
Secret Getaway

Vitamin D

BY

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Vitamin D

Synonyms:

Anti-rachitic factor

VITAMIN D

- The D vitamins are a group of sterols that have a hormone-like function.
- The active molecule, 1,25-dihydroxy cholecaliferol(1,25 diOH D3)binds to intracellular receptor proteins.
- The (1,25 diOH D3)-receptor complex interacts with DNA in the nucleus of target cells in a manner similar to that of vitamin A, and either selectively stimulates gene expression, or specifically represses gene transcription.
- The most prominent actions of (1,25 diOH D3) are to regulate the plasma levels of calcium and phosphorus.

Vitamin D

- Vitamin D is a steroid hormone that functions to regulate specific gene expression following interaction with its intracellular receptor.
- The biologically active form of the hormone is **1,25-dihydroxy vitamin D3** (1,25-(OH)2D3), also termed (**calcitriol**).
- Calcitriol functions primarily to regulate calcium and phosphorous homeostasis.

Distribution of vitamin D

1. Diet:

- **Ergocalciferol** (vitamin D2),found in plants, and **cholecalciferol** (vitamin D3),found in animal tissues, are sources of preformed vitamin D activity .
- Ergocalciferol and cholecalciferol differ chemically only in the presence of an additional double bond and methyl group in the plant sterol.

2. Endogenous vitamin precursor:

- 7-dehydrocholesterol ,an intermediate in cholesterol synthesis, is converted to cholecalciferol in the dermis and epidermis of humans exposed to sunlight. Preformed vitamin D is a dietary requirement only in individuals with limited exposure to sunlight.

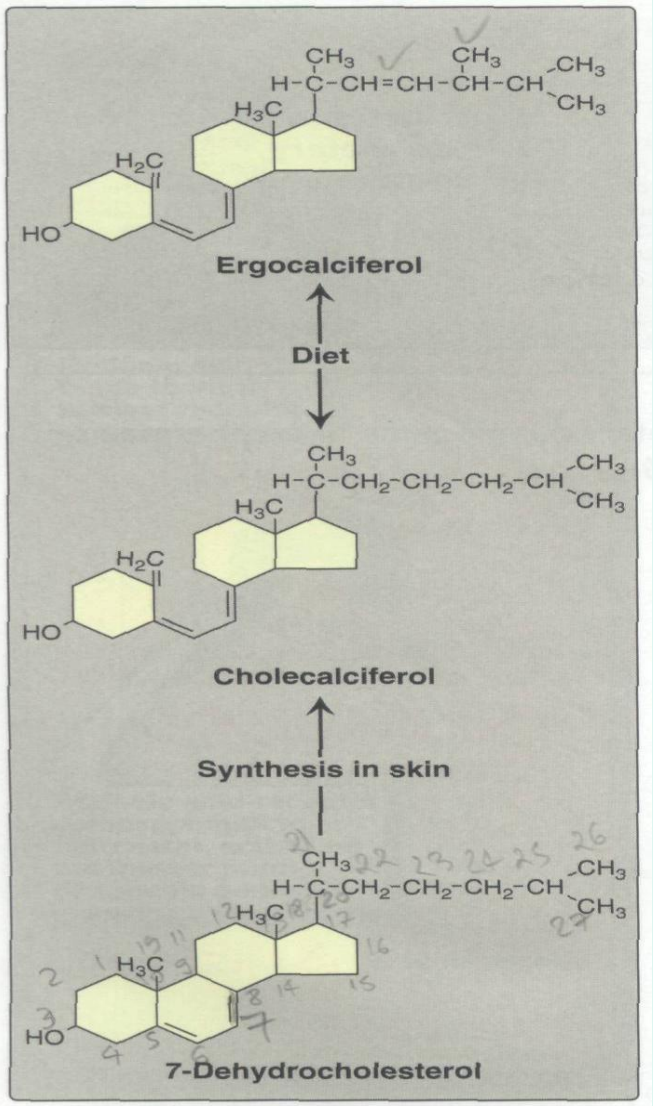


Figure 28.22
Sources of vitamin D.

Form of Vitamin D

Two forms:

Ergocalciferol (vitamin D2) , found in plants

Cholecalciferol (vitamin D3)in animals &their products

Synthesis in the body from cholesterol– **not enough**

- Cholecalciferol is synthesised by the body in the skin by the action of light.

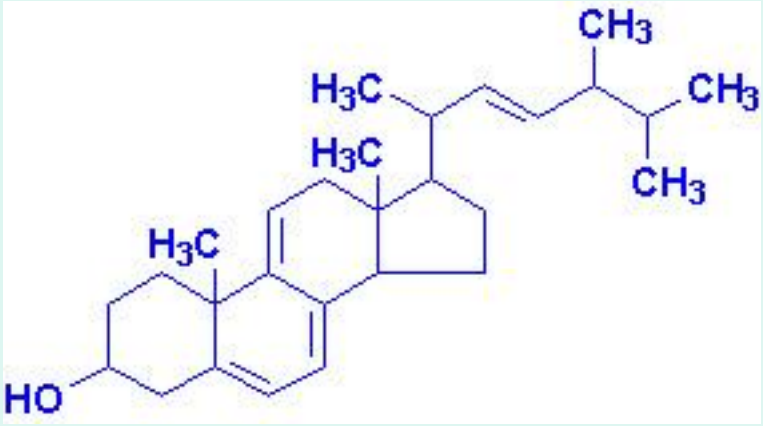
Cholesterol to 7 dehydrocholesterol —Uv light→ **Cholecalciferol**

Formed by the opening of steroid nucleus

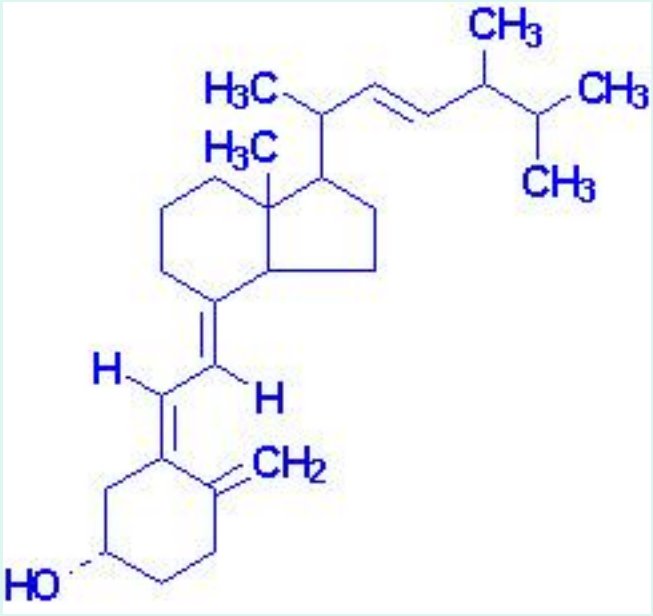
- Cholecalciferol is also known as **"sunshine vitamin"**

- Vitamin D3 is to be converted to 1, 25 dihydroxy D3 in order to exert its biological activity

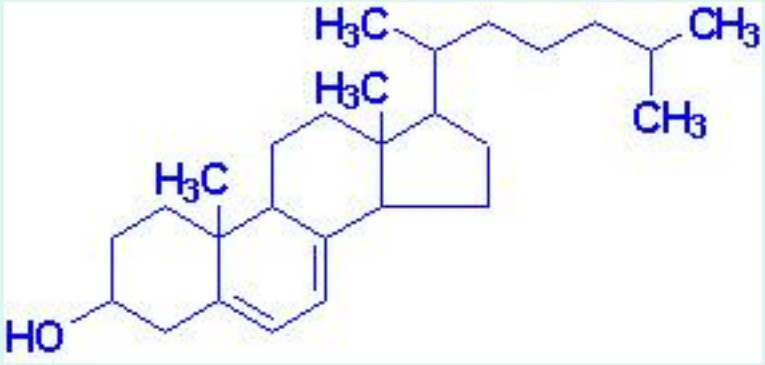
Ergosterol



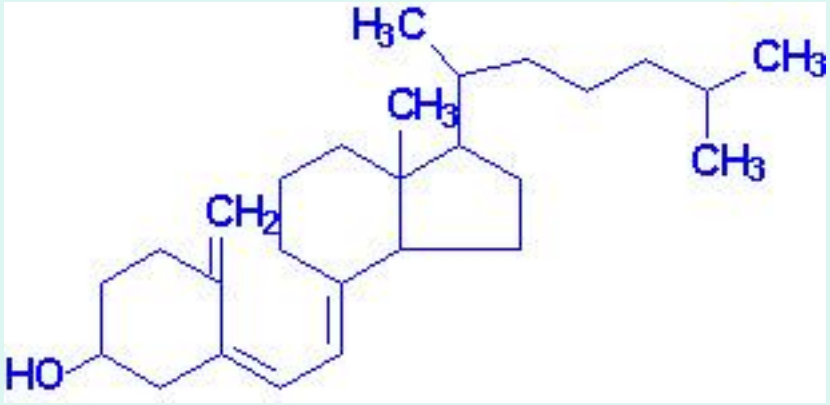
Vitamin D2



7-Dehydrocholesterol



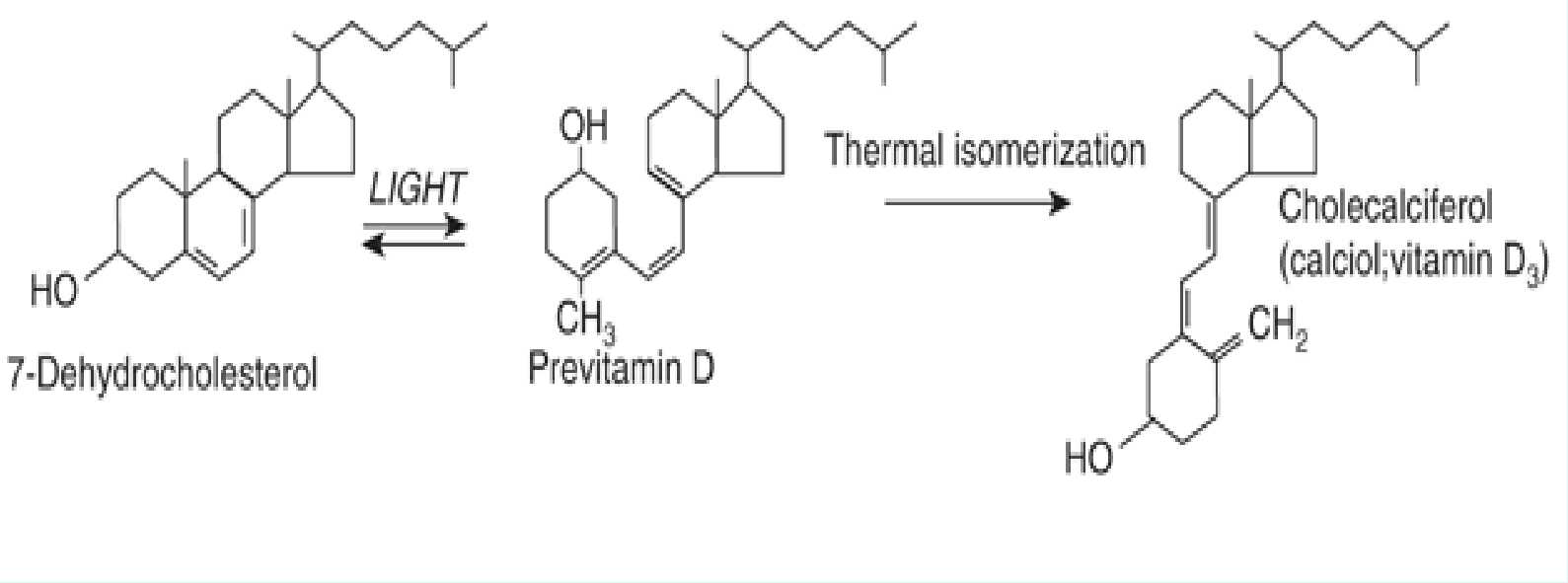
Vitamin D3



Vitamin D Is Synthesized in the Skin

- 7-Dehydrocholesterol (an intermediate in the synthesis of cholesterol that accumulates in the skin) undergoes a nonenzymic reaction on exposure to ultraviolet light, yielding previtamin D.
- This previtamin D undergoes a further reaction to form cholecalciferol, which is absorbed into the bloodstream.

The synthesis of vitamin D in the skin

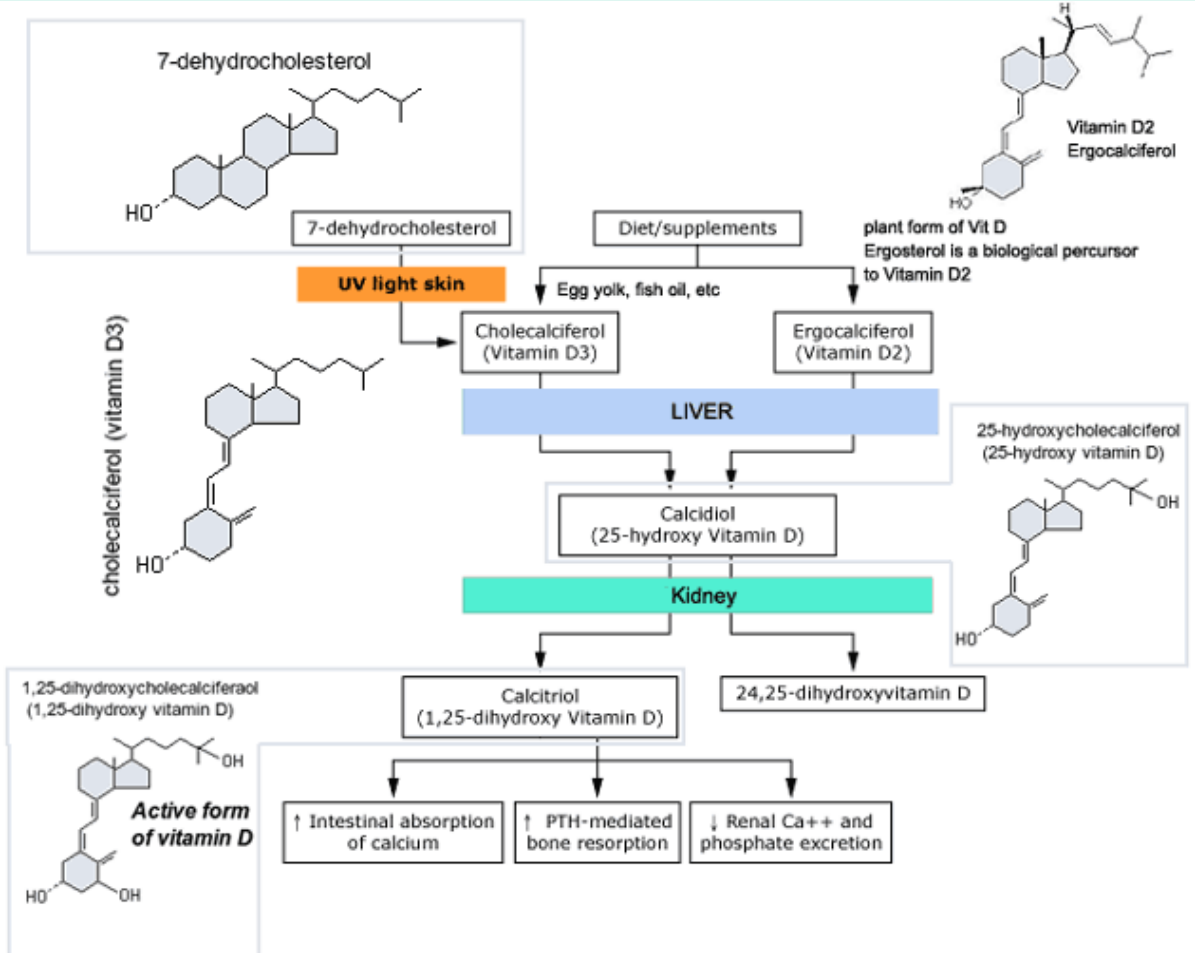


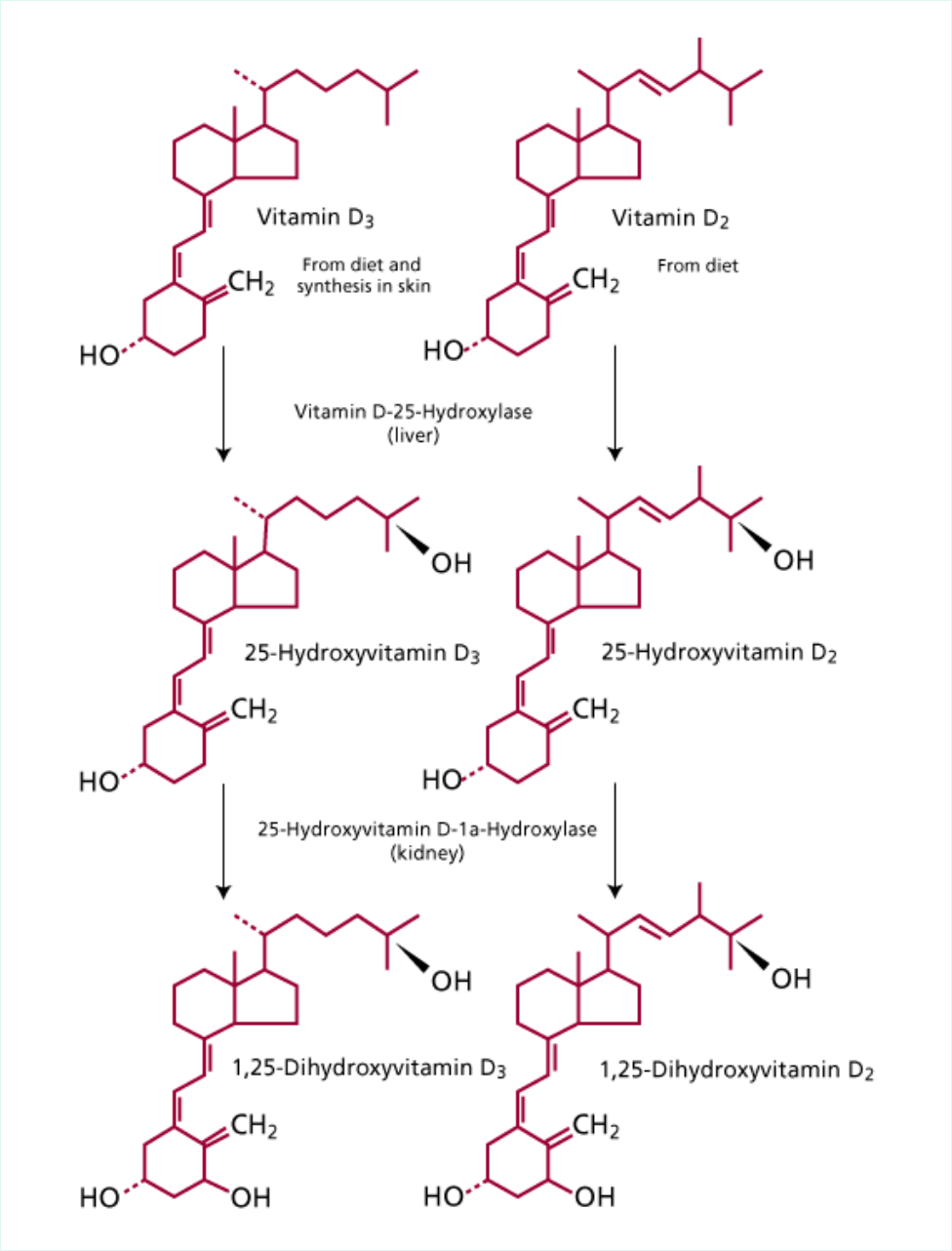
Vitamin D Is Metabolized to the Active Metabolite, Calcitriol, in Liver & Kidney

- Cholecalciferol, either synthesized in the skin or from food, undergoes two hydroxylations to yield the active metabolite, 1,25-dihydroxyvitamin D or calcitriol.
- Ergocalciferol from foods undergoes similar hydroxylation to yield ercalcitriol.
- In the liver, cholecalciferol is hydroxylated to form the 25-hydroxy-derivative, calcidiol.
- This is released into the circulation bound to a vitamin D binding globulin, which is the main storage form of the vitamin.

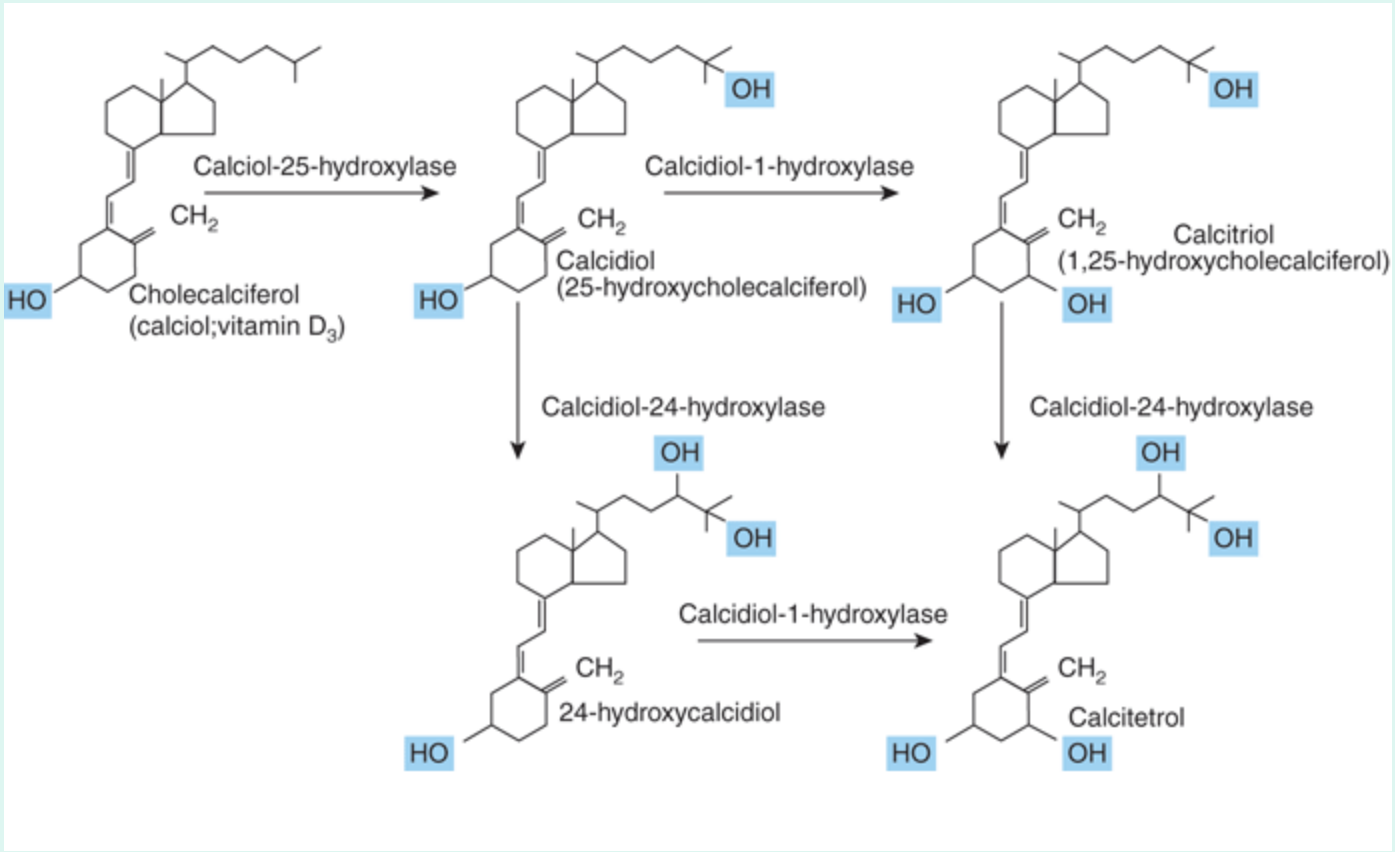
- In the kidney, calcidiol undergoes either 1-hydroxylation to yield the active metabolite 1,25-dihydroxy-vitamin D (calcitriol), or 24-hydroxylation to yield a probably inactive metabolite, 24,25-dihydroxyvitamin D (24-hydroxycalcidiol).

Chemistry of Vitamin D




Vitamin D_3
From diet and synthesis in skin
Vitamin D_2
From diet
Vitamin D-25-Hydroxylase (liver)
25-Hydroxyvitamin D_3
25-Hydroxyvitamin D_2
25-Hydroxyvitamin D-1a-Hydroxylase (kidney)
1,25-Dihydroxyvitamin D_3
1,25-Dihydroxyvitamin D_2

- Metabolism of vitamin D



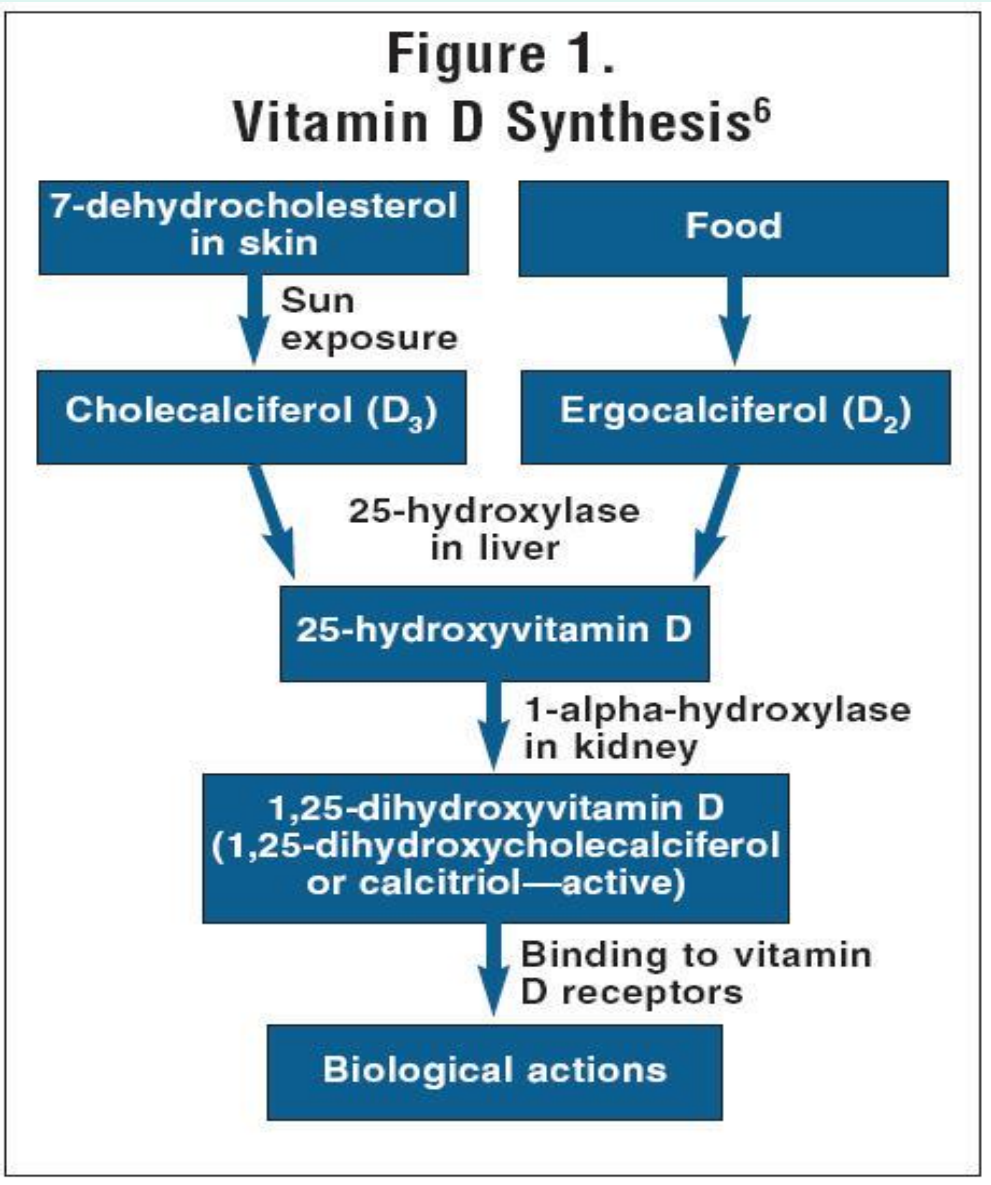


Figure 1.
Vitamin D Synthesis[6]
7-dehydrocholesterol in skin
Food
Sun exposure
Cholecalciferol (D_3)
Ergocalciferol (D_2)
25-hydroxylase in liver
25-hydroxyvitamin D
1-alpha-hydroxylase in kidney
1,25-dihydroxyvitamin D (1,25-dihydroxycholecalciferol or calcitriol—active)
Binding to vitamin D receptors
Biological actions

FORMATION & ACTIVATION OF VITAMIN D_3

7-Dehydrocholesterol

Skin

uv rays

Cholecalciferol

25 hydroxylase (liver)

25 hydroxy cholecalciferol

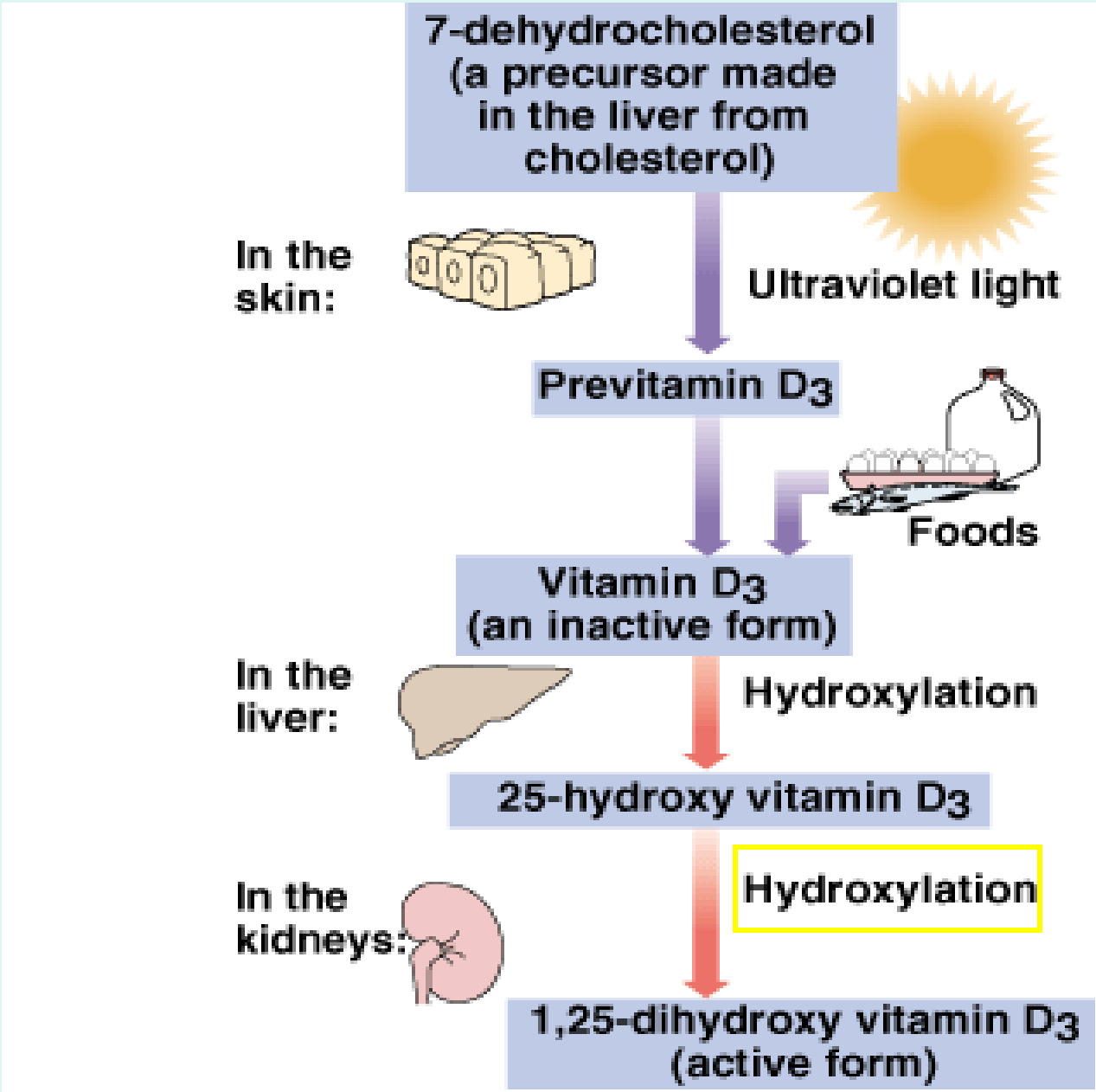
1α hydroxylase

kidney

1,25 Dihydroxycholecalciferol

(Calcitriol)

Active form of Cholecalciferol



Metabolism of vitamin D

1. **Formation of** 1,25-dihydroxy cholecaliferol(1,25 diOH D3):

- -Vitamins D2 and D3 are not biologically active, but are converted in vivo to the active form of the D vitamin by two sequential hydroxylation reactions.
- - The first hydroxylation occurs at the 25-position, and is catalyzed by a specific hydroxylase in the liver.

1. The product of the reaction, *25-hydroxycholecalciferol,* is the predominant form of vitamin D in the plasma and the major storage form of the vitamin.
2. *25-hydroxycholecalciferol* is further hydroxylated at the one position by a specific *25-hydroxycholecalciferol 1 -hydroxylase* found primarily in the kidney, resulting in the formation of 1,25-dihydroxycholecalciferol.

2. Regulation of 25- hydroxycholecalciferol 1-hydroxylase:

- 1,25-dihydroxy cholecaliferol(1,25 diOH D3)is the most potent vitamin D metabolite.
- Its formation is tightly regulated by the level of plasma phosphate and calcium ions .
- *25-hydroxycholecalciferol 1 -hydroxylase* activity is increased directly by low plasma phosphate or indirectly by low plasma calcium, which triggers the release of parathyroid hormone (PTH).
- Hypocalcemia caused by insufficient dietary calcium thus results in elevated levels of plasma 1,25 diOH D3.
- *1 -hydroxylase* activity is also decreased by excess 1,25 diOH D3 the product of the reaction.

Metabolism of Vitamin D

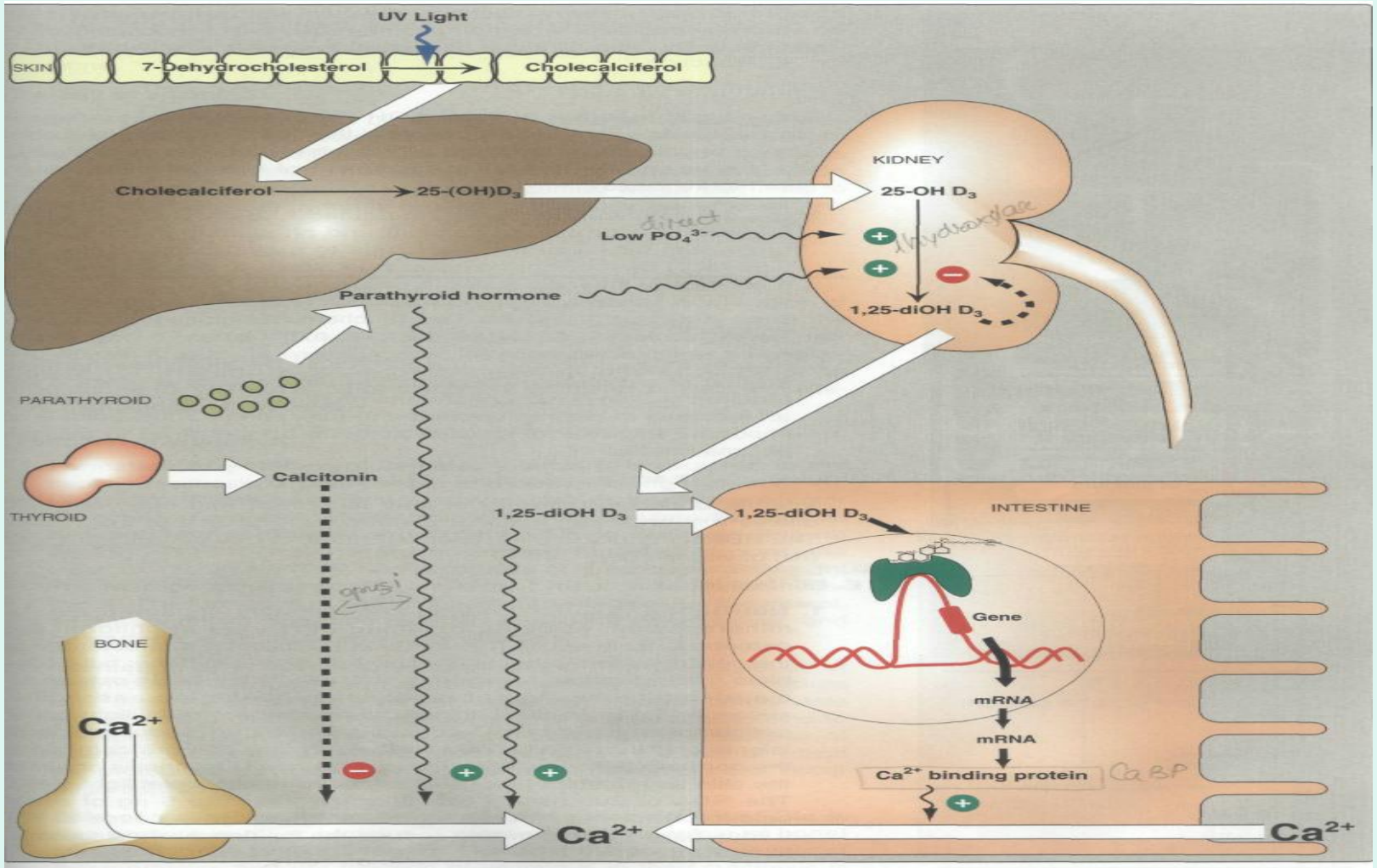


Figure 28.23
Metabolism and actions of vitamin D.

Vitamin D Metabolism Is Both Regulated by and Regulates Calcium Homeostasis

- The principal function of vitamin D is to maintain the plasma calcium concentration.

Calcitriol achieves this in three ways:

1. It increases intestinal absorption of calcium.
2. It reduces excretion of calcium (by stimulating resorption in the distal renal tubules).
3. It mobilizes bone mineral.

- Also calcitriol is involved in:

- insulin secretion.
- synthesis and secretion of parathyroid and thyroid hormones.
- inhibition of production of interleukin by activated T-lymphocytes and of immunoglobulin by activated B-lymphocytes, differentiation of monocyte precursor cells, and modulation of cell proliferation.
- it acts like a steroid hormone, binding to nuclear receptors and enhancing gene expression.
- it also has rapid effects on calcium transporters in the intestinal mucosa.

Function of vitamin D

- The overall function of 1,25-diOH D3 is to maintain adequate plasma levels of calcium.
- It performs this function by:

1. Increasing uptake of calcium by the intestine.
2. Minimizing loss of calcium by the kidney.
3. Stimulating resorption of bone when necessary.

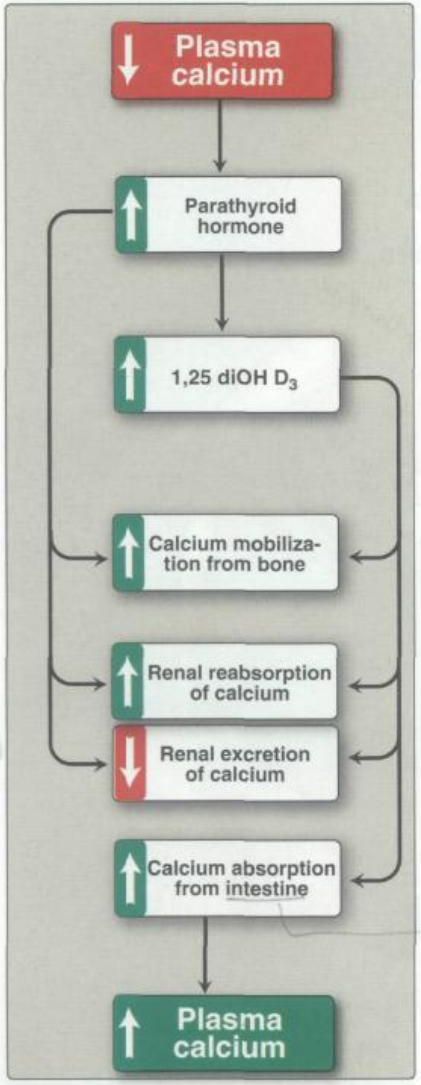


Figure 28.24
Response to low plasma calcium.

1. Effect of vitamin D on the intestine:

- 1,25 diOH D3 stimulates intestinal absorption of calcium and phosphate.
- 1,25 diOH D3 enters the intestinal cell and binds to a cytosolic receptor.
- The 1,25 diOH D3-receptor complex then moves to the nucleus where it selectively interacts with the cellular DNA. As a result, calcium uptake is enhanced by an increased synthesis of a specific calcium-binding protein.
- Thus, the mechanism of action of 1,25 diOH D3 is typical of steroid hormones .

2. Effect of vitamin D on bone:

- 1,25 diOH D3 stimulates the mobilization of calcium and phosphate from bone by a process that requires protein synthesis and the presence of PTH.
- The result is an increase in plasma calcium and phosphate. Thus, bone is an important reservoir of calcium that can be mobilized to maintain plasma levels.

Functions of Vitamin D (Calciferol)

- Maintenance of calcium balance.
- Enhances intestinal absorption of Ca2+.
- Mobilizes bone mineral.
- Regulation of gene expression and cell differentiation.

Sources and requirement of vitamin D

- Vitamin D occurs naturally in fatty fish, liver, and egg yolk.
- The RDA for adults is 5μg cholecalciferol, or 200 international units (IU) of vitamin D.

RECOMMENDED DAILY ALLOWANCE FOR VITAMIN D

Infants & Children	**10 microgram (400 IU)**
Adults	**7.5 microgram**
Pregnancy	**+5 microgram (200 IU)**
Lactation	**+5 microgram**

1 IU = 0.025 microgram of cholecalciferol

Clinical indications of Vitamin D

1. Nutritional rickets:

- Vitamin D deficiency causes a net demineralization of bone, resulting in **rickets** in children and **osteomalacia** in adults .
- **Rickets** is characterized by the continued formation of the collagen matrix of bone, but incomplete mineralization, resulting in soft, pliable bones.
- **In osteomalacia,** demineralization of preexisting bones increases their susceptibility to fracture.

Figure 28.25
Bowed legs of middle-aged man with osteomalacia, a nutritional vitamin D deficiency which results in malformation of the skeleton.

2. Renal rickets (renal osteodystrophy):

- This disorder results from chronic renal failure and, thus, the decreased ability to form the active form of the vitamin.
- 1,25 diOH cholecalciferol(calcitriol) administration is effective replacement therapy.

3. Hypoparathyroidism:

- Lack of parathyroid hormone causes hypocalcemia and hyperphosphatemia.
- These patients may be treated with any form of vitamin D, together with parathyroid hormone.

Deficiency disease of Vitamin D

- **Rickets = poor mineralization of bone.**
- **Osteomalacia = bone demineralization**
- **Renal rickets (renal osteodystrophy).**
- **Hypoparathyroidism.**

Vitamin D Deficiency Affects Children & Adults

- The main symptom of vitamin D deficiency in children is **rickets** and in adults is **osteomalacia**.
- Rickets is characterized improper mineralization during the development of the bones resulting in soft bones.
- Osteomalacia is characterized by demineralization of previously formed bone leading to increased softness and susceptibility to fracture.

Toxicity of vitamin D

- High doses of Vitamin D (100,000 IU for weeks or months) can cause loss of appetite, nausea, thirst, and stupor.
- Enhanced calcium absorption and bone resorption results in hypercalcemia, which can lead to deposition of calcium in many organs, particularly the arteries and kidneys.

Vitamin D Is Toxic in Excess:

- Some infants are sensitive to intakes of vitamin D as low as 50 μg/day, resulting in an elevated plasma concentration of calcium. This can lead to contraction of blood vessels, high blood pressure, and **calcinosis**—the calcification of soft tissues.

- Although excess dietary vitamin D is toxic, excessive exposure to sunlight does not lead to vitamin D poisoning, because there is a limited capacity to form the precursor, 7-dehydrocholesterol, and prolonged exposure of previtamin D to sunlight leads to formation of inactive compounds.

VITAMIN D AS A HORMONE

- Can be synthesised in the body
- Produced in the inactive form, which needs to be activated
- Has definite target organs – intestine, bone and kidney
- Formation of active vitamin D_3 is subjected to feedback control
- Active form maintains calcium homeostasis along with two other hormones, PTH and calcitonin

References:

1. Lippincott's review of biochemistry, 3rd edition.
1. Biochemistry Stryer 5th edition.
2. Harper,s Biochemistry 28 edition.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