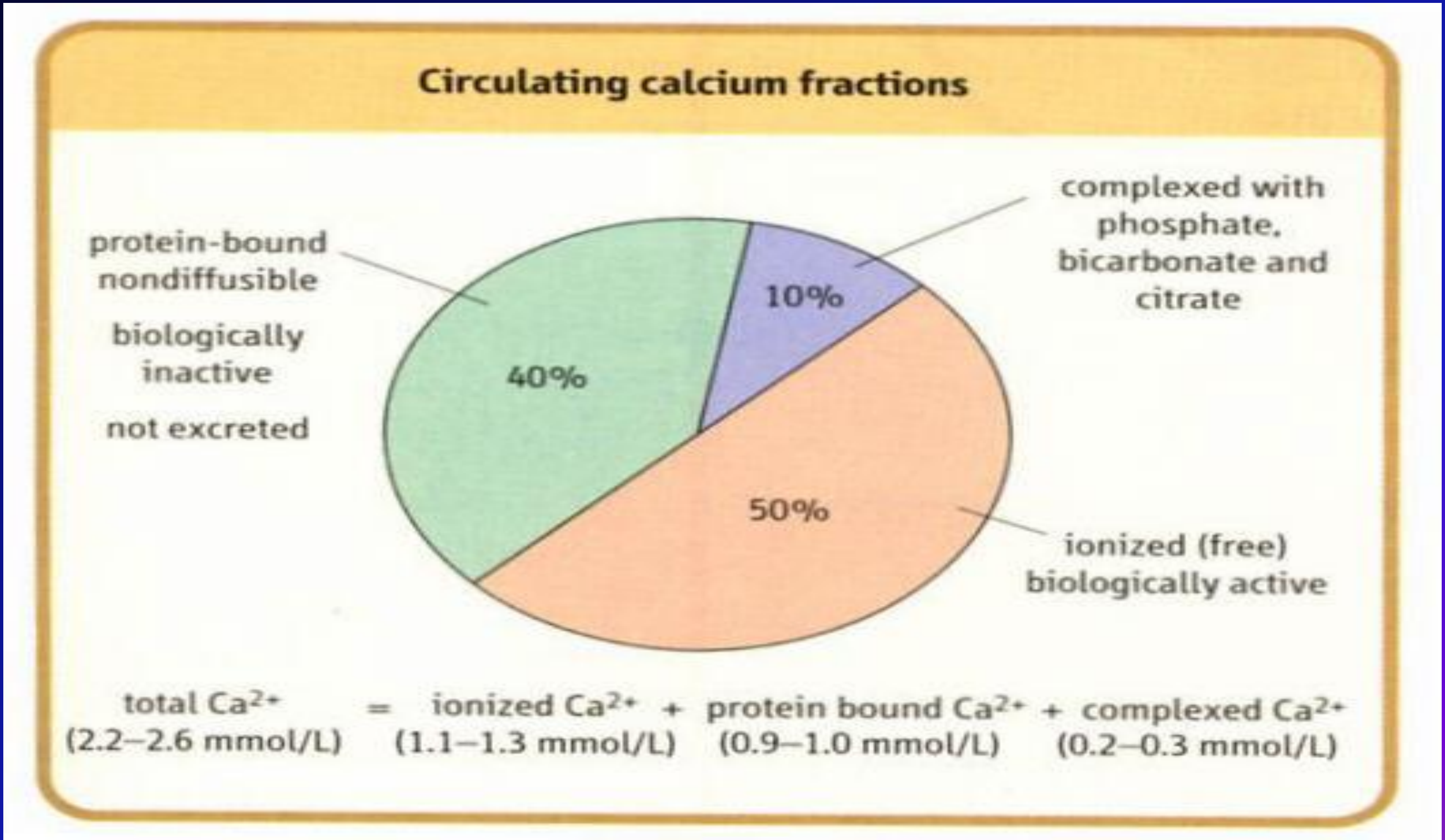
5. WHAT IS CALCIUM BALANCE?

- **Calcium balance** is the difference between the amount of calcium an organism ingests every day and how much it loses.
- Intake = output
- This balance is positive during skeletal growth in children, zero in adults, and negative in the elderly.
- Negative calcium balance: Output > intake
  - Neg Ca^{2+} balance leads to osteoporosis
- Positive calcium balance: Intake > output (growth)



- Calcium is essential, we can't synthesize it
- Only 1/3 of the calcium taken is absorbed.
- Unlike organic nutrients calcium absorption is **hormonally controlled**

6. HOW DOES CALCIUM CIRCULATE IN BLOOD?
Total Ca^{2+} : 3 Forms of Circulating Ca^{2+}



7. CALCIUM HOMEOSTASIS & HORMONAL REGULATION

- ✓ BLOOD CALCIUM LEVEL REMAINS STABLE (9 ± 1.5 mg/dL)
- ✓ CALCIUM HOMEOSTASIS IS ENSURED BY THE ACTION OF **CALCIOTROPIC HORMONES.**
- ✓ **Main Calciotropic Hormones:**

  Parathyroid hormone (PTH)

  Vitamin D (1,25 dihydroxycholecalciferol/calcitriol)

  Calcitonin (CT)

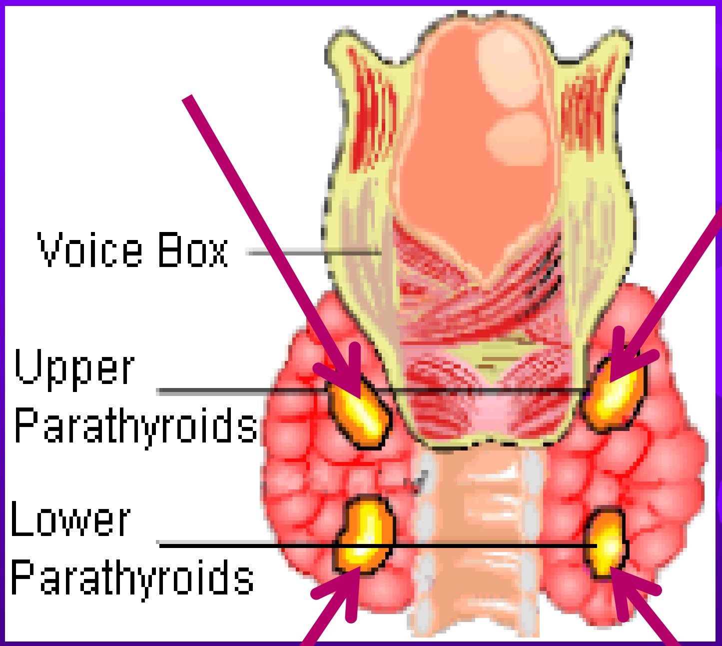
  Parathyroid hormone related protein (PTHrP)
- ✓ **Organ systems** that play an important role in Ca^{2+} metabolism

  Skeleton

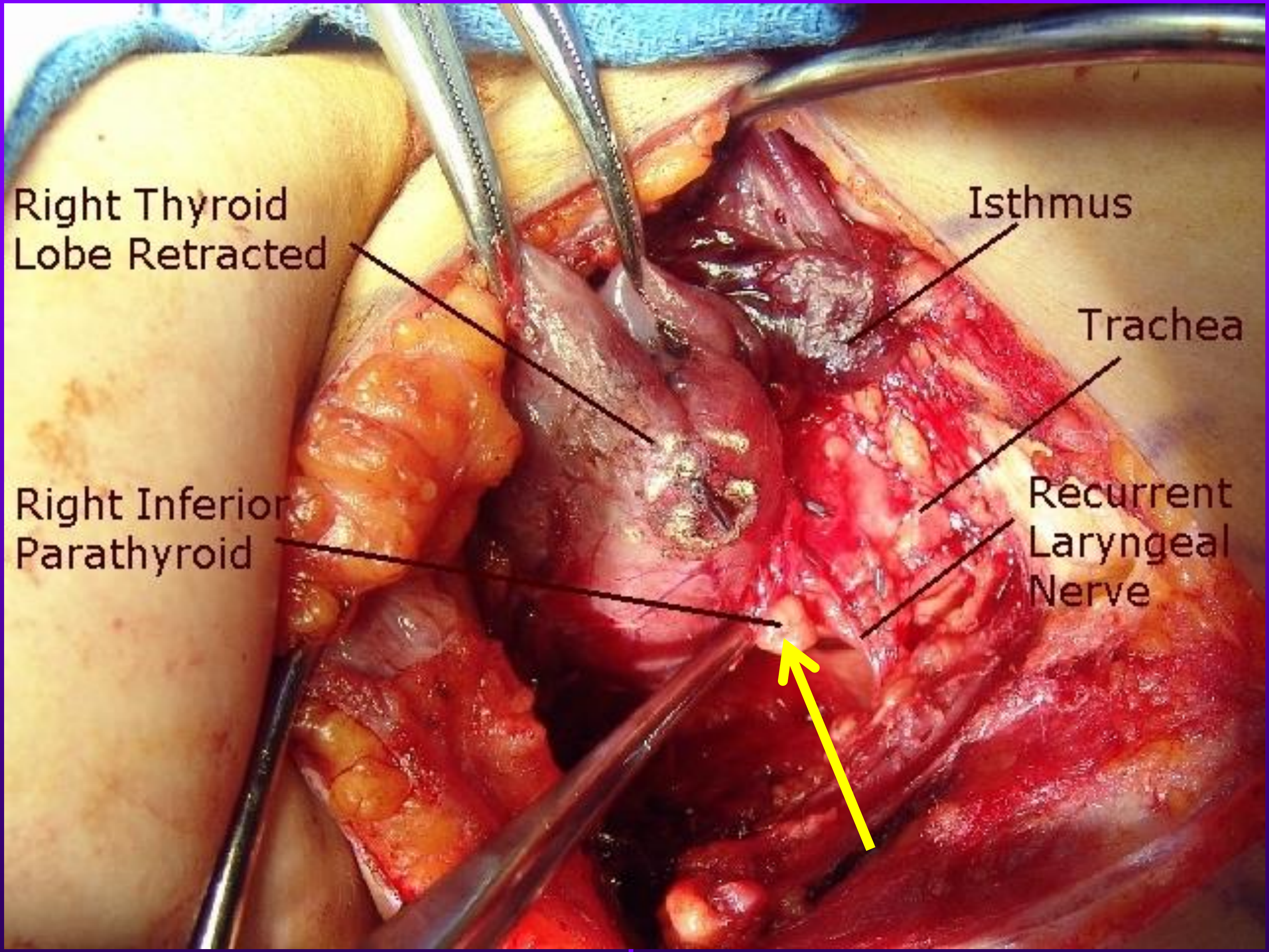
  GI tract

  Kidneys

8.1. PARATHYROID HORMONE or PARATHORMONE (PTH)

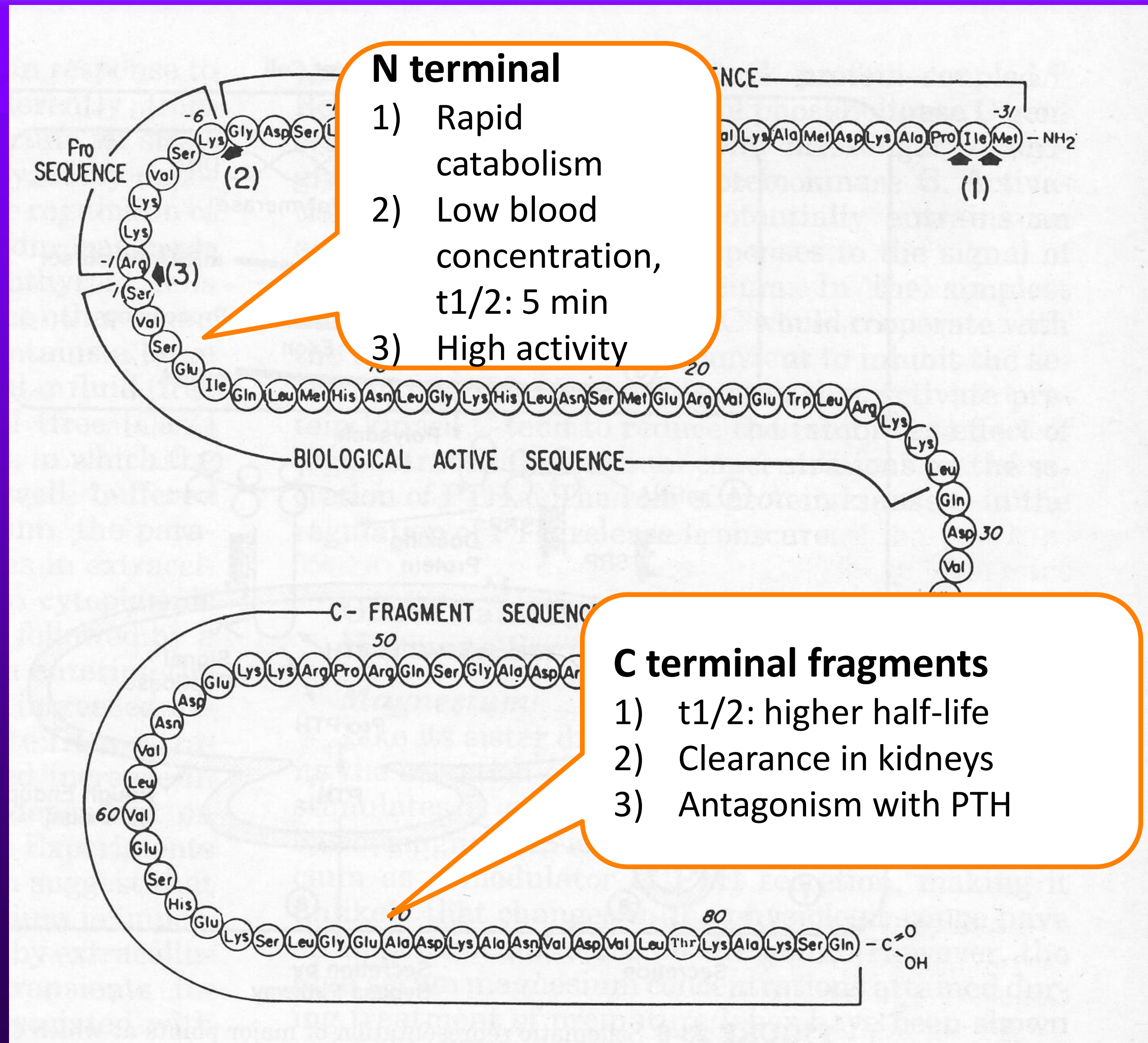


- Parathormone (PTH) is produced by the **parathyroid glands**
- Usually, 4 parathyroid glands
- The parathyroid glands are little **pea-sized glands** found behind the thyroid gland in the neck.
- If we remove all the parathyroid glands from dogs and cats, the animals will die within a few days.
- **PTH is essential for life (Regulator of Ca^{2+} homeostasis)**


Right Thyroid
Lobe Retracted
Isthmus
Trachea
Recurrent
Laryngeal
Nerve
Right Inferior
Parathyroid

8.2. PARATHYROID HORMONE (PTH) STRUCTURE

- Synthesized from PreProPTH
- 115 aa precursor giving a 90 aa prohormone
- Cleaved at -6/-7, 84 aa residues in the mature peptide (PTH)
- Only the first 29 aa in the mature PTH are the biological active sequence



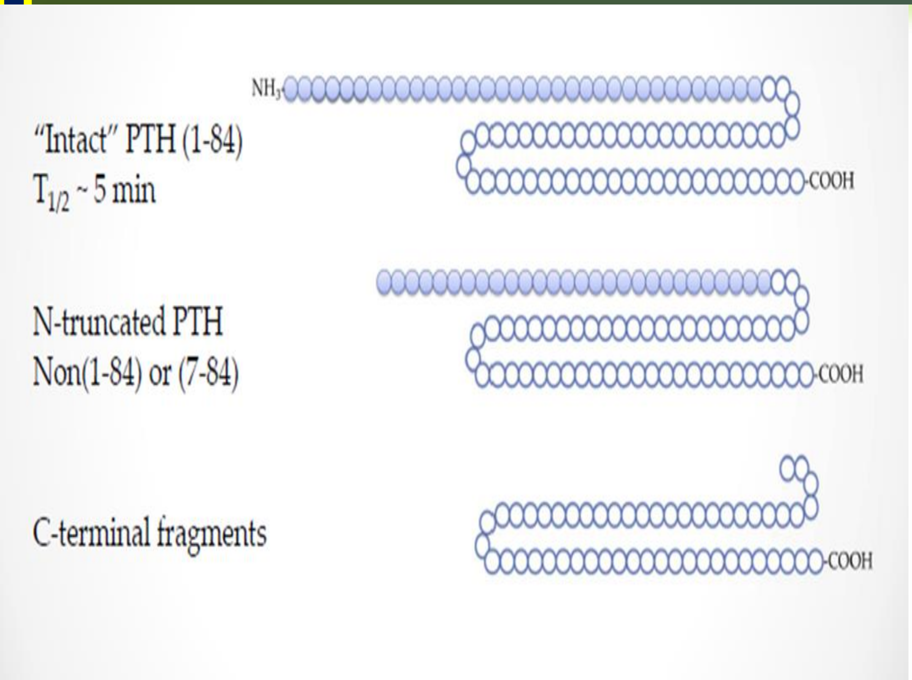
N terminal

1) Rapid catabolism
2) Low blood concentration, t1/2: 5 min
3) High activity

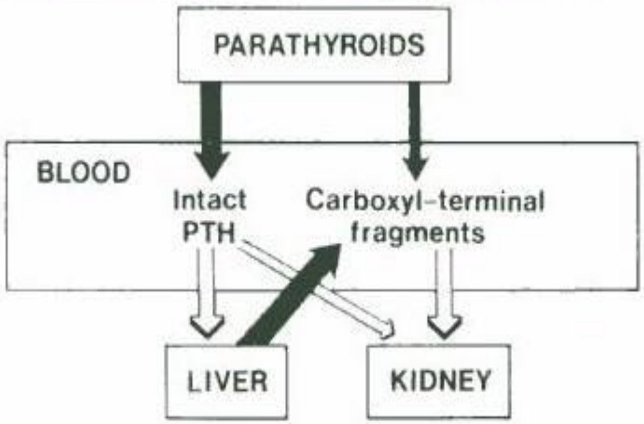
C terminal fragments

1) t1/2: higher half-life
2) Clearance in kidneys
3) Antagonism with PTH

8.3. PTH CIRCULATING FORMS



Secretion and metabolism of intact PTH and carboxyl-terminal fragments. Secretion is indicated by solid arrows, and major directions of metabolism by open arrows.



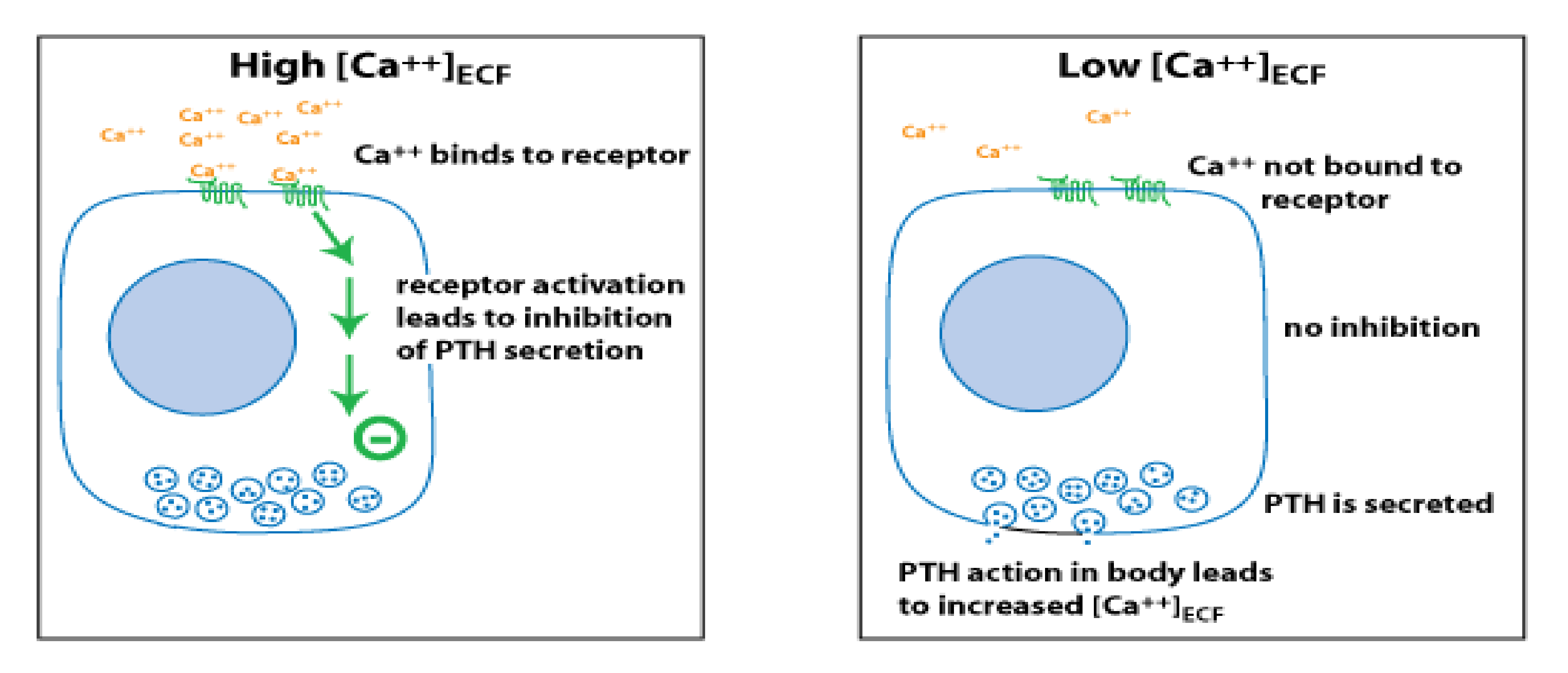
1) **Intact PTH**: active PTH of 84 aa. PTH $t_{1/2}$ (half life) is 2-3 min
2) **N-truncated PTH**: Non (1-84) or (7-84). Lacks the N-part.
3) **Inactive carboxyterminal fragments:** lack the 1-34 active domain

Liver (2/3^{rds}) and kidney (1/3rd) are major sites of fragmentation

8.4. Regulation of PTH Secretion and Biosynthesis

- Extracellular Ca^{2+} regulates the transcription and secretion of PTH through the Calcium Sensing Receptors (CaSR)
  - Low Ca^{2+} increases PTH
  - High Ca^{2+} decreases PTH
- Elevated serum phosphate concentration in turn stimulates PTH secretion, presumably by lowering extracellular calcium and increasing stability of the PTH mRNA
- High levels of 1,25 dihydroxyvitamin D inhibit transcription of PTH

Calcium Sensing Receptors (CaSR) and PTH secretion from parathyroid chief cells



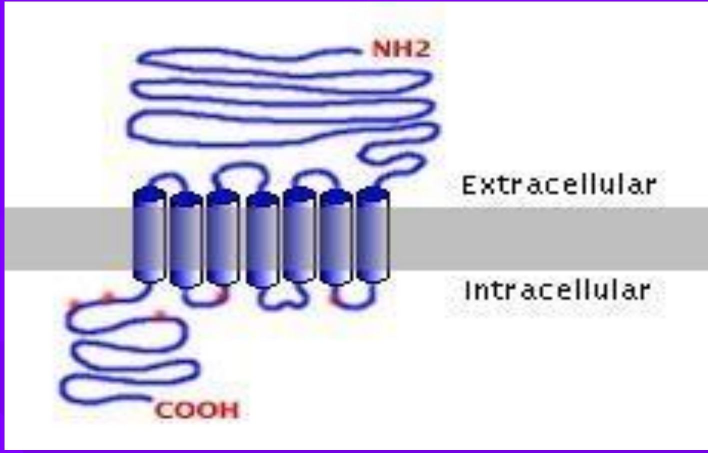
The parathyroid gland is composed of two types of cells: chief and the oxyphil.

Parathyroid chief cells, the main type of parathyroid gland cells, secrete PTH. Oxyphil cells secrete PTHrP, calcitriol, and some other factors.

Calcium Sensing Receptors (CaSR) and PTH secretion from parathyroid chief cells

- ↑ Ca^{++}
  - ↓ Synthesis of PTH
  - ↓ release of PTH
- ↓ Ca^{++}
  - ↑ Synthesis of PTH
  - ↑ release of PTH

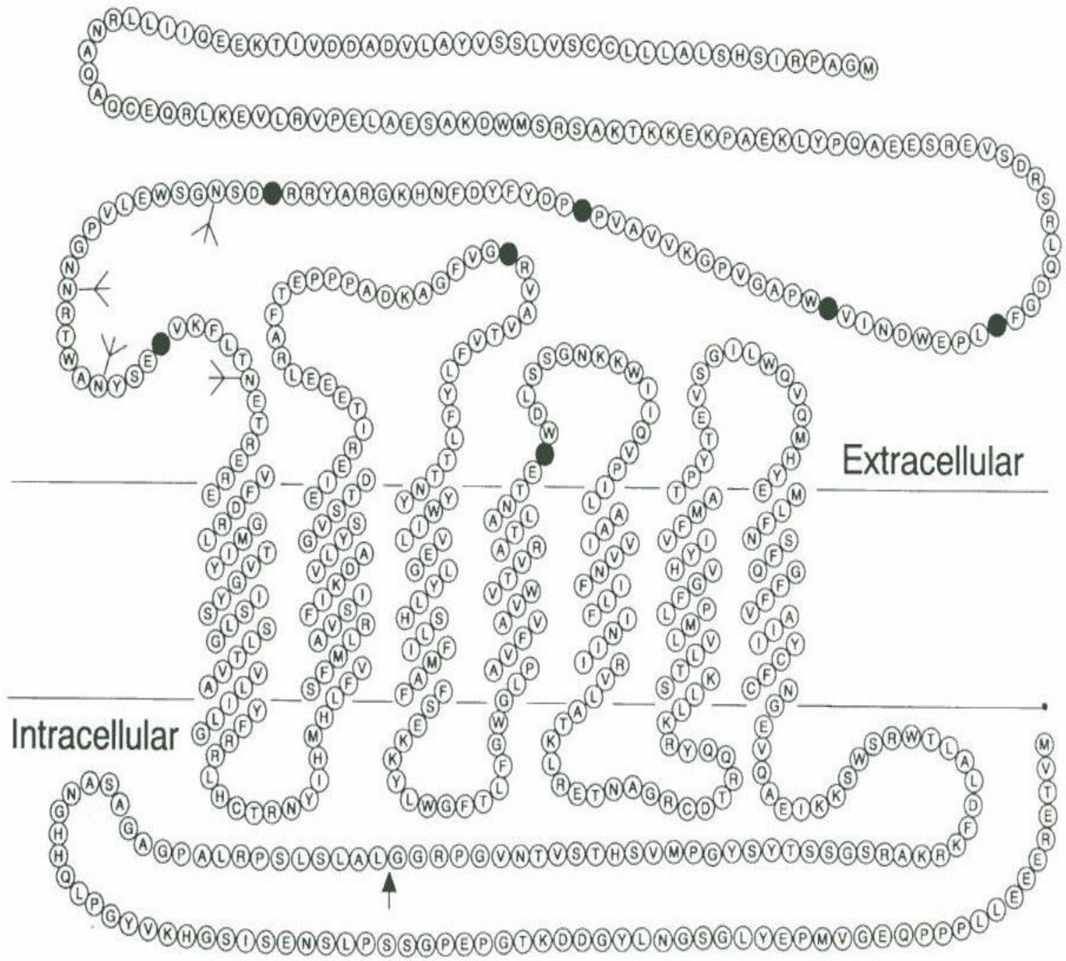
Calcium Sensing Receptor (CaSR)



- Parathyroid chief cells contain a Ca^{2+} sensing receptor (CaSR)
  - 7 transmembrane segments (7 TM receptors)
  - mM affinity for Ca^{2+}
  - GPCR of the G_{PLC}
    - Generates inositol 1,4, 5-trisphosphate which → increases intracellular Ca^{2+}
    - There are two paradoxes:
      - The receptor responds to decreasing concentrations of calcium
      - Low extracellular Ca^{2+} increases intracellular Ca^{2+} which leads to the release of PTH

8.5. Parathyroid Hormone Receptors

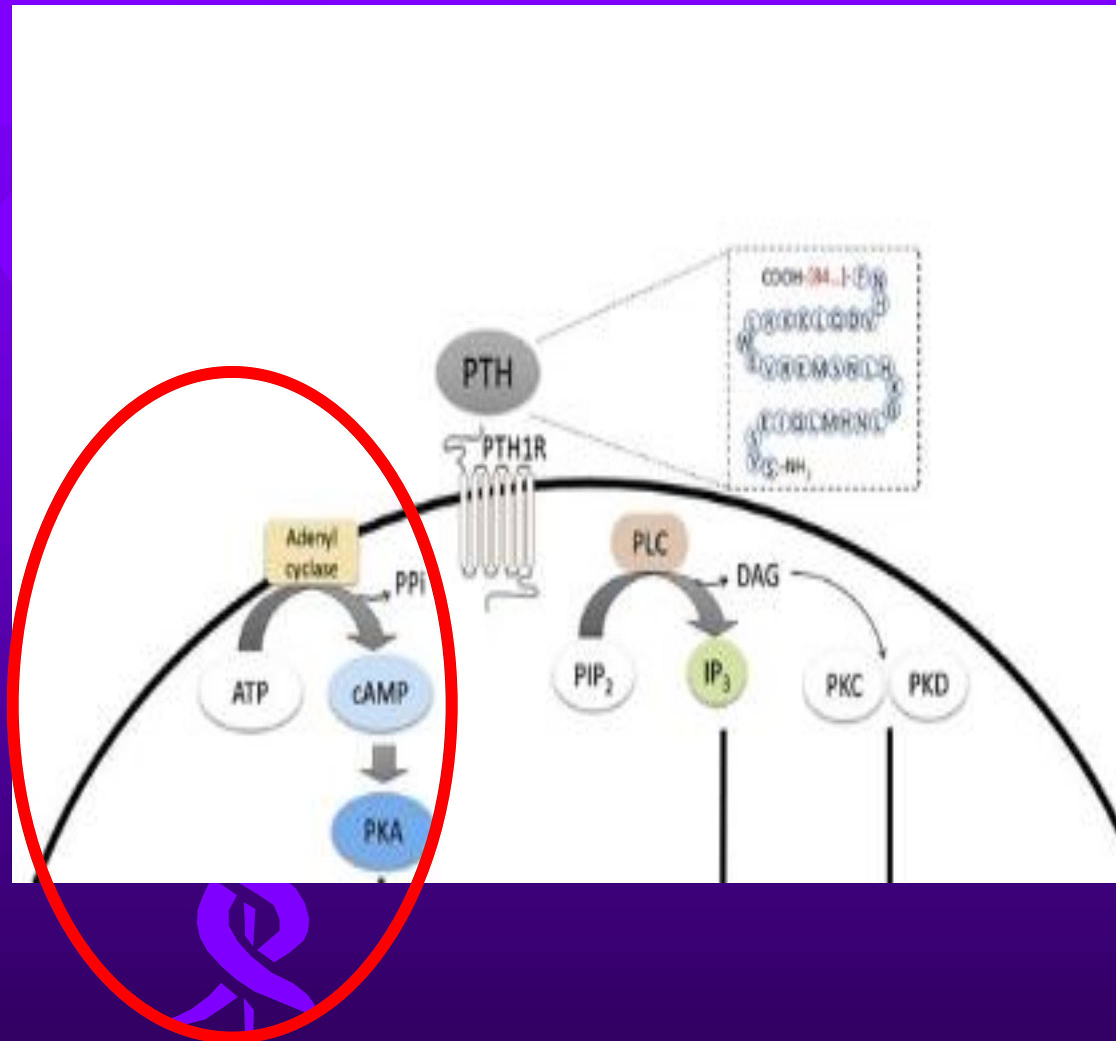
- 7 TM
- GPCR
- PTH acts on target organs mainly through receptor type 1 (PTH1R). As an endocrine hormone, the predominant physiologic effect of PTH is to raise blood calcium through actions in the bone, gut and kidney.
- Another receptor: in PTH2R (CNS, pancreas, testes, placenta)



Schematic representation of the PTH/PTHrP receptor (NH_2 terminus at top) from kidney cells, potential N-glycosylation sites (⅄), and cysteine residues that are conserved in the calcitonin receptor (●). In OK-H, residues 508 to 515 (to the left of the arrow) are WPCSALD. The peptide ends eight residues after the arrow.

8.7. PTH Intracellular Signaling

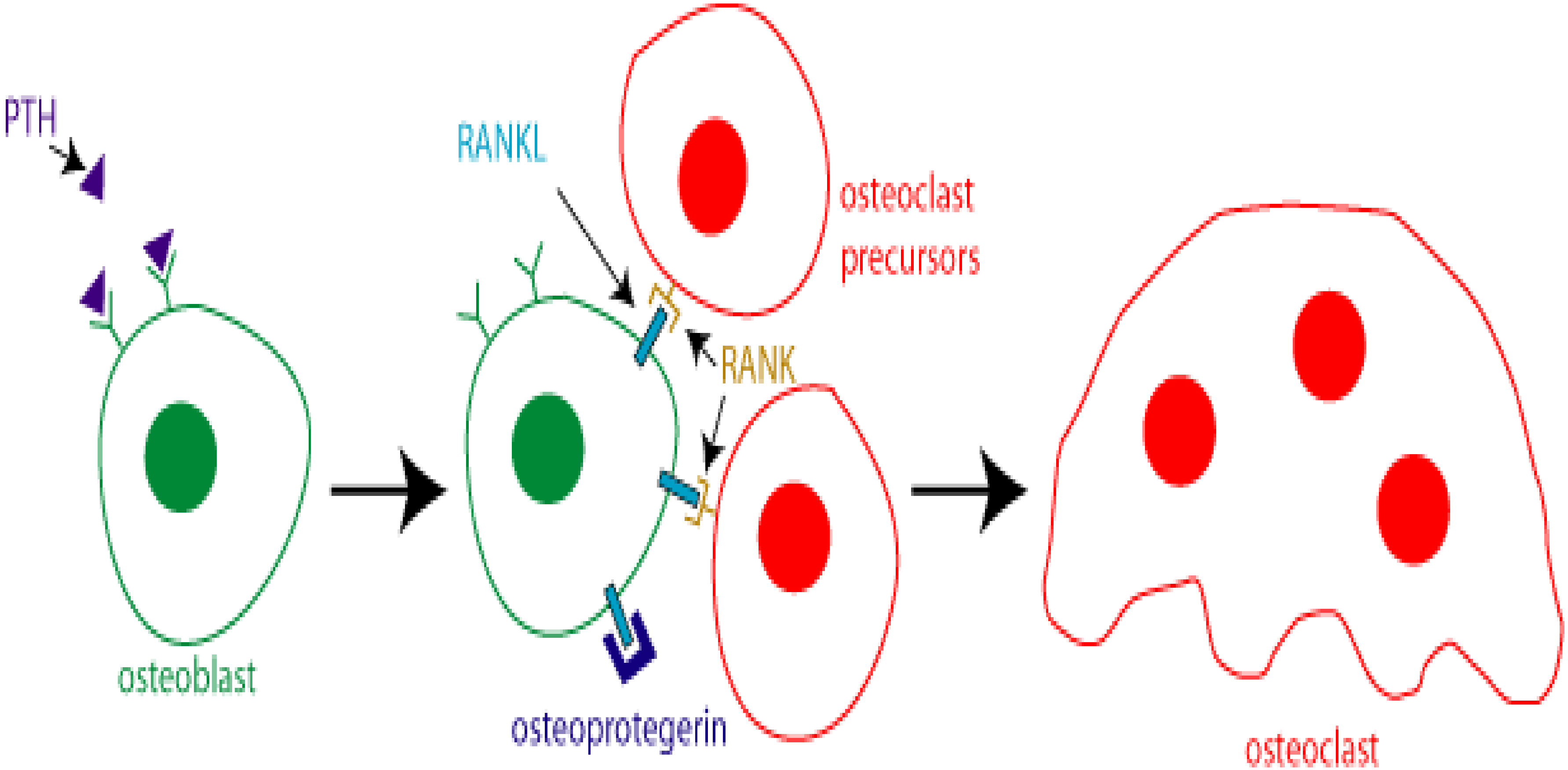
- Intracellular signaling downstream of PTH1R primarily occurs via a Gαs/cAMP-linked signaling system.



8.8. PTH Metabolic Actions

- Fine tunes Ca^{2+} levels in blood
  - It increases Ca^{2+}
  - It decreases P_i
- PTH acts directly **on BONE to stimulate resorption** and **release of Ca^{2+}** into the extracellular space (slow)
  - Gs protein-coupled receptors in osteoblasts increase cAMP and activate PKA, **inhibiting osteoblast function**
  - This occurs when PTH is secreted continuously; the opposite occurs when it is given once daily by injection (in this case, PTH stimulates osteoblast function)
- PTH **increases Ca^{2+} absorption** in **SMALL INTESTINE**
- Two effects on **KIDNEYS:**
  - PTH acts **on KIDNEY** to **increase calcium reabsorption and phosphate excretion** via Gs protein-coupled receptors
    - Parathyroid hormone acts on distal tubule
    - Calcitonin inhibits
  - Stimulates transcription of 1-alpha hydroxylase for Vitamin D activation in kidney
    - In turn, vitamin D increases calcium and phosphate absorption in the gut

HOW DOES PTH ACT ON BONE?



This slide is explained by the next 2 slides

- ✓ **Bone mass** in adults is determined by the relative activity of bone formation by **osteoblasts** and bone resorption by **osteoclasts**. If bone resorption is greater than bone formation, there is a loss of bone mass leading first to osteopenia and then to osteoporosis.

- ✓ **Osteoblasts** are responsible for producing the calcified layer of bone. They secrete calcium, phosphate, osteoid proteins, cytokines, RANKL (ligand) and osteoprotegerin (OPG). PTH and vitamin D control osteoblast function.

- ✓ **Osteoclasts** are the cells responsible of bone resorption. They are large motile multinucleated cells derived from the same hematopoietic stem cells from which macrophages are derived. Osteoclasts secrete acids and enzymes that dissolve calcium phosphate in bone.

- ✓ **Surprisingly,** although osteoclasts are responsible for resorbing bone and theoretically should be the targets of PTH to try to increase blood calcium, they have no receptors for PTH.

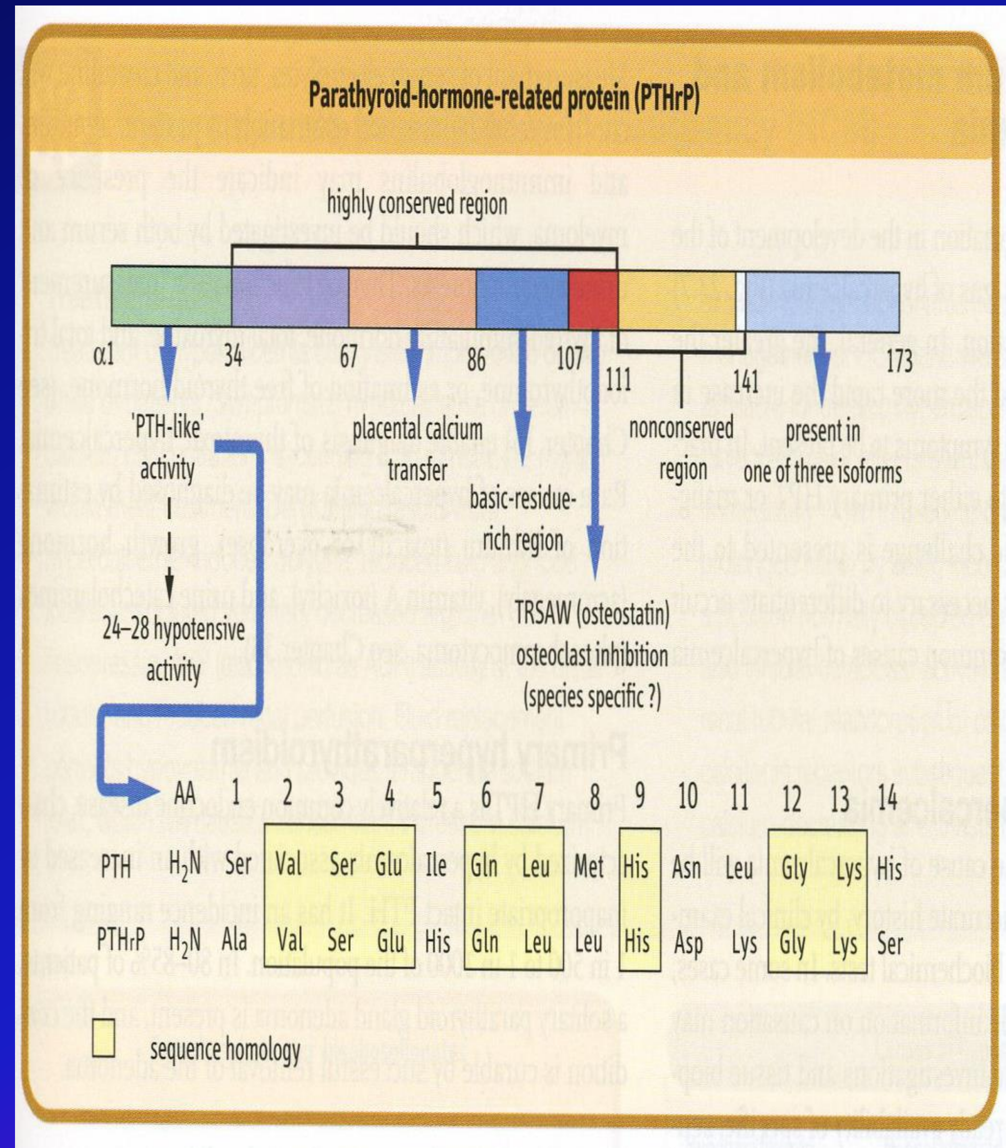
- ✓ Instead, the effects of PTH are mediated by a variety of paracrine molecules including **Osteoprotegerin (OPG),** also known as osteoclastogenesis inhibitory factor, and an osteoclast differentiation factor **called RANKL**. PTH receptors are found in osteoblasts. When PTH stimulates osteoblasts, they secrete factors that regulate osteoclast activity and differentiation.

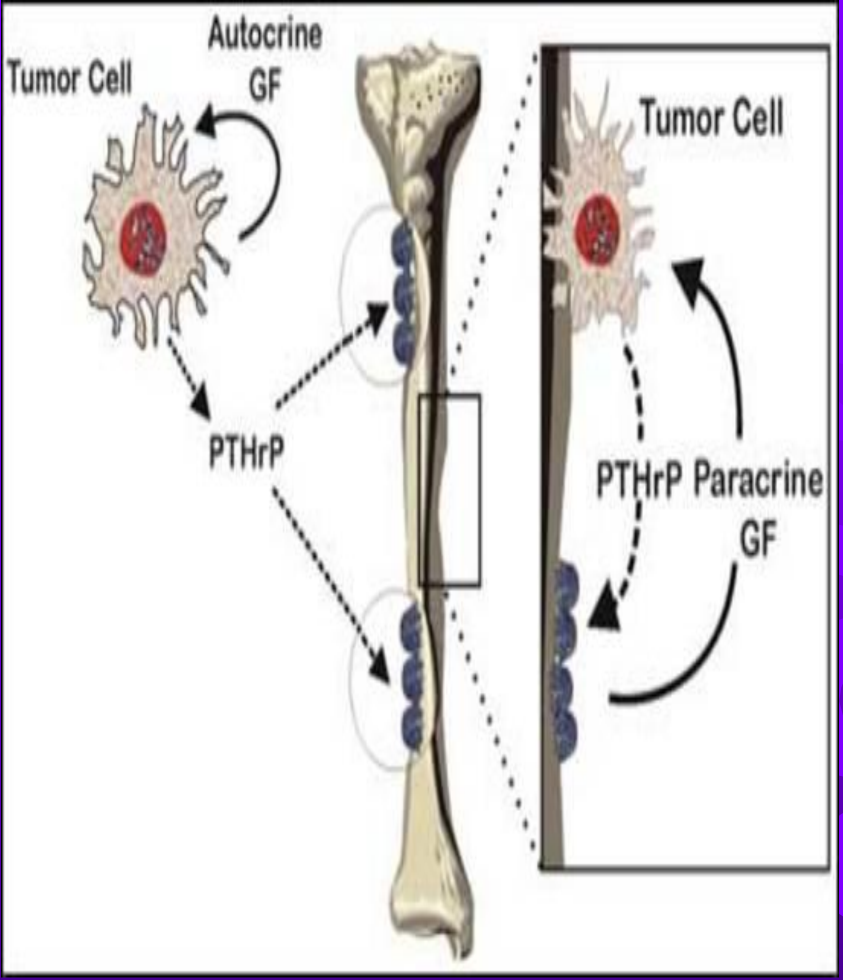
- ✓ The **key osteoblast signaling molecule RANKL** which binds to RANK in osteoclast precursors and mature osteoclasts. Activated RANK receptors increase acid secretion from mature osteoclasts and promote the formation of new osteoclasts. At the same time, that osteoblasts secrete RANKL, they also secrete a molecule called OPG, which binds to RANKL to prevent it from binding to RANK. PTH acts on osteoblasts to inhibit the synthesis of osteoprotegerin which inhibits RANKL.

- ✓ By adjusting the ratio of RANKL and OPG, **osteoblasts are able to control osteoclast activity**

9. PTHrP; Parathyroid Hormone related Protein

- It is synthesized as 3 isoforms from alternative splicing (139, 141, 173 aa)
- Can activate the PTH receptor
- Plays a physiological role in lactation, possibly as a hormone for the mobilization and/or transfer of calcium to the milk
- May be important in fetal development





-PTHrp may also be produced by tumor cells playing a role in the development of hypercalcemia of malignancy

-Some lung cancers are associated with hypercalcemia

-Other cancers can be associated with hypercalcemia

9. CLINICAL CORRELATIONS

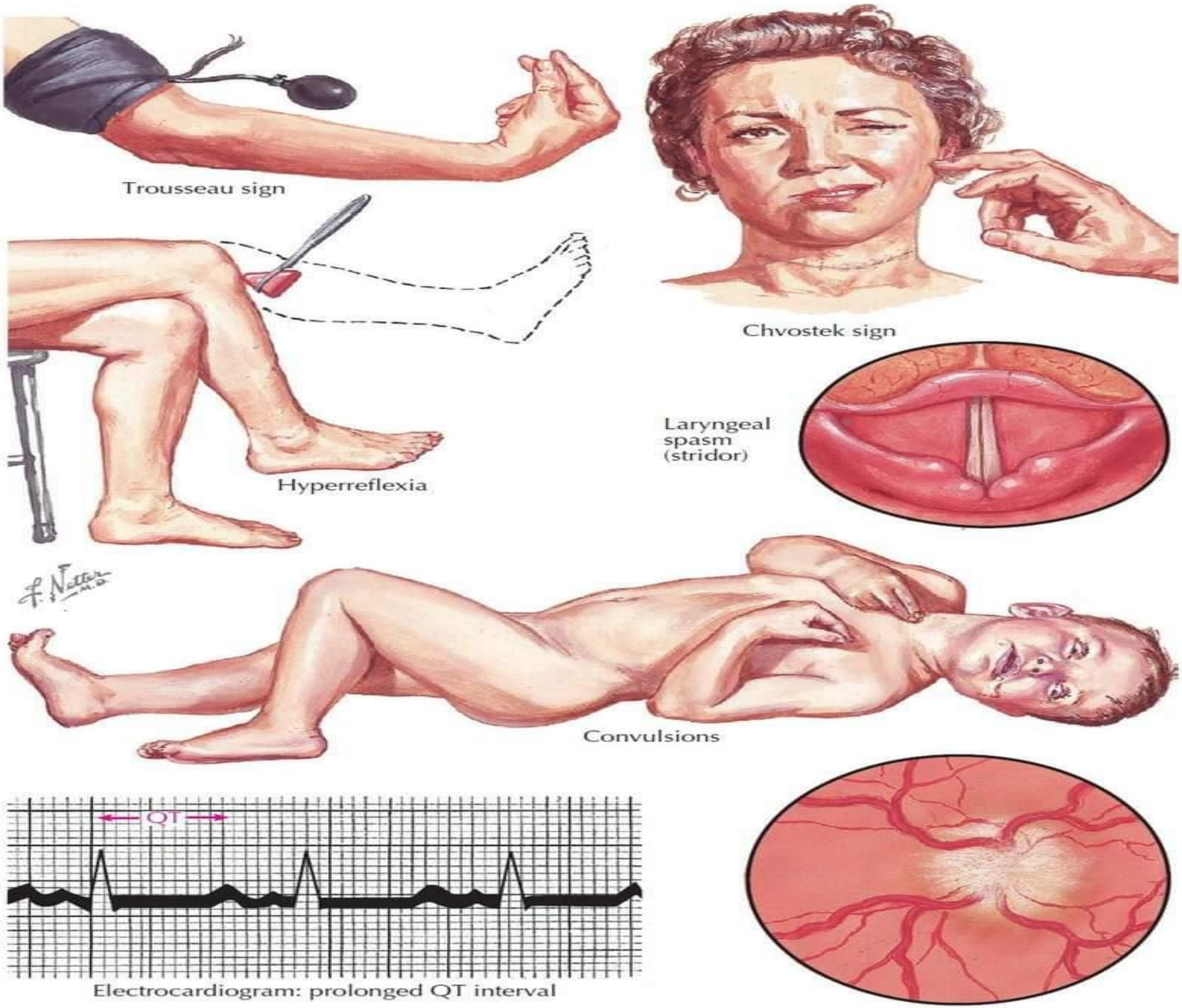
Let's understand better PTH actions by studying cases with low and high calcium….

Main Causes of Hypocalcemia

Hypoparathyroid	Nonparathyroid	PTH Resistance
Postoperative	Vitamin D deficiency	Pseudo-hypoparathyroidism
Idiopathic	Malabsorption	
Post radiation	Liver disease	
	Kidney disease	
	Vitamin D resistance	

One important cause of low calcium is the dysfunction of parathyroid glands (which do not produce PTH)

Clinical Manifestations of Hypocalcemia



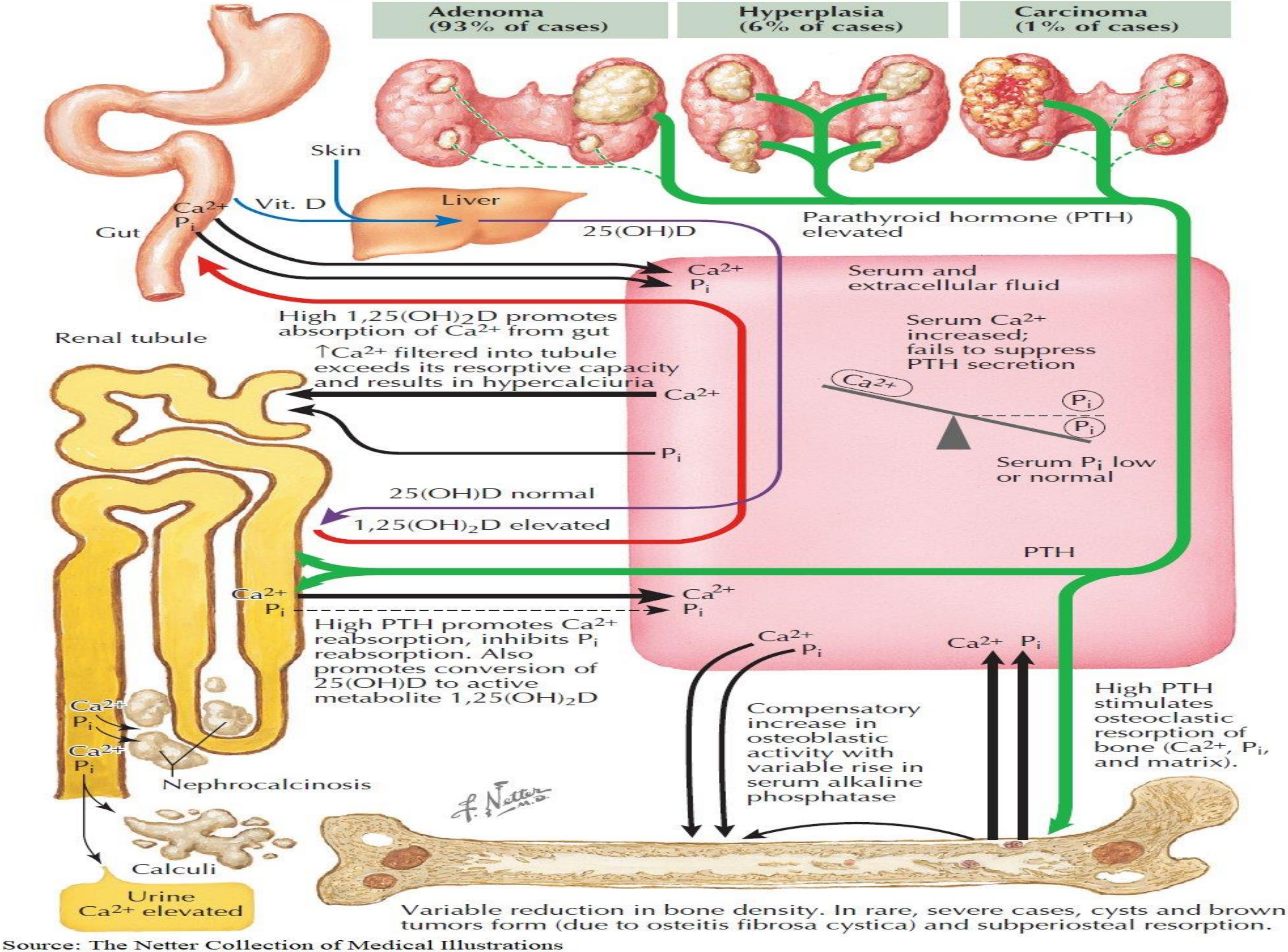
Source: The Netter Collection of Medical Illustrations

Main Causes of Hypercalcemia

Common	Uncommon
Hyperparathyroidism	Renal failure
Malignant disease, e.g. some lung cancers	Sarcoidosis
Vitamin D toxicity (excessive intake)	Multiple myeloma

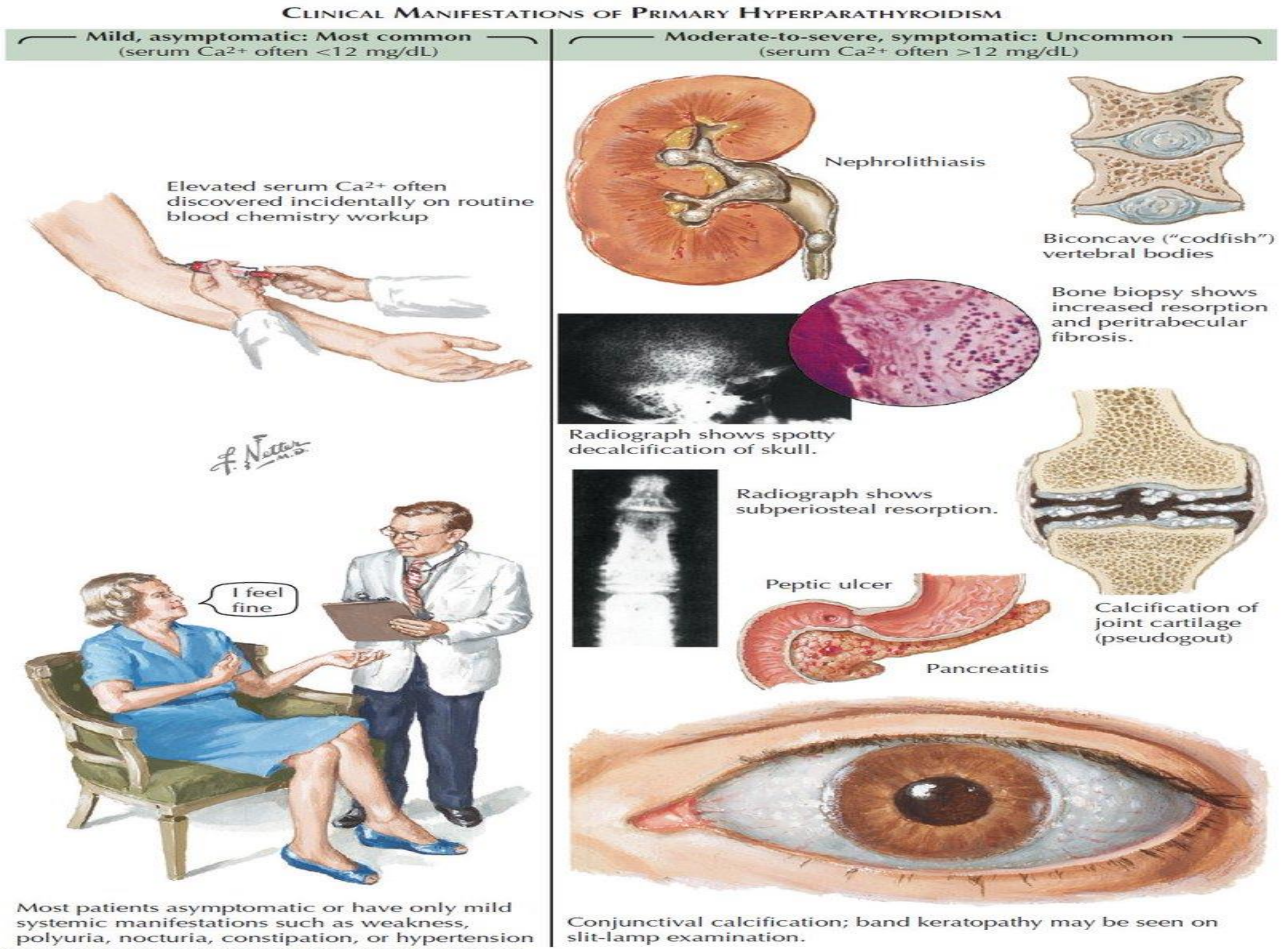
One important cause of high calcium is the hyperfunction of parathyroid glands (which produce elevated PTH)

Pathophysiology of Primary Hyperparathyroidism



Source: The Netter Collection of Medical Illustrations

Parathyroid gland adenoma



Source: The Netter Collection of Medical Illustrations

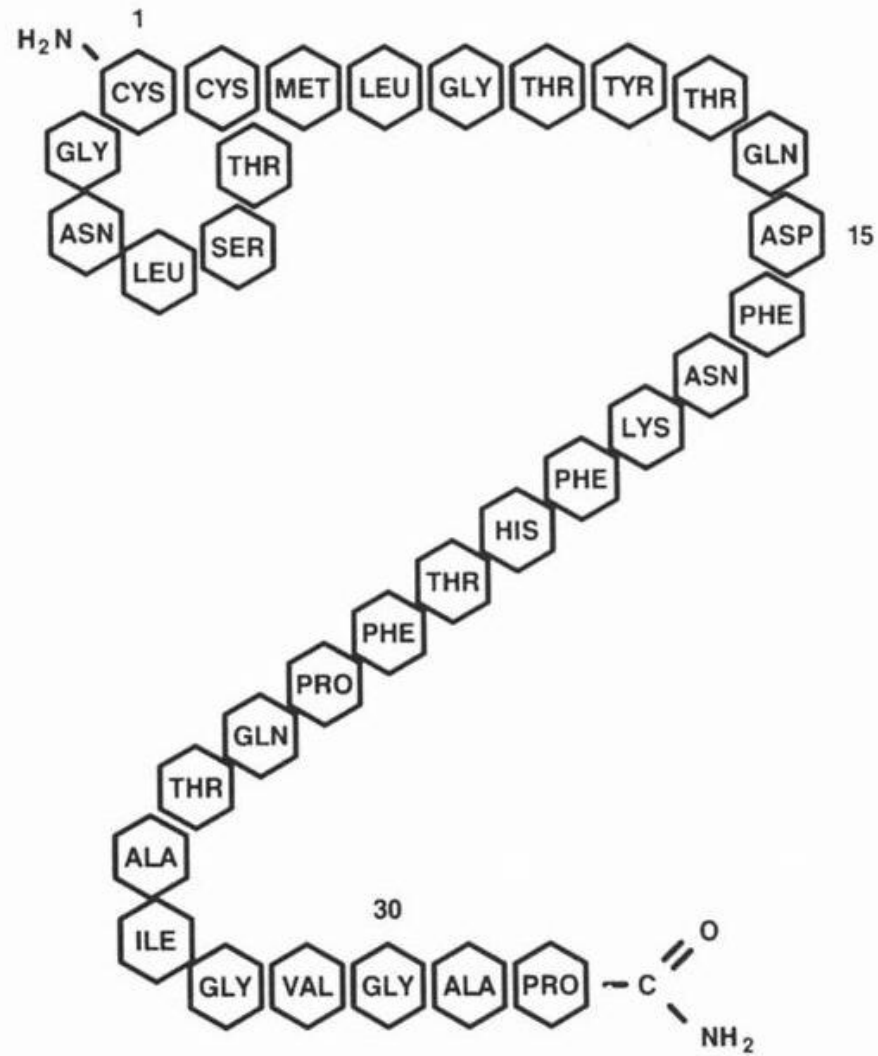
Primary hyperparathyroidism

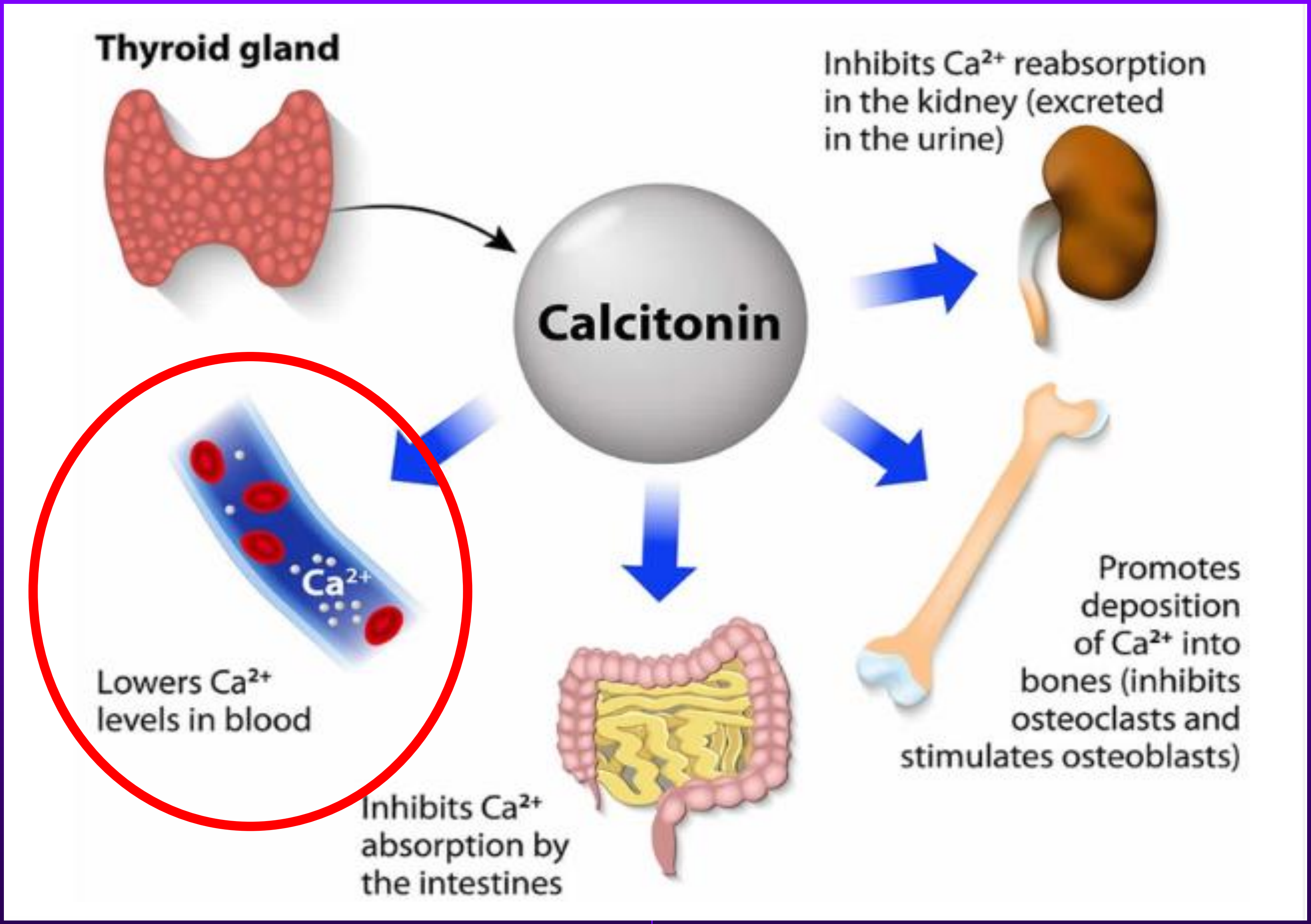
- ✓ 80% Most people are asymptomatic
- ✓ STONES (Renal stones may be a common single presenting complaint)
- ✓ BONES (osteoporosis, bone aches, etc)
- ✓ MOANS abdominal (constipation, nausea, anorexia, etc)
- ✓ GROANS neuromuscular and psychic groans (fatigue, depression, memory loss, etc)

10. Calcitonin

- Product of parafollicular C cells of the thyroid gland
- 32 aa
- Inhibits osteoclast mediated bone resorption
    - This decreases serum Ca^{2+}
- Promotes renal excretion of Ca^{2+} & phosphate
- Inhibits intestinal absorption of Ca^{2+}

The sequence of human calcitonin. The molecule contains a seven-membered ring linked by a disulfide bridge at the N terminus.

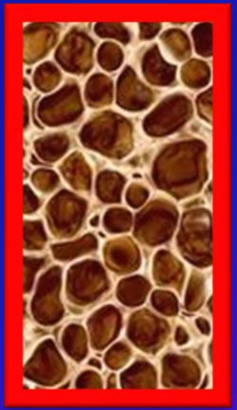


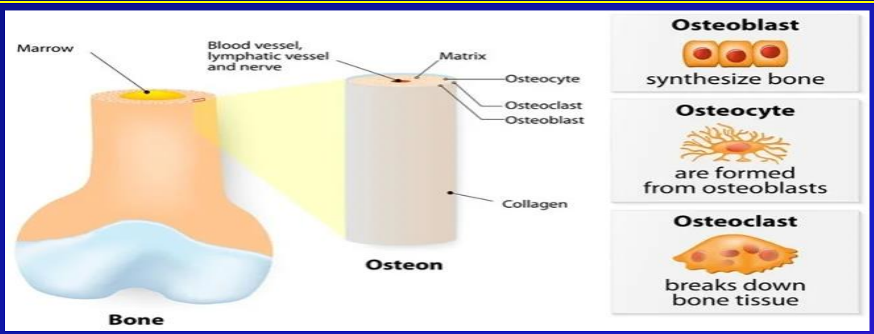

Thyroid gland
Calcitonin
Inhibits Ca^{2+} reabsorption in the kidney (excreted in the urine)
Ca^{2+}
Lowers Ca^{2+} levels in blood
Inhibits Ca^{2+} absorption by the intestines
Promotes deposition of Ca^{2+} into bones (inhibits osteoclasts and stimulates osteoblasts)

CALCITONIN

Secretion of calcitonin is **stimulated by**: an increase in serum Ca^{2+} and gastrin or pentagastrin

Probably not essential for human survival and not so important in the metabolism of calcium as PTH and vitamin D.

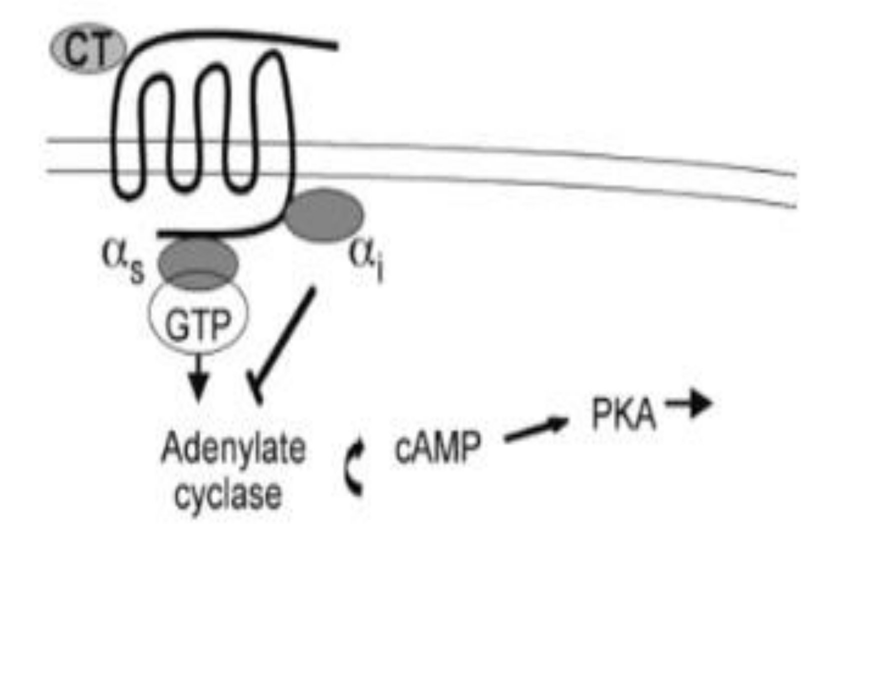




Calcitonin inhibits (blocks) the activity of osteoclasts, which are cells that break down bone. Calcitonin strongly inhibits bone-resorbing activity of osteoclasts reducing serum calcium. It antagonizes the action of PTH

Calcitonin receptor and signaling

- 7 transmembrane segment receptor
- Stimulates mainly cAMP production in bone and kidney



11. VITAMIN D

ncology

Improved Survival in Cancer Patients With High Vitamin D Levels

Pam Harrison
May 01, 2014

Bone, Muscle & Joint Health | Cleveland Clinic News Wire | Diet & Nutrition | Family Health | Men's Health | Wellness | Women's Health

Do You Really Need to Take Vitamin D Supplements?

Menopause and medications are 2 reasons the answer may be 'yes'

By Bone, Muscle & Joint Team | 5/2/14 1:01 p.m.

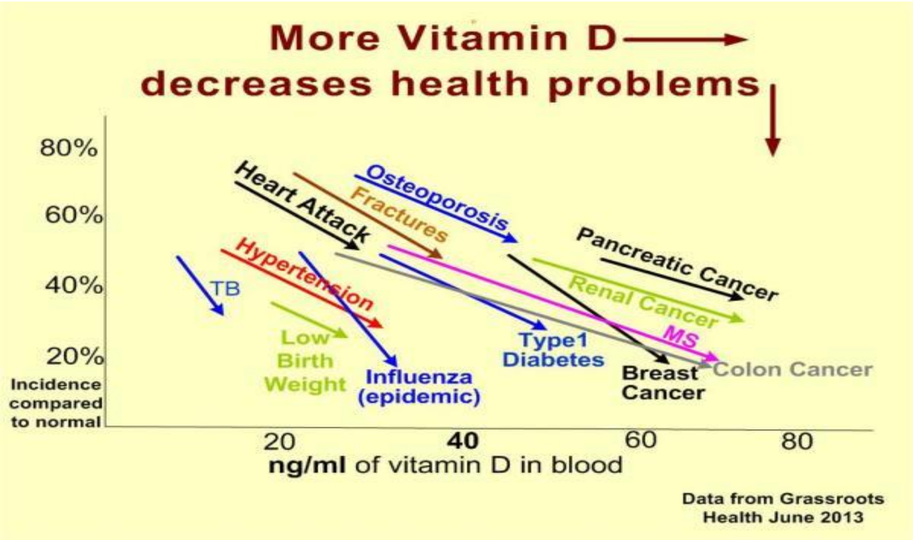
Share 1 | Like 3.1k | Tweet 8 | g+1 0 | Email 18 | Pin it | Print

Fred Hutch researchers help you understand what you need to know about the sunshine vitamin

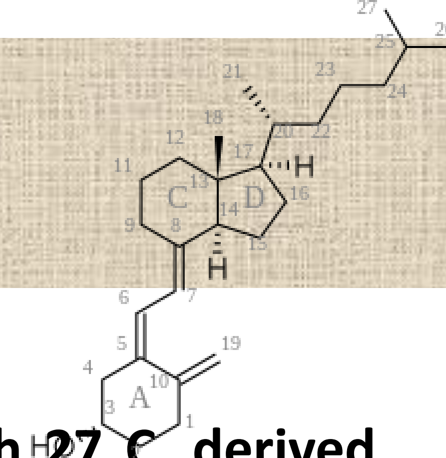
April 21, 2014

By Diane Mapes

Illustration by Kim Carney



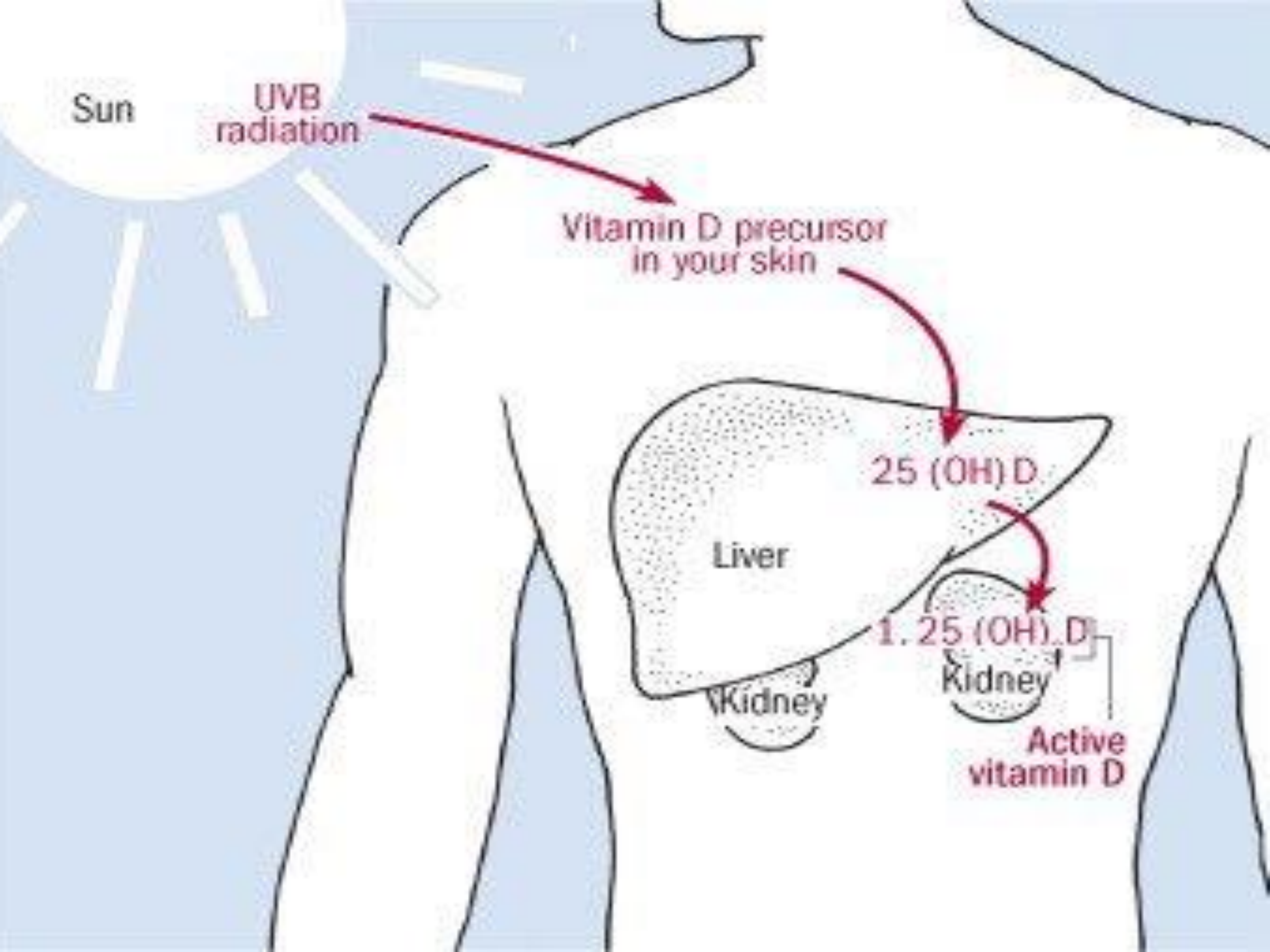
11.1. WHAT IS VITAMIN D?



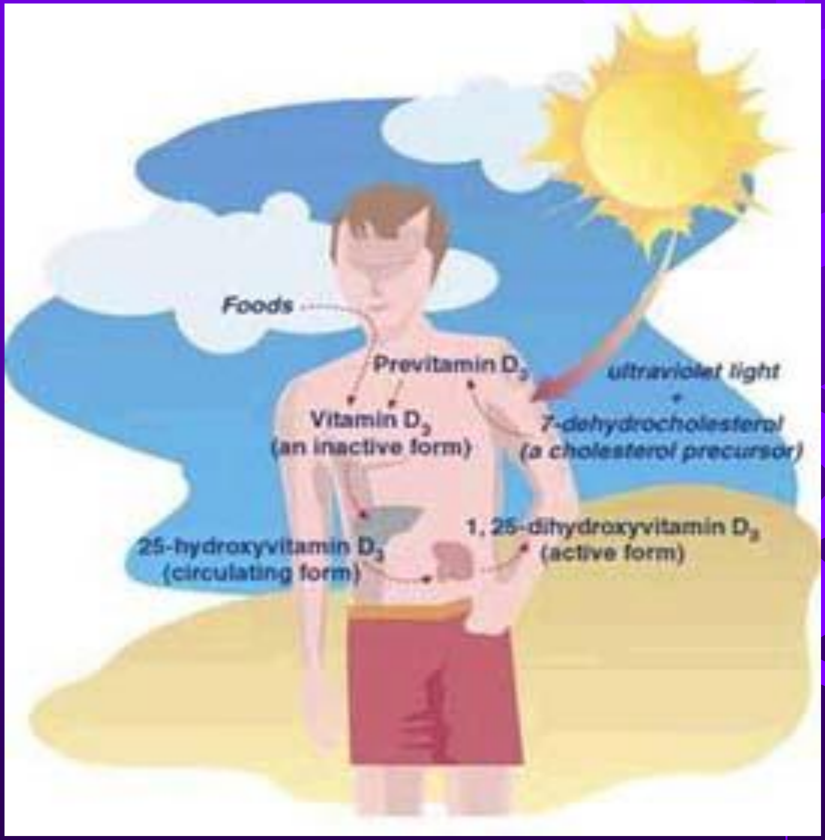
A group of fat-soluble secosteroids (D2 & D3) with 27 C, derived from cholesterol:

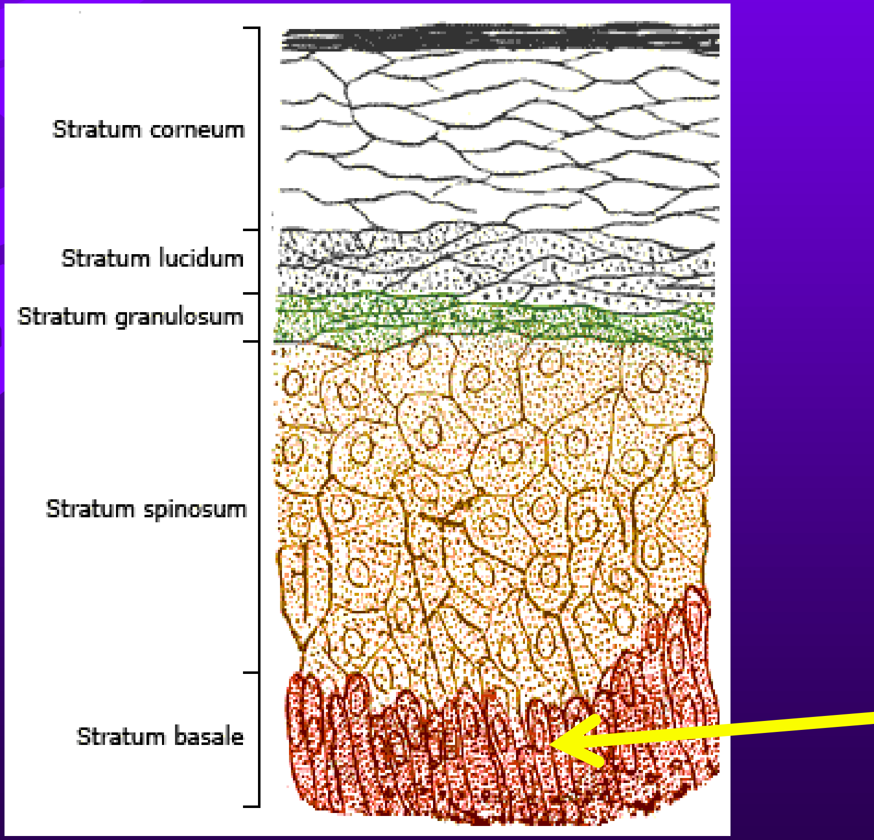
-Vitamin D2 (ergocalciferol) is a type of vitamin D found in food and dietary supplements. It is a real fat-soluble vitamin because it is not produced by the body.

-Vitamin D3 (Cholecalciferol) is a type of vitamin D that is made by the skin when exposed to sunlight; it is also found in some foods and dietary supplements. Within the epidermal layer of skin, 7-dehydrocholesterol (precursor) undergoes an electrocyclic reaction as a result of UVB light at wavelengths (290-315 nm), making previtamin D3 (pre-cholecalciferol). The definition of vitamins includes that the substance cannot be synthesized by the body and must be ingested. However, cholecalciferol is synthesized by the body during UVB radiation exposure

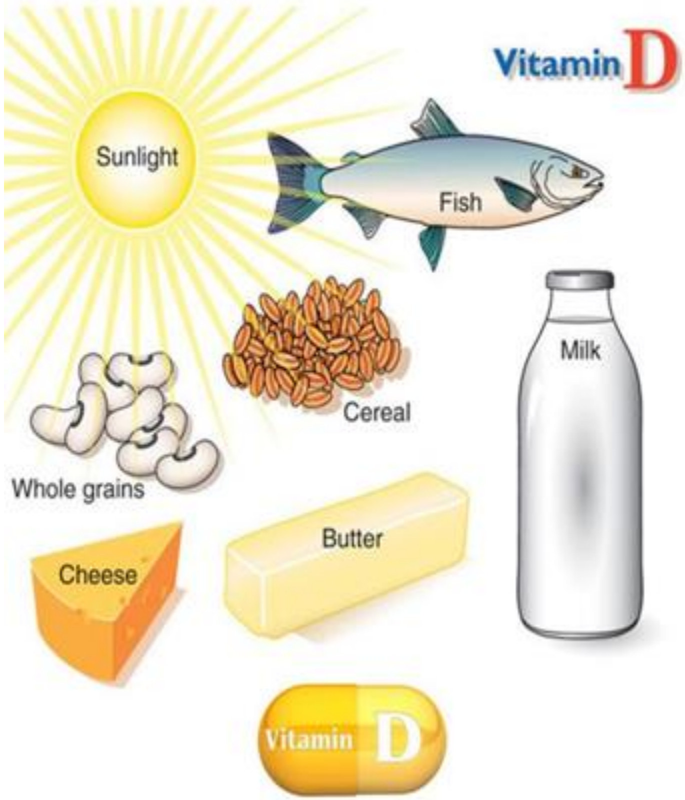

Sun
UVB
radiation
Vitamin D precursor
in your skin
25 (OH) D
Liver
Kidney
Kidney
Active
vitamin D

- **10-30 min exposure of the body and face to sunlight daily is sufficient for the body's vitamin D needs.**

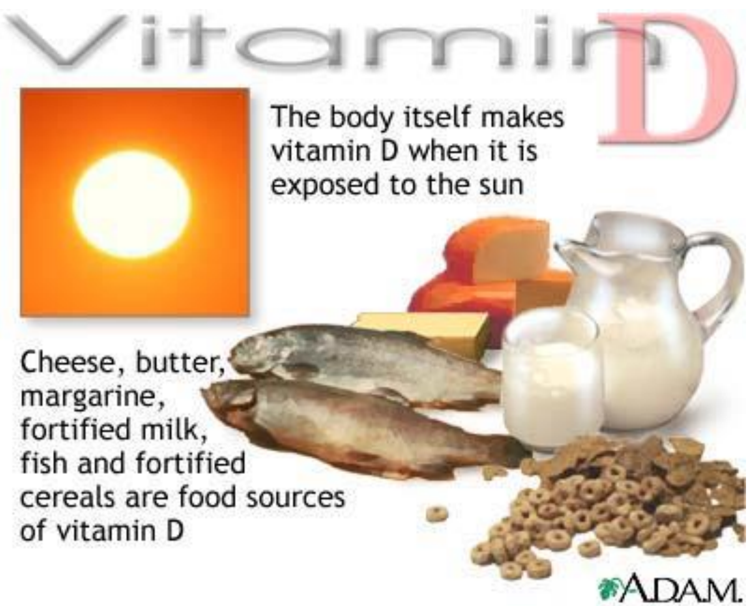




11.2. MAIN VITAMIN D SOURCES



- ✓ SUN EXPOSURE
- ✓ FOOD (D3 & D2)
- ✓ Dietary and vitamin supplements

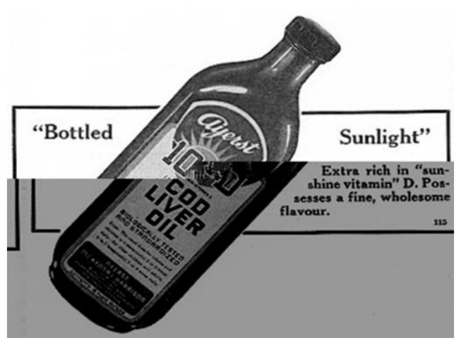


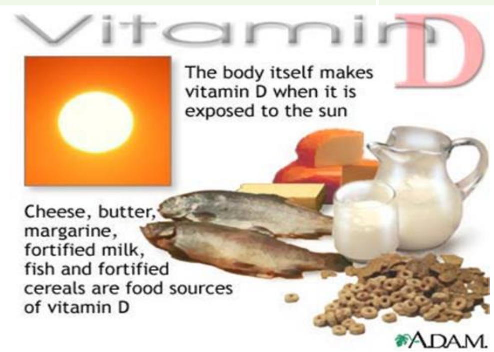
Vitamin D food sources

FOOD		IU
Cod liver oil (D3)	1 tbsp	**1360**
Salmon (D3)	3 oz	530
Sardines (D3)	3 oz	231
Mackerel (D3)	3 oz	213
Egg (D3)	1 large	0.53
Cheese (D3)	1 cup	26

Food	Serving	IU
Fortified milk (D3)	8 oz	98
Fortified soy milk(D3)	8 oz	100
Fortified juice (D3)	8 oz	100
Fortified cereals (D3)	≈ 1 cup	40-50
Mushrooms (D2) *	1 cup	786

* Vitamin D_2; 40 IU = 1 μg



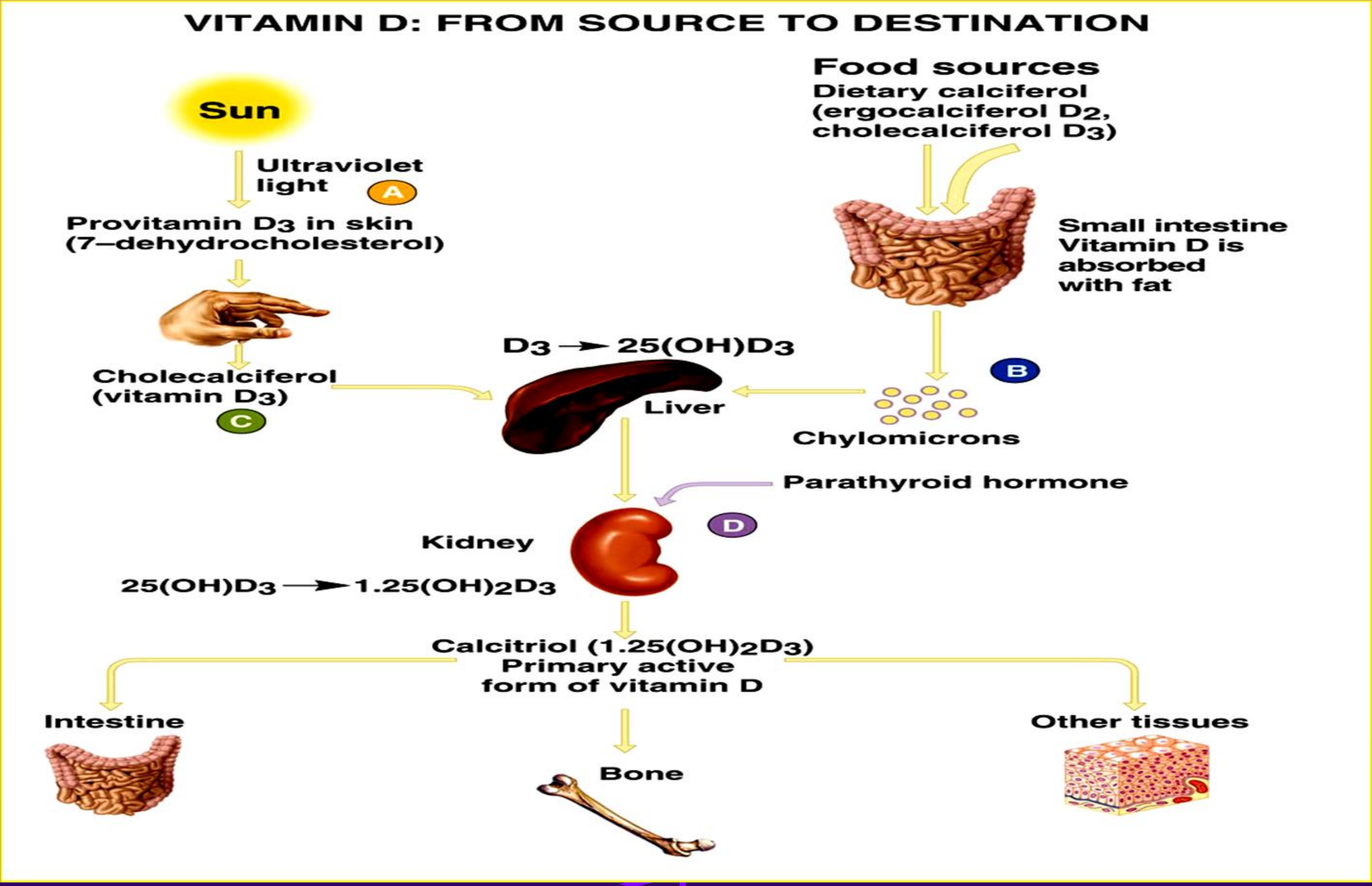


http://www.mayoclinic.org/drugs-supplements/vitamin-d-and-related-compounds-oral-route-parenteral-route/description/DRG-20069609
http://lpi.oregonstate.edu/infocenter/vitamins/vitaminD/index.html
http://ndb.nal.usda.gov/ndb/search/list

Cod liver oil

For centuries, cod liver oil was and still is **the most widely consumed fish oil in the world.** Of course, it differs from other fish oils, because it is produced from the liver of cod (or other related fish), while the other fish oils are produced from the flesh of fatty fish (salmon, herring, sardine, etc). This fact gives it the particularity of being **much richer in fat-soluble vitamins A, D, E and K2.**

FOODS ENRICHED (fortified) WITH VITAMIN D and CALCIUM



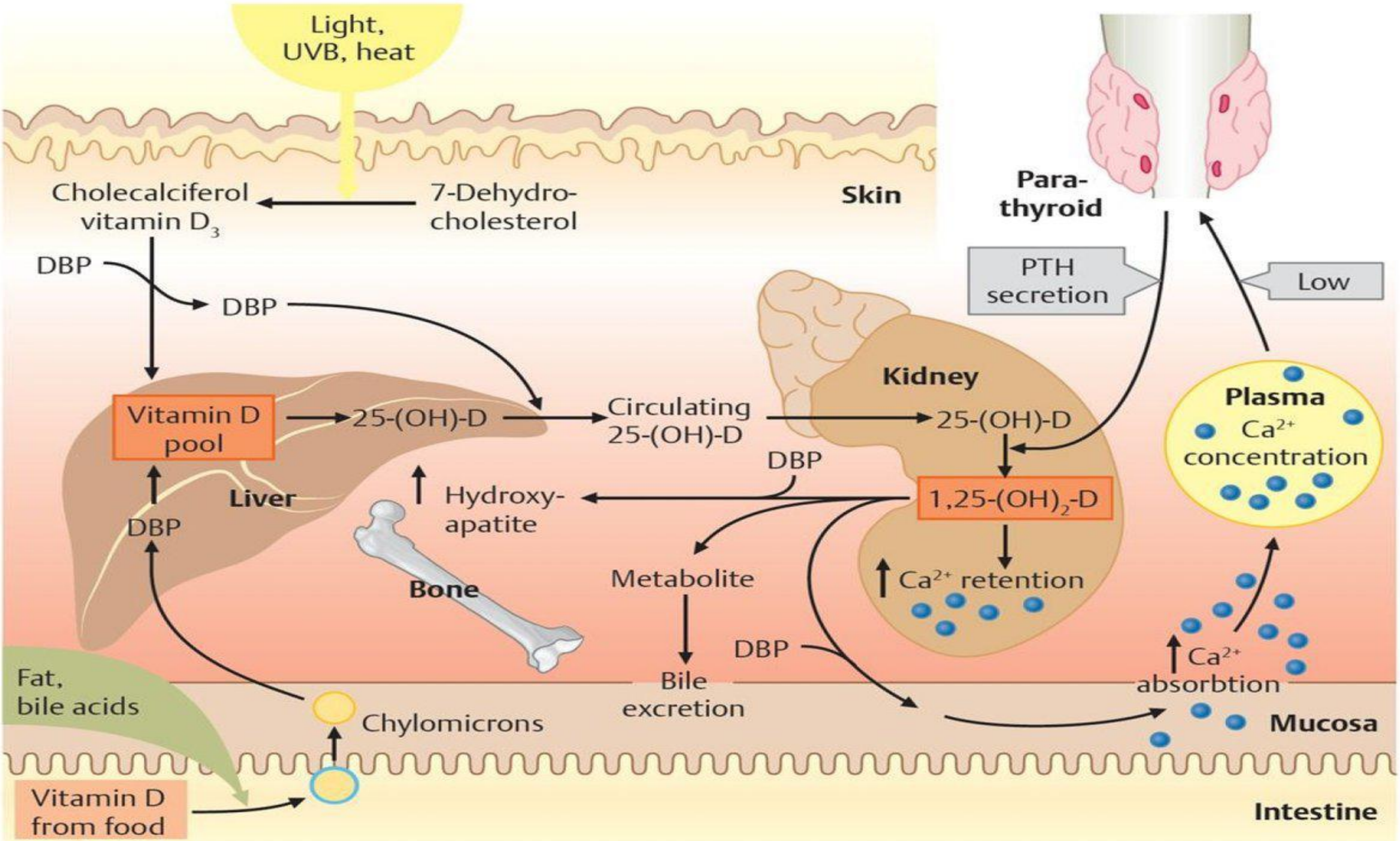
This slide is explained by the next slide

11.3 The three steps in the synthesis and activation of vitamin D

- **Cholecalciferol is synthesized in the skin from 7-dehydrocholesterol under the action of UVB**. It reaches an equilibrium after several minutes depending on the intensity of the UVB in the sunlight – determined by latitude, season, cloud cover, and altitude – and the age and degree of pigmentation of the skin
- Cholecalciferol binds to **vitamin D-binding protein (DBP)** in the bloodstream, and is transported to the liver. .Then, we have **hydroxylation in the endoplasmic reticulum of** hepatocytes of cholecalciferol to calcifediol (25-hydroxycholecalciferol) by 25-hydroxylase. Blood levels of this molecule largely reflect the amount of cholecalciferol produced in the skin combined with any vitamin D2 or D3 ingested.
- **Hydroxylation in the kidneys of 25-hydroxycholecalciferol to calcitriol** by 1-alpha-hydroxylase is tightly regulated: it is stimulated by parathyroid hormone and serves as the major control point in the production of the **active circulating hormone calcitriol** (1,25-dihydrocholecalciferol D).

Vitamin D metabolism

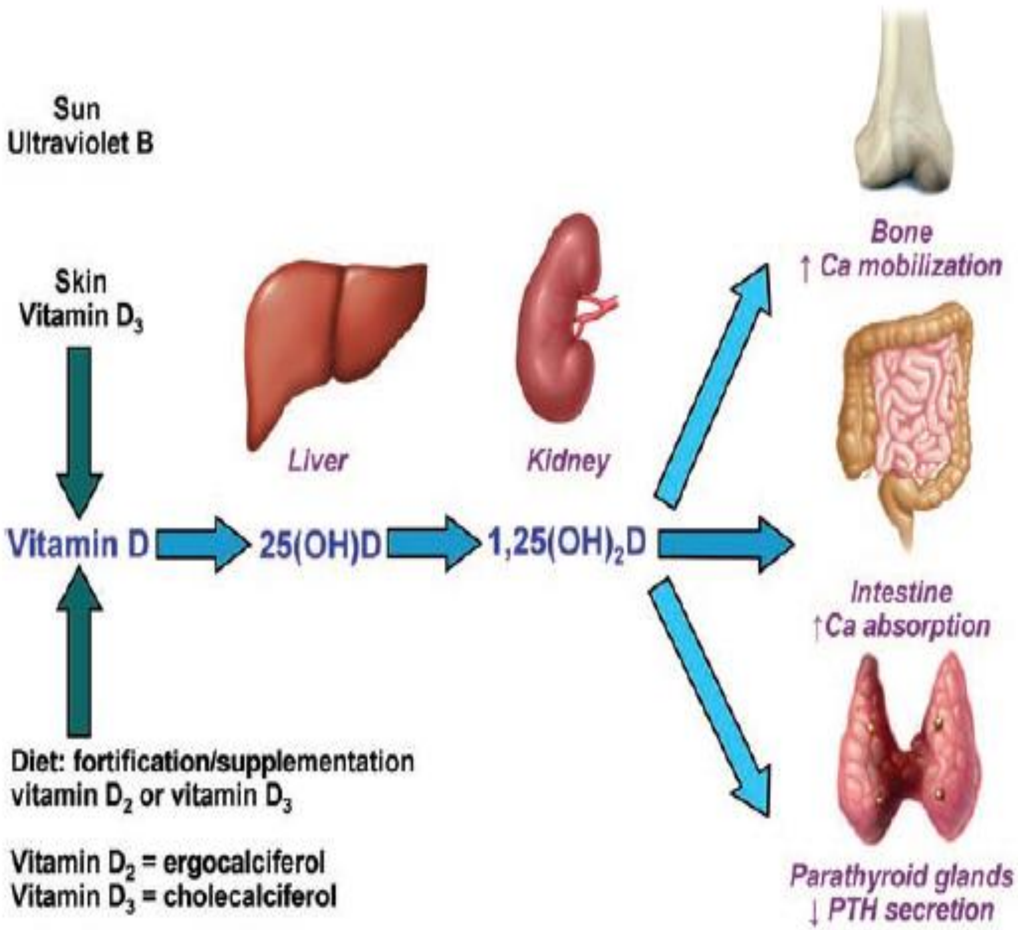
Ultraviolet light B (UVB) converts 7-dehydrocholesterol to cholecalciferol (vitamin D_3). Ingested vitamin D is fat soluble and is transported to the liver in chylomicrons. All free vitamin D is transported in the blood and liver by a specific vitamin D–binding protein (DBP). The liver converts vitamin D to 25-hydroxycholecalciferol 25-(OH)-D, which is then transported to the kidneys, where it is converted to its active form 1,25-$(OH)_2$-D, under the influence of parathyroid hormone. The effects of this are increased mineralization of bone, increased calcium and phosphate reabsorption in the kidneys, and increased calcium absorption in the gut. Excess vitamin D is excreted into bile.



DBP (Vitamin D binding protein)

Pharmacology - An Illustrated Review (Thieme Illustrated Review Series) - Simmons, Mark

11.4 Main metabolic actions of calcitriol

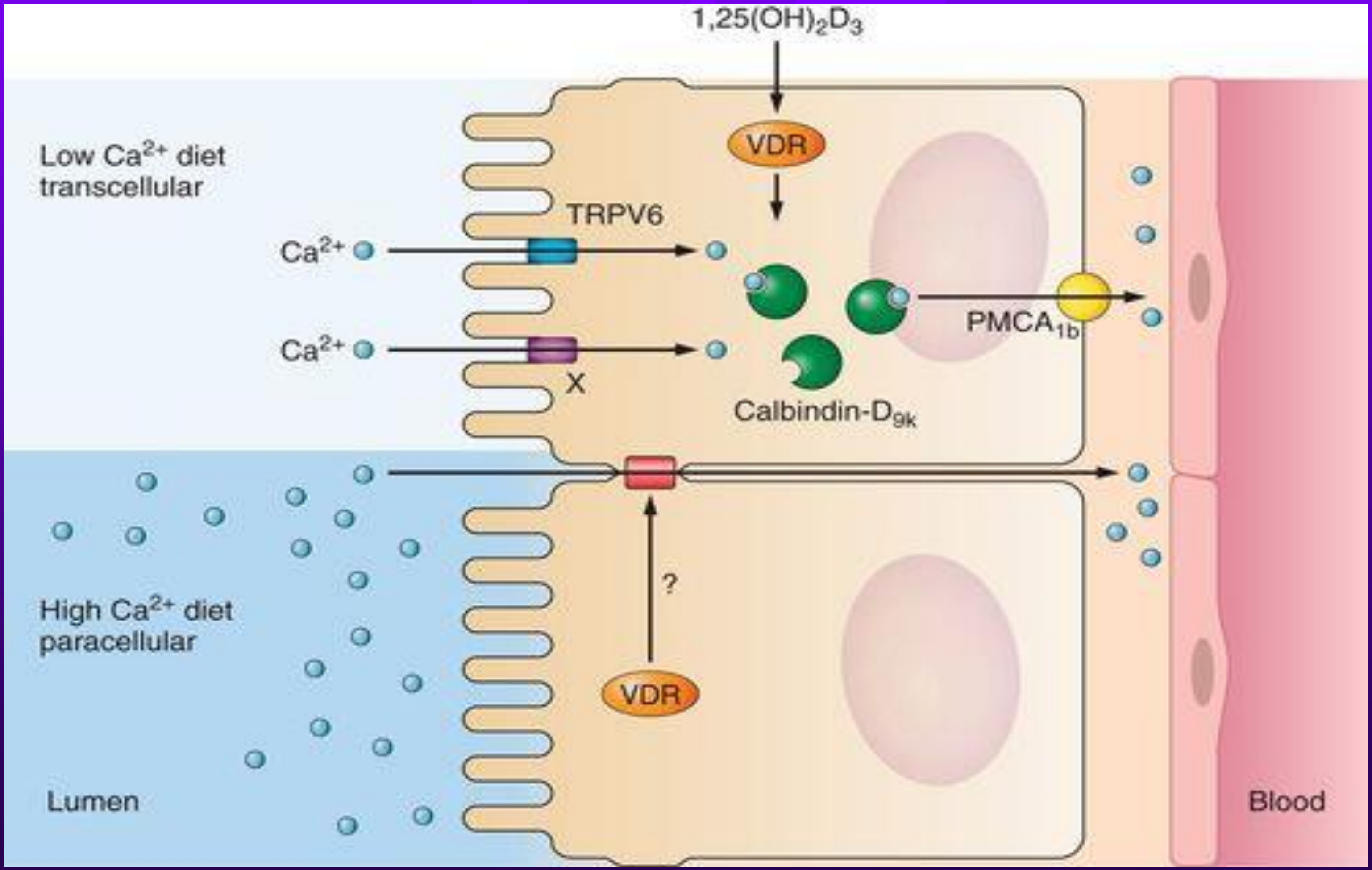


The active 1 ,25(OH)2D3 (calcitriol) has different effects on various target tissues

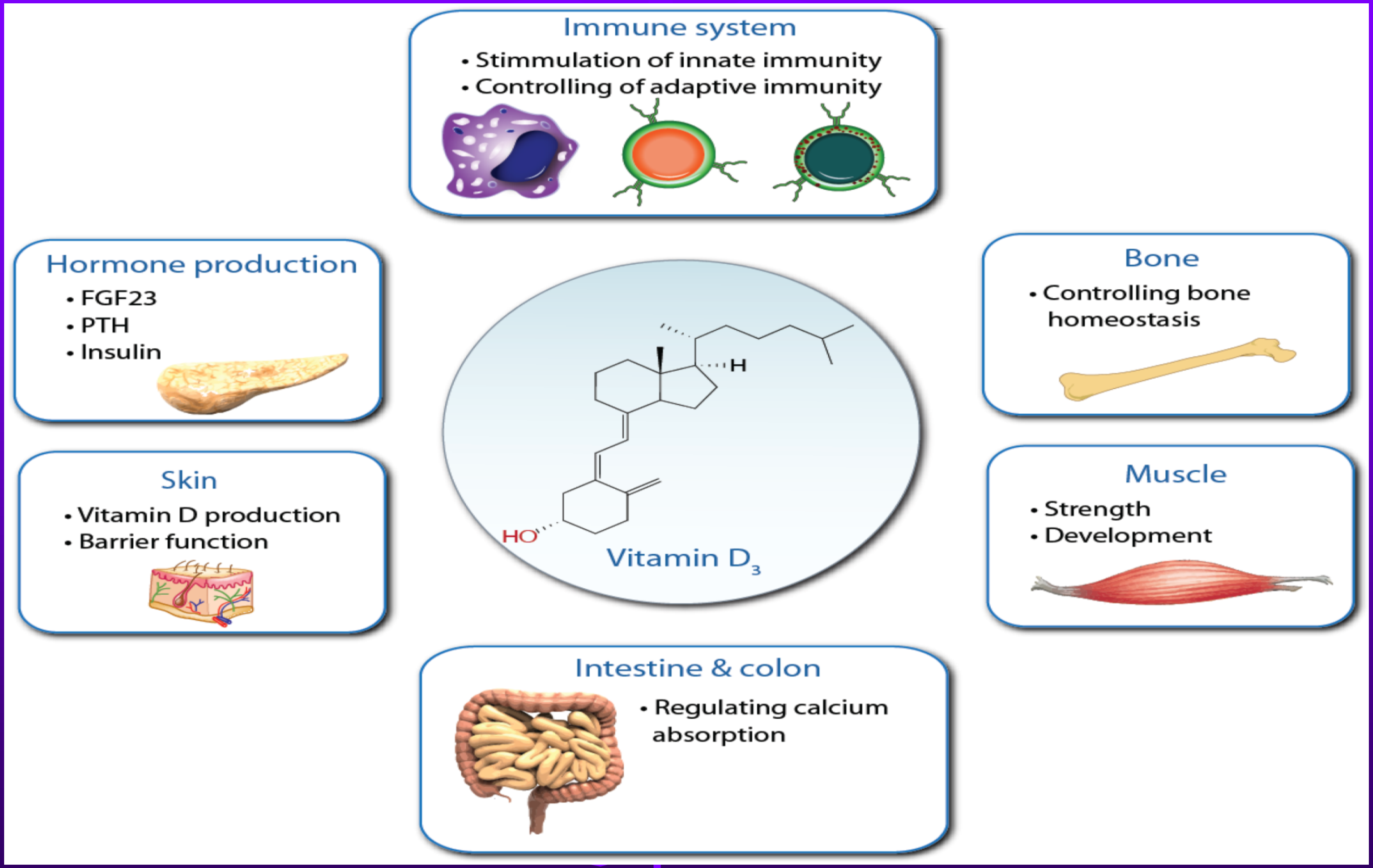
1. **Intestine:** It facilitates the absorption of Ca^{2+} from the intestinal villi by induction of a transport system. It also increases the absorption of phosphate
2. Mobilizes Ca^{2+} from **bones.** It acts mainly on osteoblasts
3. **Kidneys:** Increases the reabsorption of Ca^{2+} and phosphate
4. **Parathyroid glands:** It suppresses PTH

In the intestine, an important function of $1{,}25(OH)_2D$ is the stimulation of transcellular intestinal calcium transport by increasing the expression of the apical membrane calcium channel TRPV6 and calcium binding protein calbindin.

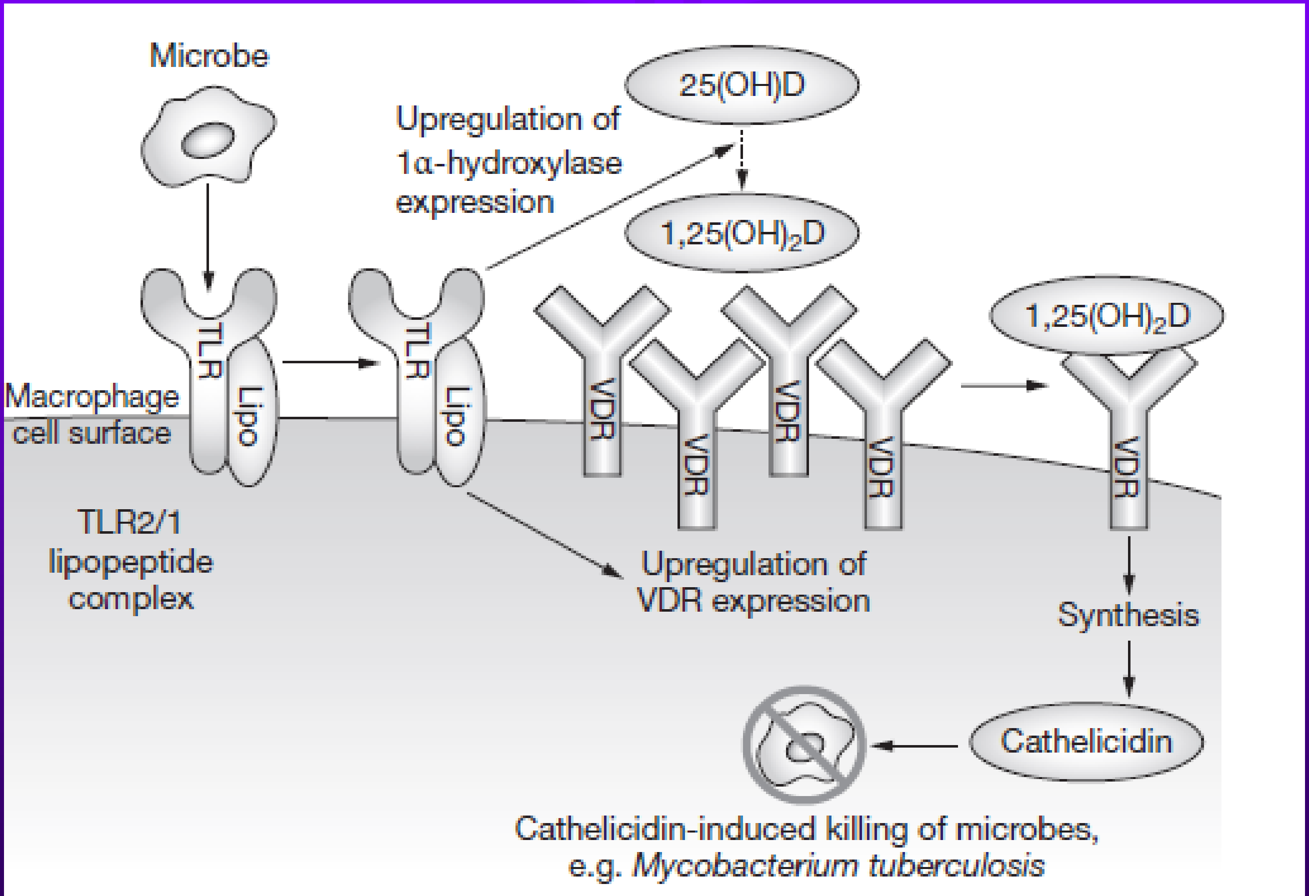
Calbindins are calcium binding proteins that can transport calcium into the intestinal cell or prevent its entry.



Other pleiotropic functions of vitamin D…

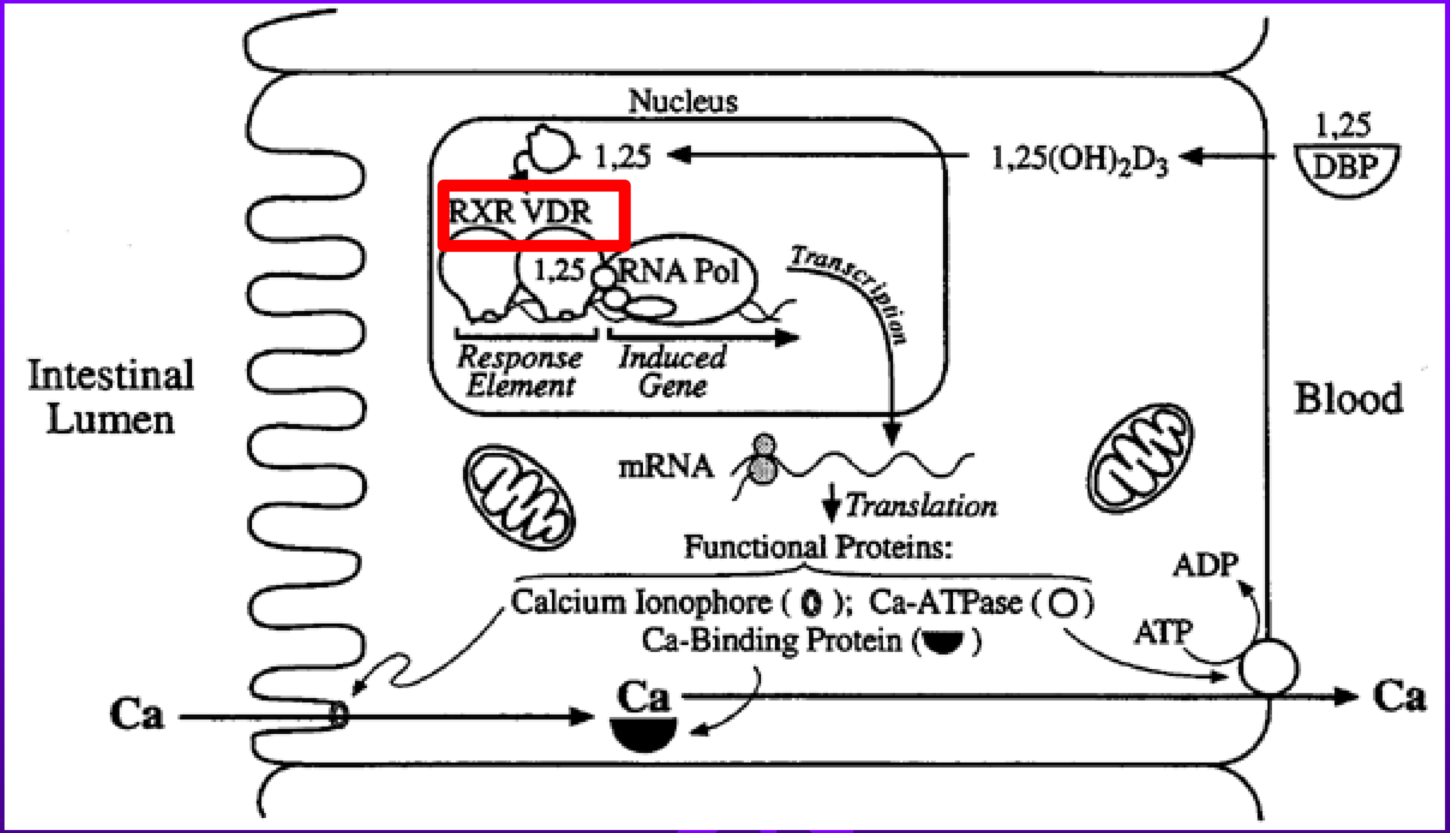


VITAMIN D INDUCES NATURAL IMMUNITY AND ANTIMICROBIAL ACTIVITY

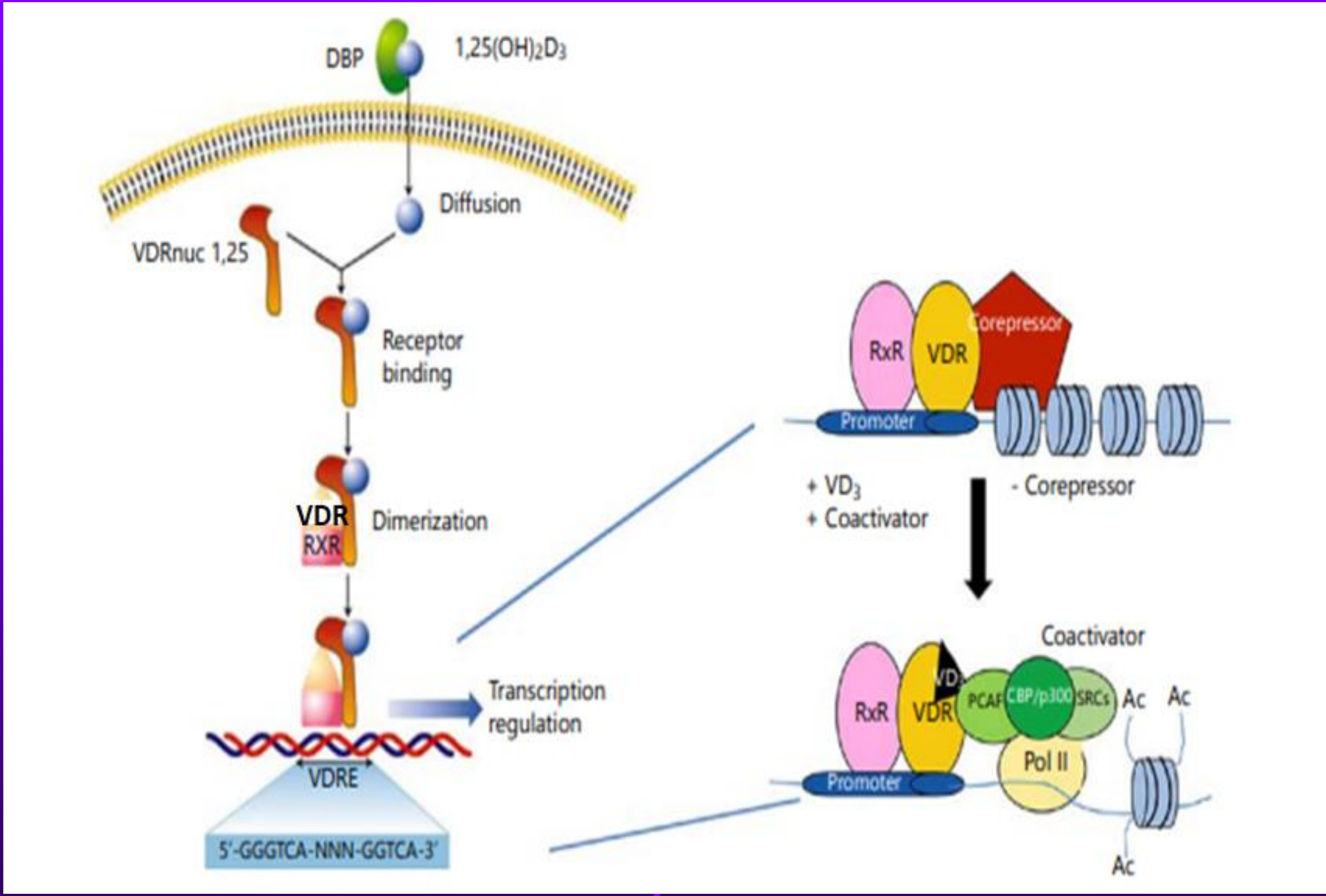


Wolffe A et al. Nature Clin Pract Rheumatol 2008; 4: 580-5

11.5 VITAMIN D RECEPTOR AND SIGNALING

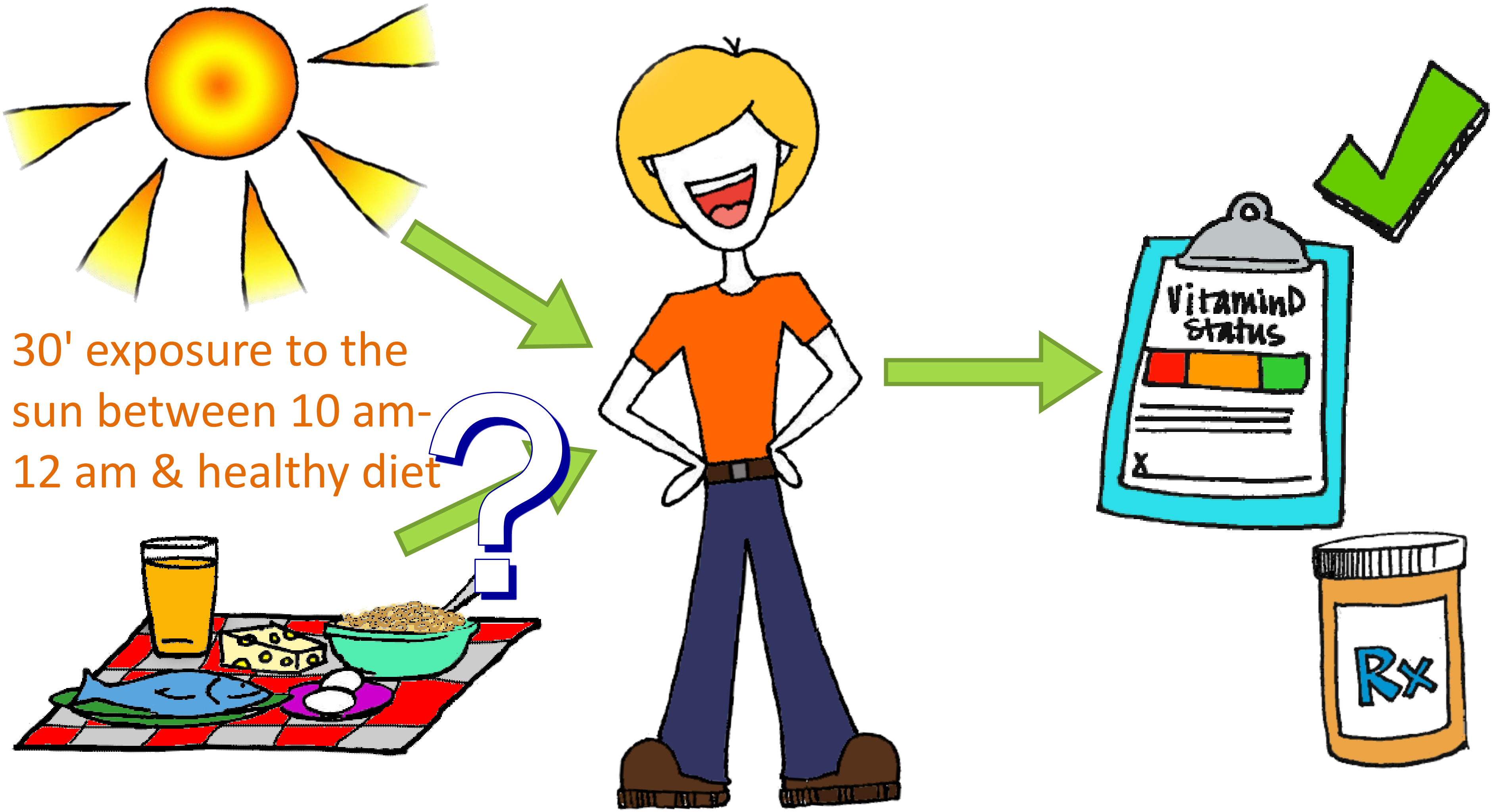


Vitamin D activity is mediated through binding of 1,25(OH)2D to the vitamin D receptor (VDR), which can regulate transcription of other genes involved in cell regulation, growth, and immunity. VDR modulates the expression of genes by forming a heterodimer complex with retinoid-X-receptors (RXR).



Gil A et al. Ann Nutr Metab 2018;72:87–95

The big picture



11.6 WHO ARE AT RISK OF VITAMIN D DEFICIENCY?

- ✓ People with chronic diseases, in institutions & inadequate nutrition
- ✓ People with dark skin
- ✓ Age >65 years
- ✓ Breastfeeding infants
- ✓ Obesity (BMI: >30 kg/m^2)
- ✓ Use of sunscreen (> SPF 30) & sun protective clothing

11.7. LEVELS OF 25-OHD

- Normal serum values: values >30 ng/ml (75 nmol/l).
- Deficiency with values: <20-30 ng/ml (50 nmol/l)
- The goal is to maintain levels >30 ng/ml.
- For better protection, the ideal concentration: 50-70 ng/ml.
- There is unanimous agreement that serum 25-OHD levels should not be <10 ng/ml (severe deficiency)
- Possible toxicity: > 80-100 ng/mL

11.8. WHY DO GREEKS HAVE LOW 25OHD LEVELS?

>1/3 of Greeks have 25-OHD deficiency (mean value: 25.08 ng/ml) → Mediterranean paradox

1) Demographics (↑ population age)
2) Skin phototype (↑ melanin decreases the synthesis of cholecalciferol)
3) ↓ exposure to the sun
4) Use of sunscreens
5) Diet
6) Latitude (↓ UV in autumn & winter)
7) Genetic factors
8) Air pollution
9) Obesity

10. CLINICAL CORRELATIONS

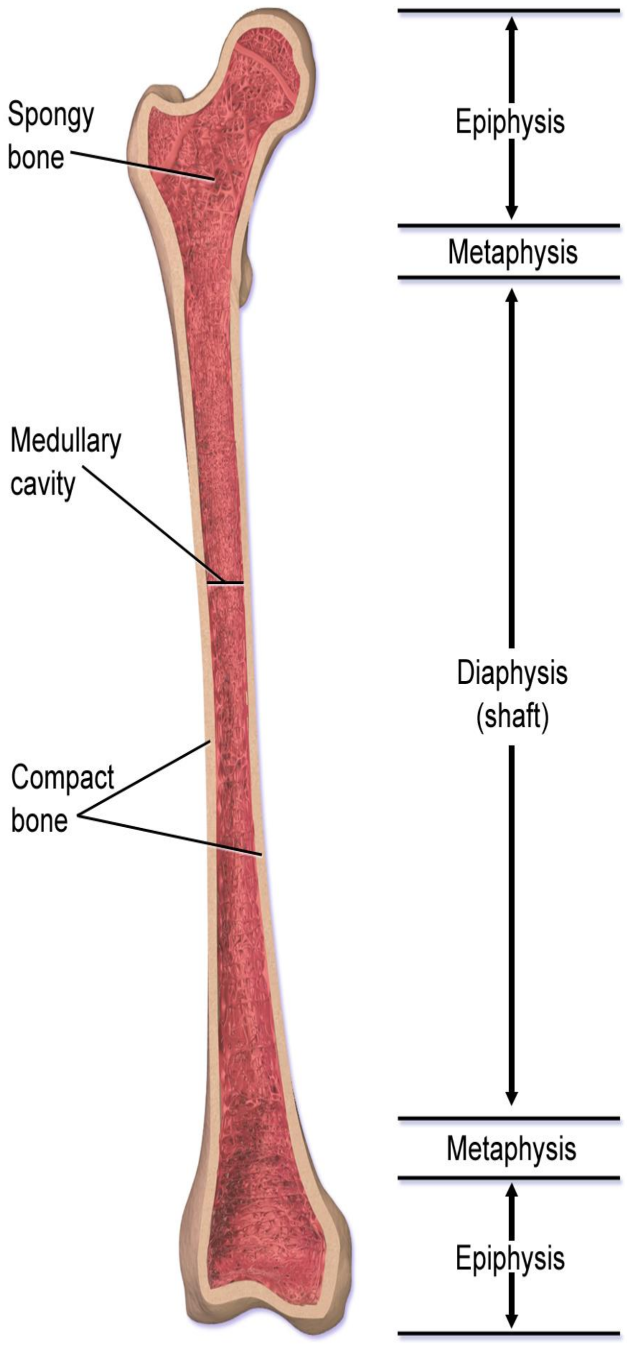
Let's understand better vitamin D actions by studying cases

VITAMIN D DISORDERS

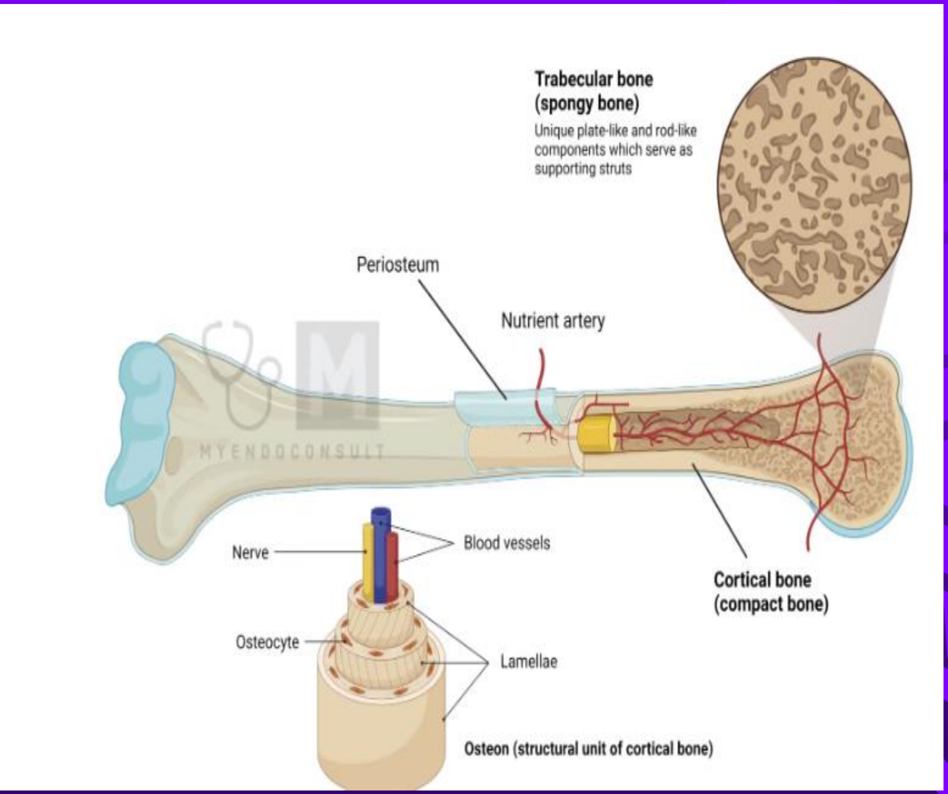
- **Rickets** (in childhood) and **osteomalacia** (in adulthood) are characterized by defective bone calcification. Bone alterations in children cause deformities of the skeleton. Simple rickets is due to either insufficient intake of vitamin D or insufficient exposure to UV radiation.

- **Hypervitaminosis D** leads to hypercalcemia, bone demineralization and nephrocalcinosis (fat-soluble vitamin)

Structure of a Long Bone

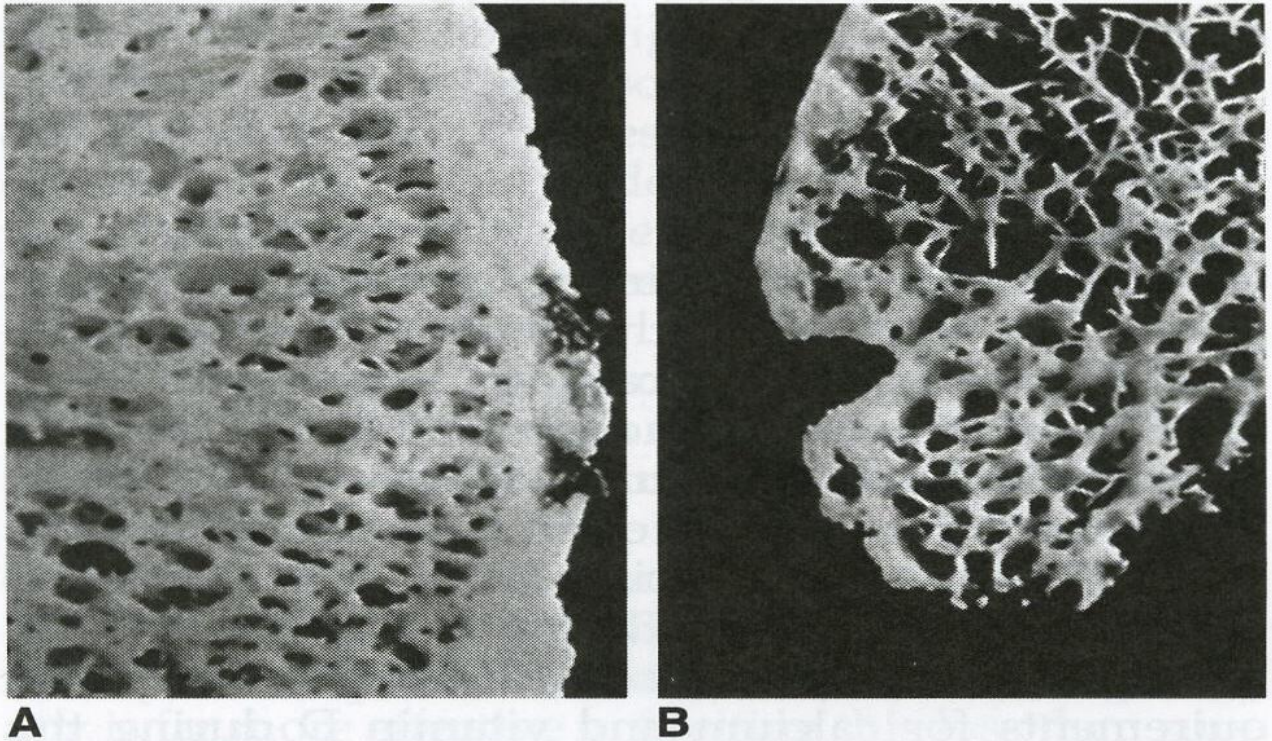


11. Osteoporosis: the most common metabolic bone disease



- Osteoporosis is characterized by a significant reduction in bone mineral density compared with age- and sex-matched norms
- Affects 20 million Americans and leads to 1.3 million fractures in the US per year
- Women lose 50% of their trabecular bone and 30 % of their cortical bone
- 30% of all postmenopausal women will sustain an osteoporotic fracture as will 17% of all men
- The cost of health care and lost productivity is $14 billion in the US annually

Normal and Osteoporotic Bone



• Difference between normal bone **(A)** and osteoporotic bone **(B)**.

There is a decrease in both bone mineral and bone matrix

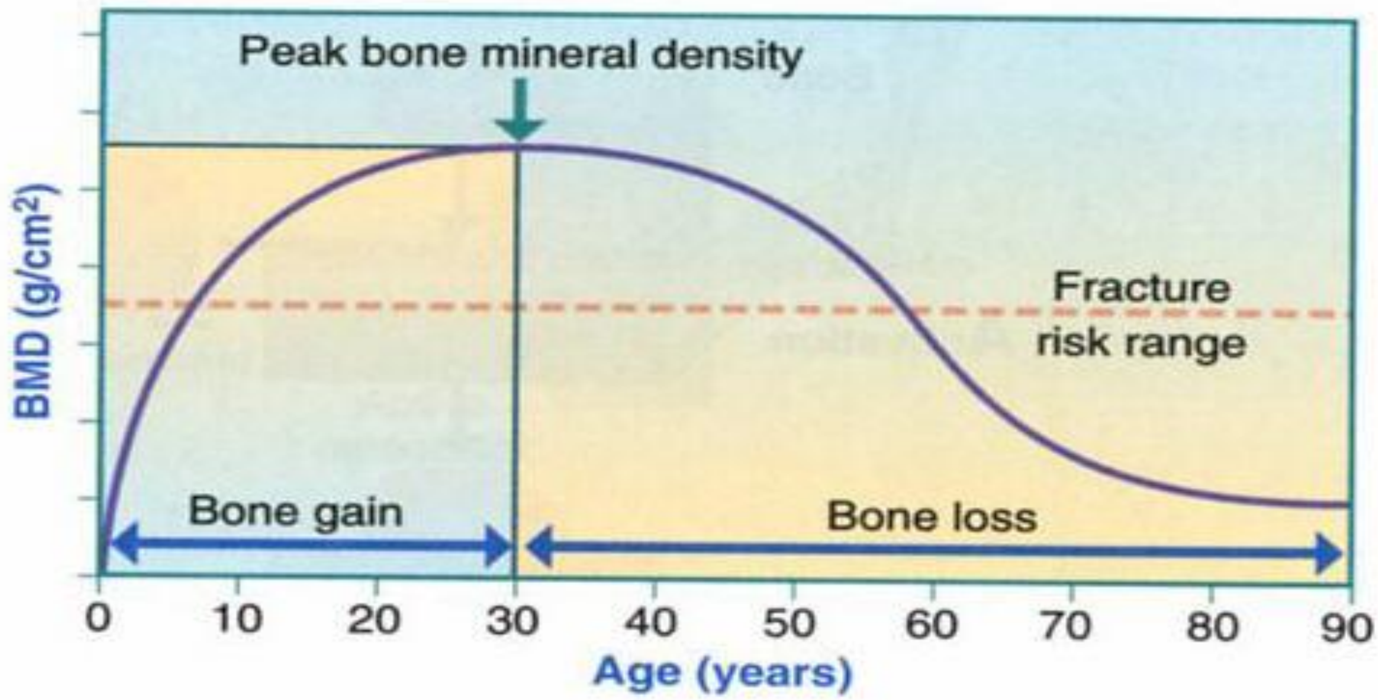
Factors that Affect Peak Bone Mass

- Gender (M>F), males have greater BMD than females
- Race (Blacks >Whites)
- Genetics (osteoporosis runs in families and this may be the predominant factor)
  - Estrogen receptor gene
  - Type I collagen gene
  - Vitamin D receptor gene
- Gonadal steroids

(estrogen and testosterone increase bone mass)

- Growth hormone (increases bone mass)
- Calcium intake (supplements work)
- Exercise (increases bone mass)

Bone Density as a Function of Age



- Early gain and later loss of bone in females. Peak bone mineral density (BMD) is typically achieved by age 30. Menopause occurs at approximately age 50 or within a few years thereafter. Postmenopausal women typically enter the fracture risk range after age 60. Men have a more gradual decline in BMD, which starts at 50 years of age. (Copyright of John J. B. Anderson and Sanford C. Garner.)

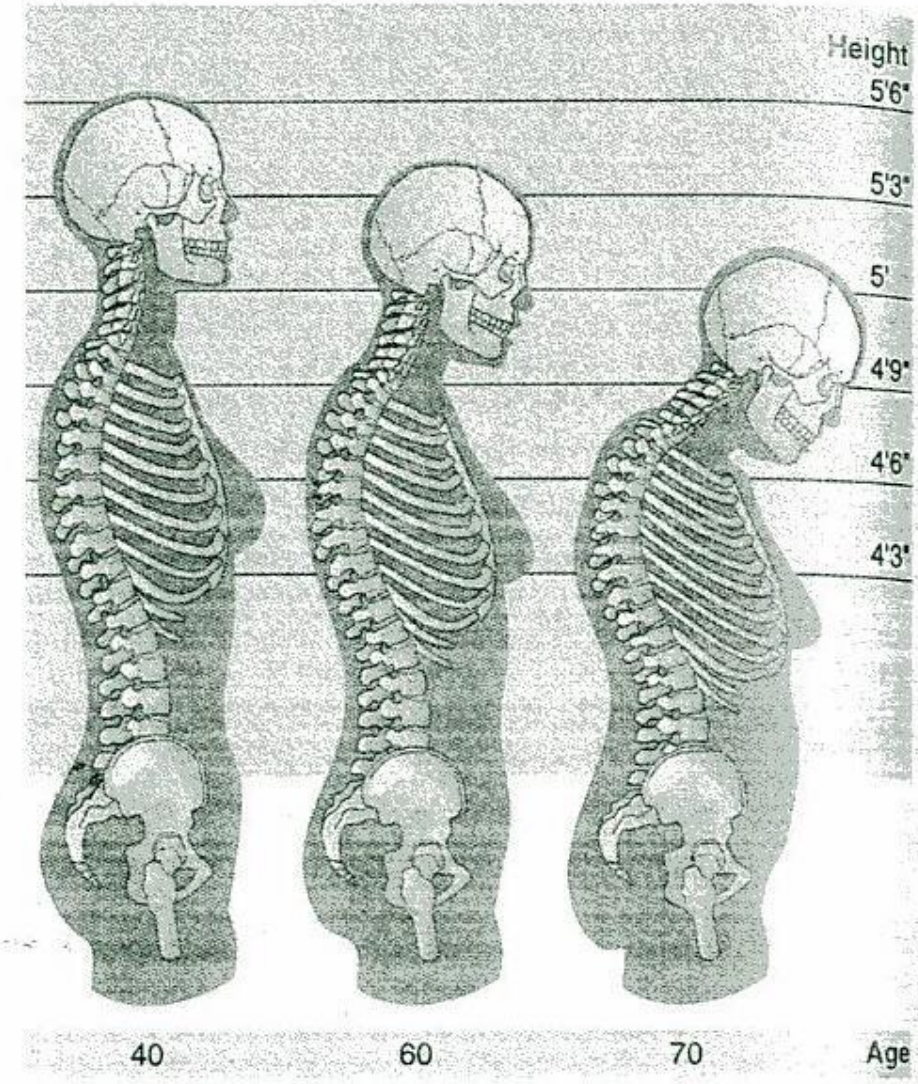
A silent disorder….why;

Osteoporotic fractures

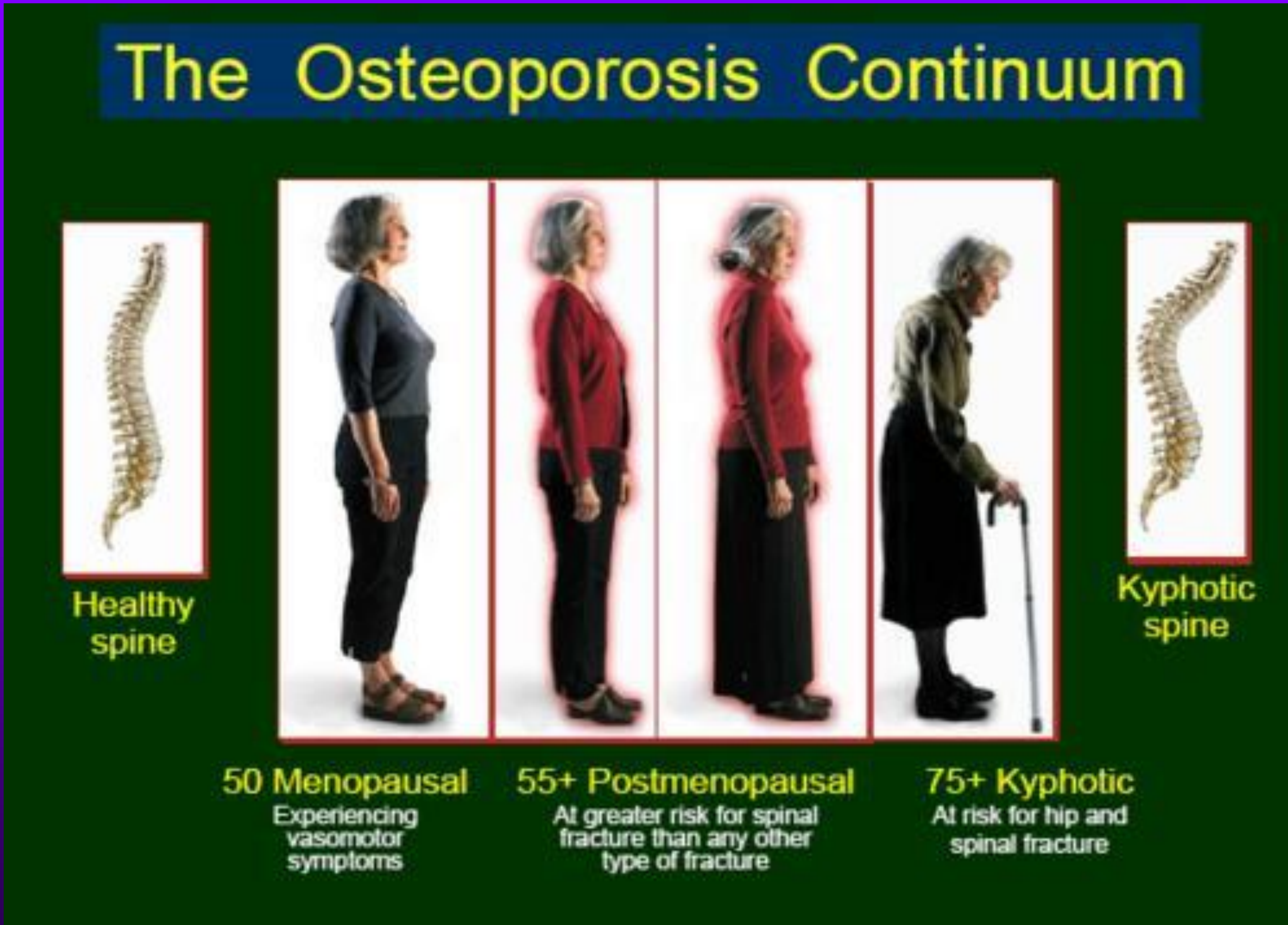
"**Osteoporotic" fractures** are differentiated from "**traumatic" fractures** because they are caused by low or moderate force (such as falling from a standing position and being challenged without any violence at all)

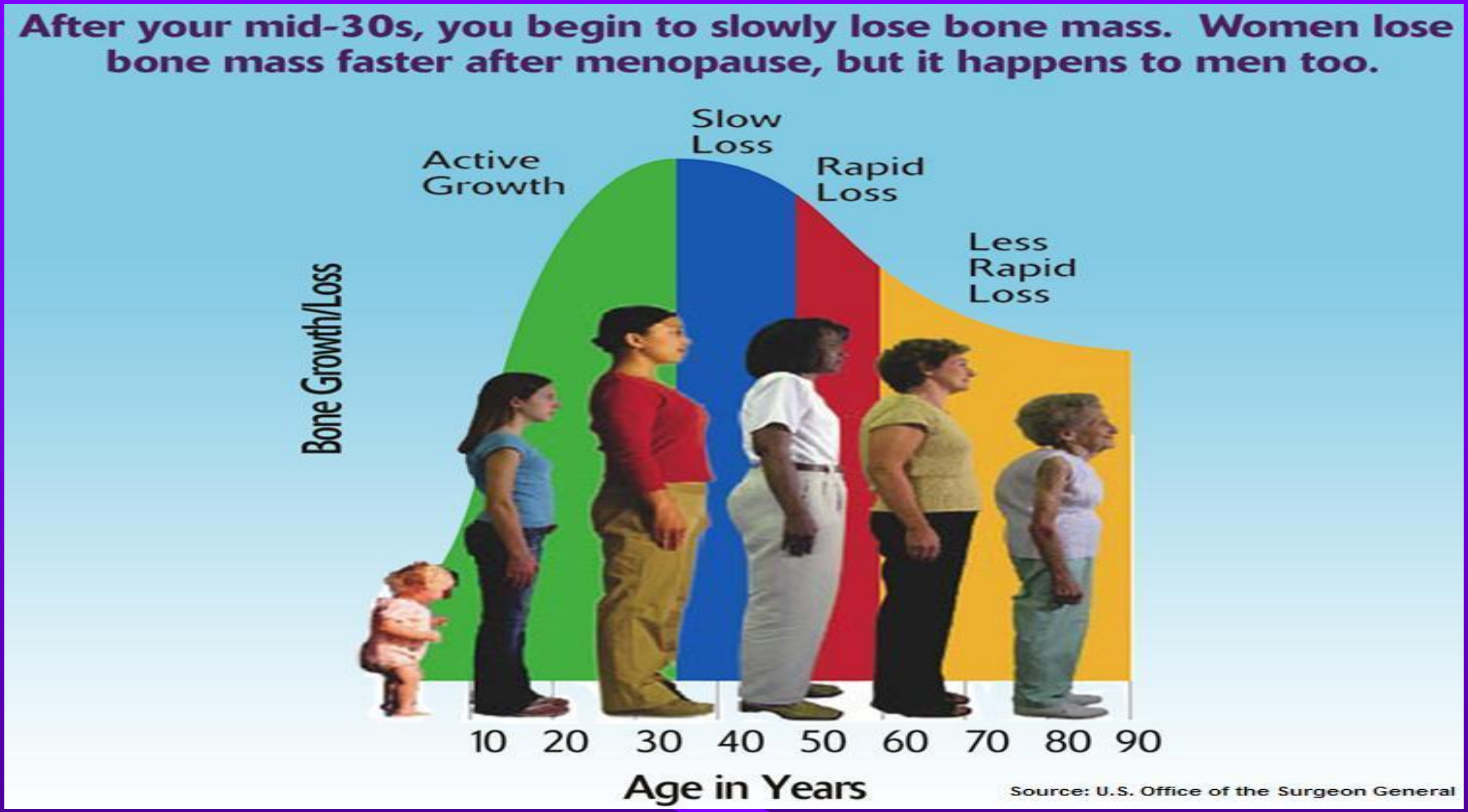
- ❖ **Backache**
- ❖ **Bone pain**
- ❖ **Reduced activities**
- ❖ **Anxiety – depression**
- ❖ **Sleep Disorders**
- ❖ **Poor quality of life**

Sequelae of Osteoporosis



• Normal spine at 40 years of age and osteoporotic changes at 60 and 70 years of age. These changes can cause a loss of as much as 6 to 9 inches in height and result in the so-called dowager's hump *(far right)* in the upper thoracic vertebrae. (From Ignatavicius D, Bayne MV: *Medical-surgical nursing: a nursing process approach*, Philadelphia, 1991, WB Saunders.)


The Osteoporosis Continuum
Healthy spine
Kyphotic spine
50 Menopausal
Experiencing vasomotor symptoms
55+ Postmenopausal
At greater risk for spinal fracture than any other type of fracture
75+ Kyphotic
At risk for hip and spinal fracture



Bone loss and small fractures as well as compression of the spine lead to kyphosis and reduced stature, characteristic of osteoporosis in the elderly

Selected Web Sites

■ Relevant Web Sites

American Association of Clinical Endocrinologists
www.aace.com
Menopause and Osteoporosis
www.menopause.org/
National Osteoporosis Foundation
www.nof.org/
Osteoporosis On-Line
www.osteoporosis.ca/OSTEO/D02-01.html

SUMMARY

- ✓ Calcium (Ca^{2+}) circulates in the blood mainly as a bivalent free ion (50%, active biologically), bound to proteins (40 %, not biologically active) and complexed with phosphate, citrate, bicarbonate and other acids (10 %).
- ✓ **Calciotropic hormones** that play an important role in Ca^{2+} homeostasis and metabolism are: parathyroid hormone (PTH), calcitonin and vitamin D/calcitriol.
- ✓ The main stimulus for PTH secretion is: ↓ calcium and ↑ phosphate.
- ✓ **PTH** is produced by the parathyroid glands. PTH: 1) mobilizes Ca^{2+} from bone, 2) increases Ca^{2+} reabsorption and increases phosphate excretion in kidneys, 3) stimulates the hydroxylation of 25-OH-calciferol (1α-hydroxylase), and 4) increases Ca^{2+} absorption in small intestine .

- ✓ **Calcitonin**, produced by thyroid parafollicular C, is a peptide hormone of 32 aa that decreases serum Ca^{2+}, by inhibiting osteoclast mediated bone resorption, by promoting renal excretion of Ca^{2+} & phosphate and by blocking intestinal absorption of Ca^{2+}.

- ✓ **Calcitriol (activated vitamin D)** presents various effects on target organs: 1) Intestine: It facilitates the absorption of Ca^{2+} from the intestinal villi by induction of a transport system. It also increases the absorption of phosphate, 2) It mobilizes Ca^{2+} from bones acting mainly on osteoblasts, 3) Kidneys: it increases the reabsorption of Ca^{2+} and phosphate, 4) Parathyroid glands: It suppresses PTH

LEARNING OBJECTIVES-Students should be able to answer the following questions OR to:

- How is calcium distributed in the organism?
What is the role of calcium?
- What are the food sources of calcium? What are the suggested daily calcium needs?
What is calcium balance?
- How does calcium circulate in blood?
- How is calcium homeostasis achieved? Which hormones regulate calcium?
- What is the general chemical structure of parathyroid hormone (PTH)?
- Where is PTH synthesized? • What are the main PTH circulating forms?
- How is PTH Secretion and Biosynthesis regulated?
- How do Calcium Sensing Receptors function?
- What are the main metabolic actions of PTH?
- How does PTH act on bone?
- How does PTH act on target tissues (receptors-signaling)?
- What are the role and function of Parathyroid Hormone related Protein (PTHrp)?

LEARNING OBJECTIVES-Students should be able to answer the following questions OR to:

- What is the general chemical structure of calcitonin?
- Where is calcitonin synthesized?
- What are the main metabolic actions of calcitonin?
- How does calcitonin act on target tissues (receptors-signaling)?
- What is vitamin D?
- Where is vitamin D produced?
- Recognize the main sources of vitamin D.
- How is vitamin D synthesized and activated?
- Explain the main metabolic actions of calcitriol.
- What are calbindins?
- How does calcitriol act on target tissues (receptors-signaling)?
- Who are at risk of vitamin D deficiency?

Multiple choice questions-SAMPLE

1. **Which of the following hormones are the MAIN hormones regulating calcium homeostasis?**

A. Parathormone, Calcitriol and Calcitonin

B. Parathormone, Insulin and Glucagon

C. Calcitriol, estradiol and testosterone

D. Parathormone-related protein, parathormone and testosterone

E. Calcitonin, vitamin D and oxytocin

2. **Parathormone is secreted from:**

A. Thyroid gland

B. Parathyroid glands

C. Thymus

D. Parathyroid and thyroid glands

Study material

- Only slides

ENJOY LIFE AND STUDYING!!!