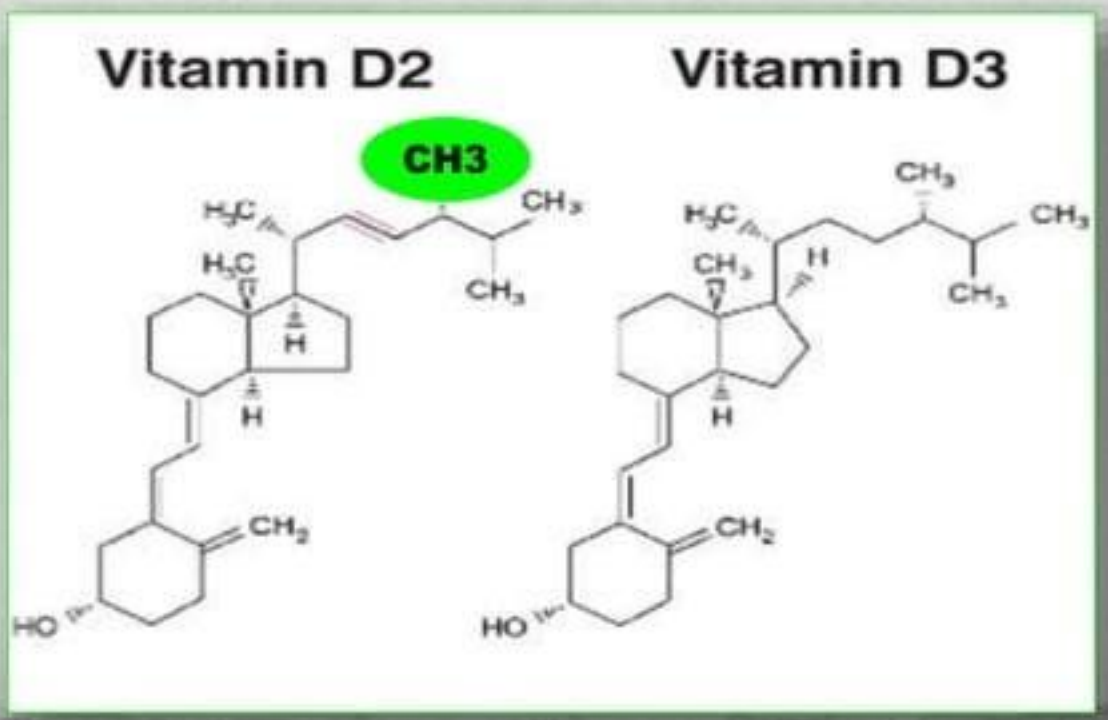
Vitamin D

- Vitamin-D is a fat soluble vitamin
- Vitamin – D is a sterol, it contains steroid nucleus (Cyclopentanoperhydrophenanthrene ring)
- Vitamin – D function like a *hormone*
- *Forms of vitamin D:*
- Vitamin D in the diet occurs in two forms
- Vitamin D2 (Ergocalciferol)
- Vitamin D3 (Cholecalciferol)

Chemistry

- Ergocalciferol (vitamin D2) is formed from ergosterol and is present in plants

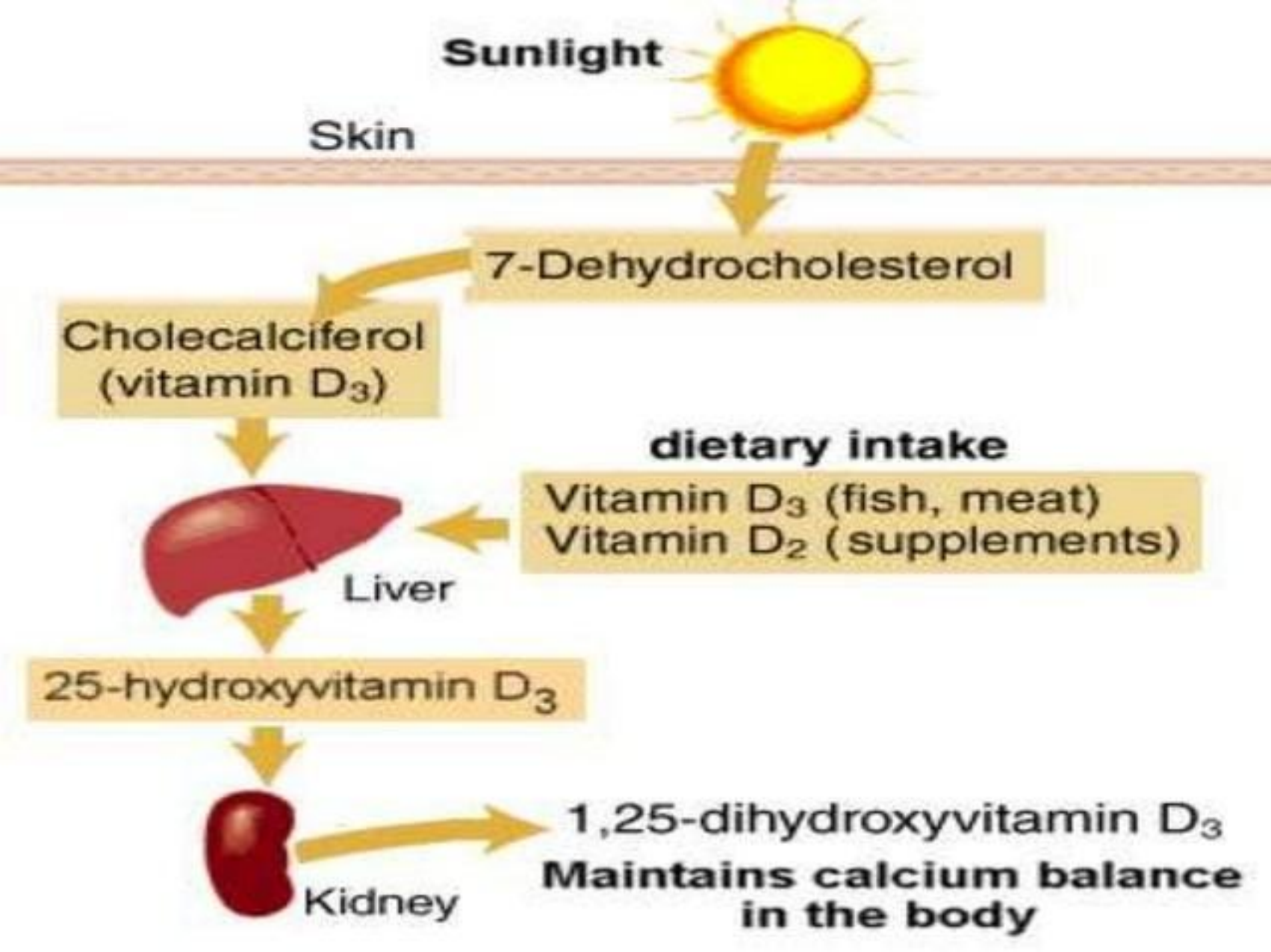


- Cholecalciferol (vitamin D3) is found in animals
- Both the sterols are similar in structure except that ergocalciferol has an additional methyl group and a double bond
- Ergocalciferol and Cholecalciferol are sources for vitamin D activity and are referred as provitamins

VITAMIN D IS A SUN-SHINE

- During the course of cholesterol biosynthesis 7-dehydrocholesterol is formed as an intermediate
- On exposure to sunlight, 7-dehydrocholesterol is converted to cholecalciferol in the skin (dermis and epidermis)
- Dark skin pigment (melanin) adversely influences the synthesis of cholecalciferol

- Skin is the largest organ in the body
- The production of vitamin D in the skin is directly proportional to the exposure to sunlight and inversely proportional to the pigmentation of skin
- Excessive exposure to sunlight does not result in vitamin D toxicity since excess provitamin D3 are destroyed by sunlight itself


Sunlight
Skin
7-Dehydrocholesterol
Cholecalciferol
(vitamin D_3)
dietary intake
Vitamin D_3 (fish, meat)
Vitamin D_2 (supplements)
Liver
25-hydroxyvitamin D_3
Kidney
1,25-dihydroxyvitamin D_3
Maintains calcium balance
in the body

Absorption:

- Diet from animal sources such as animal liver contains vitamin D3
- Diet from plant sources contains vitamin D2
- Absorption: vitamin D2 and D3 are absorbed from upper small intestine and bile is essential
- Mechanism: vitamin D3 and D2 form mixed micelles by combining with bile salts (micelles)
- Mixed micelles are presented to mucosal cells
- Absorption occurs by passive transport

Transport

- *Vitamin D binding globulin:* vitamin D is transported from intestine to the liver by binding to vitamin D binding globulin
- 25 – Hydroxy D3 and 1,25 – dihydroxy D3 are also transported in the blood by binding to vitamin D binding globulin
- Storage:
- 25 – hydroxycholecalciferol is the major storage and circulatory form of vitamin D

Metabolism and biochemical functions

- **Synthesis of 1,25 – Dihydroxycholecalciferol:**
- Active form: the active form of vitamin D is 1,25 – Dihydroxycholecalciferol and is also called as calcitriol
- Cholecalciferol is first hydroxylated at 25th position to 25 – hydroxycholecalciferol by a specific hydroxylase present in liver
- Kidney possesses a specific enzyme, 25 – hydroxycholecalciferol 1 – hydroxylase

- 25 – hydroxycholecalciferol 1 – hydroxylase hydroxylates 25 – hydroxycholecalciferol at position 1 to produce 1,25 – Dihydroxycholecalciferol (1,25-DHCC)
- 1,25 – DHCC contains 3 hydroxyl groups (1, 3, 25) and called as calcitriol
- Both hydroxylase enzymes (of liver and kidney) require cytochrome P450, NADPH and molecular oxygen for hydroxylation process

REGULATION

- Formation of 1,25 – DHCC is regulated by the regulation of renal 1 α – hydroxylase
- 1 α – hydroxylase activity is increased by hypocalcemia
- Hypocalcemia stimulates PTH secretion which, in turn, increases 1 α – hydroxylase
- 1 α – hydroxylase activity may be feedback inhibited by 1,25 – DHCC

Clinical importance

- In chronic renal failure, 1 α – hydroxylase activity is decreased leading to decreased synthesis of 1,25 – DHCC
- The condition leads to renal osteodystrophy (renal rickets)
- Condition is treated by giving 1,25 – DHCC preparations
- 1 α – hydroxylase deficiency can also occurs as inherited disorder or due to hypoparathyroidism

Regulation of plasma calcium and phosphorous

- Vitamin D regulates the plasma levels of calcium and phosphorous
- Plasma calcium levels are regulated by effects of 1,25 – DHCC on small intestine, kidney and bone
- It maintains the plasma calcium levels by increasing absorption of calcium from small intestine, increasing reabsorption of calcium by renal distal tubules and increasing mobilization of calcium from bone

Biochemical functions

- Calcitriol (1,25 – DHCC) acts at three different levels to maintain plasma calcium
- Action on intestine:
- Calcitriol increases the intestinal absorption of calcium and phosphate
- In the intestinal cells, calcitriol binds with a cytosolic receptor to form a calcitriol-receptor complex

- This complex interacts with a specific DNA leading to the synthesis of a specific calcium binding protein
- This protein increases calcium uptake by intestine
- The mechanism of action of calcitriol is similar to that of steroid hormone
- Action on bone:
- In osteoblasts of bone, calcitriol stimulates calcium uptake for deposition as calcium phosphate

- Calcitriol is essential for bone formation
- Calcitriol along with parathyroid hormone increases the mobilization of calcium and phosphate from the bone
- Causes elevation in the plasma calcium and phosphate
- *Action on kidney:*
- Calcitriol is also involved in minimizing the excretion of calcium and phosphate through the kidney by decreasing their excretion and enhancing reabsorption

24,25 - Dihydroxycholecalciferol

- 24,25 – DHCC is another metabolite of vitamin D
- It is synthesized in kidney by 24 - hydroxylase
- Calcitriol concentration is adequate, 24 – hydroxylase acts leading to the synthesis of a less important compound 24,25 – DHCC
- To maintain calcium homeostasis, synthesis of 24,25 – DHCC is important

Vitamin D is a hormone - Justification

- Calcitriol is considered as an important calciotropic hormone, while cholecalciferol is the prohormone

1. Vitamin D3 (cholecalciferol) is synthesized in the skin by the UV – rays of sunlight
2. The biologically active form of vitamin D, calcitriol is produced in the kidney
3. Calcitriol has target organs-intestine, bone and kidney

4. Calcitriol action is similar to that of steroid hormones

   It binds to a receptor in the cytosol and the complex acts on DNA to stimulate the synthesis of calcium binding protein

5. Calcitriol synthesis is self-regulated by a feedback mechanism i.e., ***calcitriol decreases its own synthesis***

6. Actinomycin D inhibits the action of calcitriol, calcitriol exerts its effect on DNA leading to the synthesis of RNA (transcription)

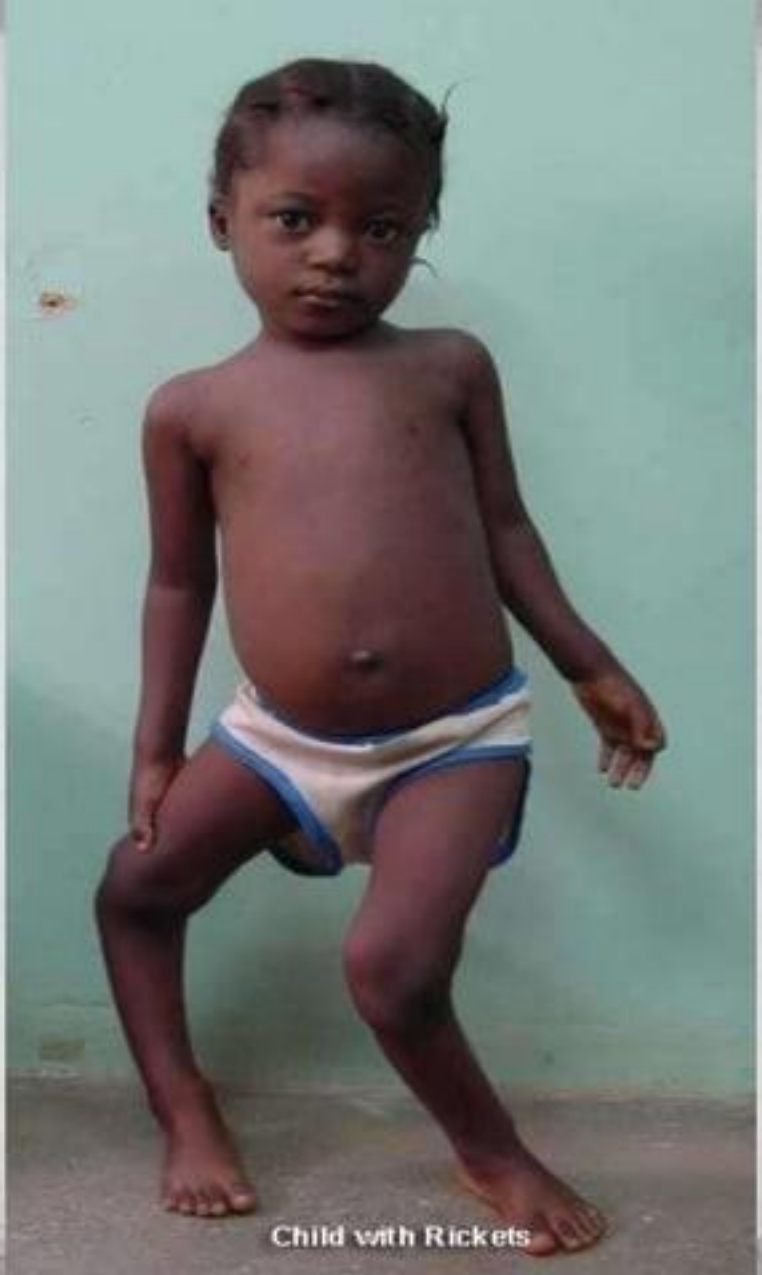
Recommended dietary allowance (RDA)

- Children - 10 gm/day or 400 IU/day
- Adults - 5 gm/day or 200 IU/day
- Pregnency,lactation -10 gm/day or 400 IU/day
- Above the age of 60 yrs - 600 IU /day
- Sources of vitamin D:
- Exposure to sunlight produces cholecalciferol
- Good sources includes – fatty fish, fish liver oils, egg yolk etc
- Milk is not a good source

Deficiency of vitamin D

- Deficiency of vitamin D causes rickets in children and osteomalacia in adults
- Rickets:
- It is a vitamin D deficiency state in children
- Causes: Dietary deficiency and non-exposure to sunlight
- Rickets in children is characterized by bone deformities due to incomplete mineralization

- Causing enlargement and softening of bones
- Delay in teeth formation
- The weight bearing bones are bent to form bow-legs
- Decreased serum calcium
- Deformation of muscles: potbelly due to weakness of abdominal muscles
- Biochemical findings:
- Decreased serum calcium (9-11mg/dl)
- Decreased plasma phosphorous (3-4.5 mg/dl)
- Increased plasma alkaline phosphatase (30-130 IU)


Child with Rickets

OSTEOMALACIA

- Vitamin D deficiency in adults
- Causes: Inadequate exposure to sunlight or low dietary intake
- Features: Demineralization occurs mainly in spine, pelvis and lower extremities
- Bowing of the long bones may occur due to weight of the body
- Flattening of pelvis bones may cause difficulty during labour

Renal Rickets

- In chronic renal failure, 1 α – hydroxylase activity is decreased leading to decreased synthesis of 1,25 – DHCC
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VITAMIN D TOXICITY

- Vitamin D is stored mainly in liver
- Vitamin D is most toxic in overdoses
- Toxic effects include demineralization of bones and increased calcium absorption from intestine, leading increased plasma calcium (hypercalcemia)
- Hypercalcemia is associated with deposition of calcium in many soft tissues such as kidney and arteries
- It leads to formation of stones (renal calculi)
- High consumption is associated with loss of appetite, nausea, increased thirst, loss of weight etc