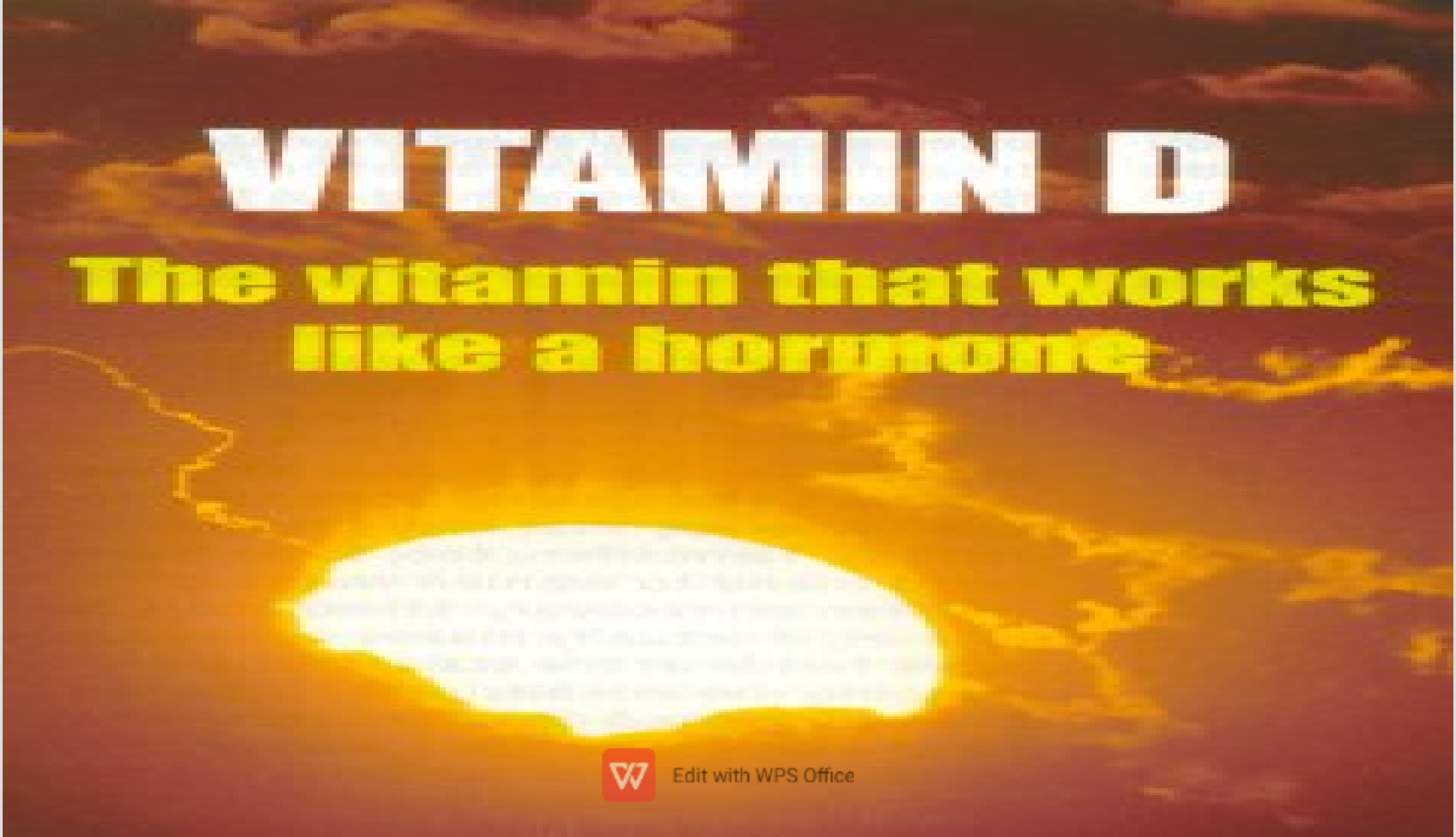
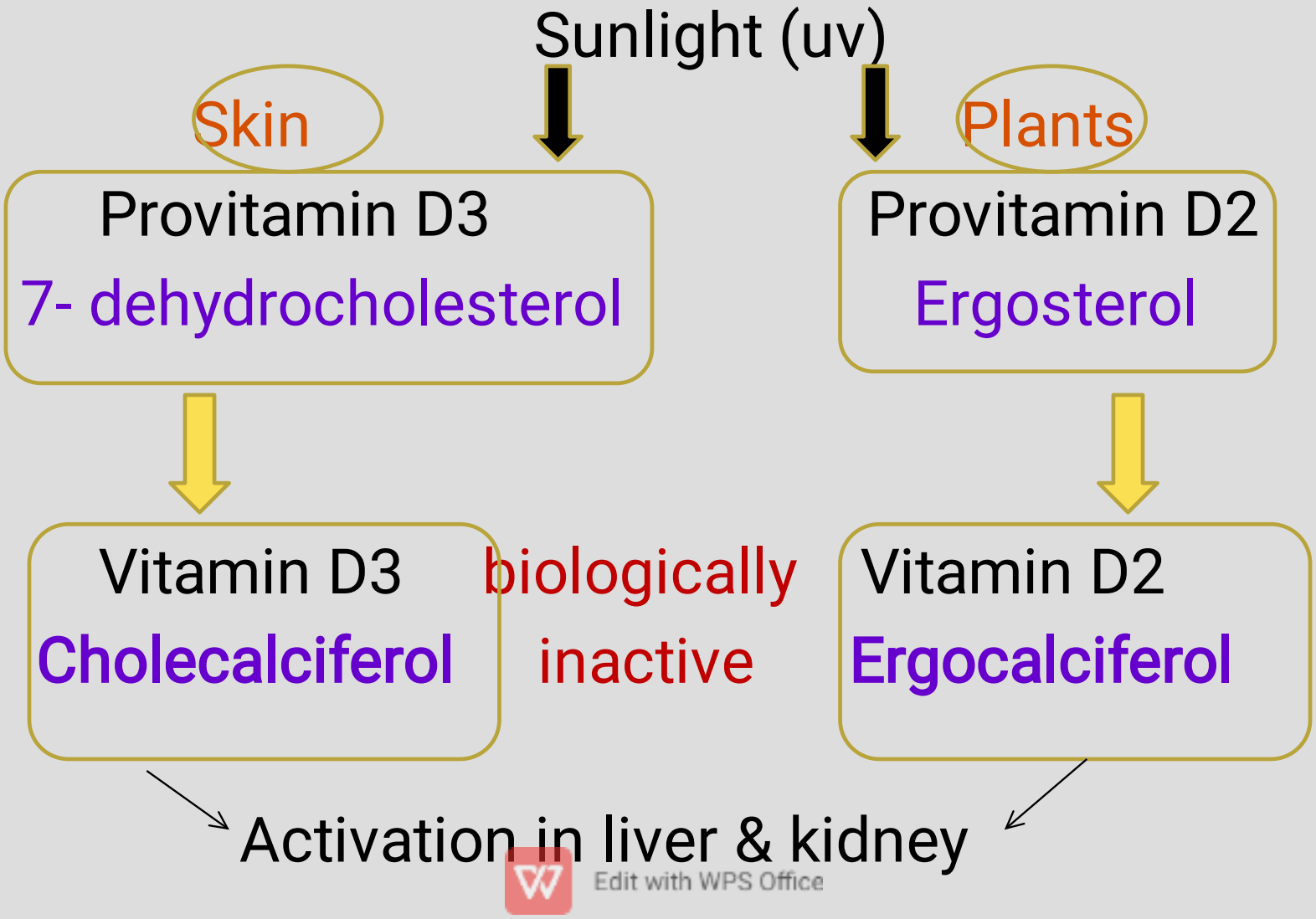


- Vitamin D / Anti- Rachitic factor / Sun shine vitamin

# CHEMISTRY- 

- Physiologically imp -
- Vitamin  D2 & D3

# Formation of vitamin D



- Inactive natural precursors of vitamin D are

1. Ergosterol (Provitamin $D_2$) in Plants gives Ergocalciferol (vitamin D2) &
2. 7 – Dehydrocholesterol (Provitamin $D_3$) in skin gives Cholecalciferol (vitamin D3)

by ultraviolet radiations.

Both vitamins D2 & D3 are of equal potency

- On UV photolysis,

a. Ring is opened to formed secosterol

b. cis double bond between $5^{th}$ & $6^{th}$ C is isomerized to trans

# ACTIVATION OF VITAMIN D

Cholecalciferol (D3)

*25 hydroxylase*

(microsomal Monooxygenase)

$O_2$, cyt P 450, NADPH

**LIVER**

25 –Hydroxy-cholecalciferol

*1 α hydroxylase*

(mitochondrial Monooxygenase)

$O_2$, cyt P 450, NADPH

**KIDNEY**

1, 25 –Dihydroxy-cholecalciferol

(**Calcitriol**)

**Active** →

# ACTIVATION OF VITAMIN D

## Vitamin D is a prohormone

1. Liver

- Hydroxylation @ 25$^{th}$ position
- Enz- 25 hydroxylase is a microsomal monoxygenase
- Requires cyt –P-450,NADPH, molecular $O_2$
- 25-hydroxy cholecalciferol is the major form in circulation & major storage form

## 2. Kidney

- Hydroxylation at 1$^{st}$ position

- 1-α hydroxylase – mitochondrial enzyme in PCT

- Requires cyt –P-450, NADPH, molecular O2, $Mg^{2+}$ & iron sulfur protein - ferrodoxin

- 1,25 Dihydroxycholecalciferol (DHCC) -active form of vit D

- Contains 3 – OH groups @ 1,3 & 25 – so CALCITRIOL

- Calcitriol is a hormone

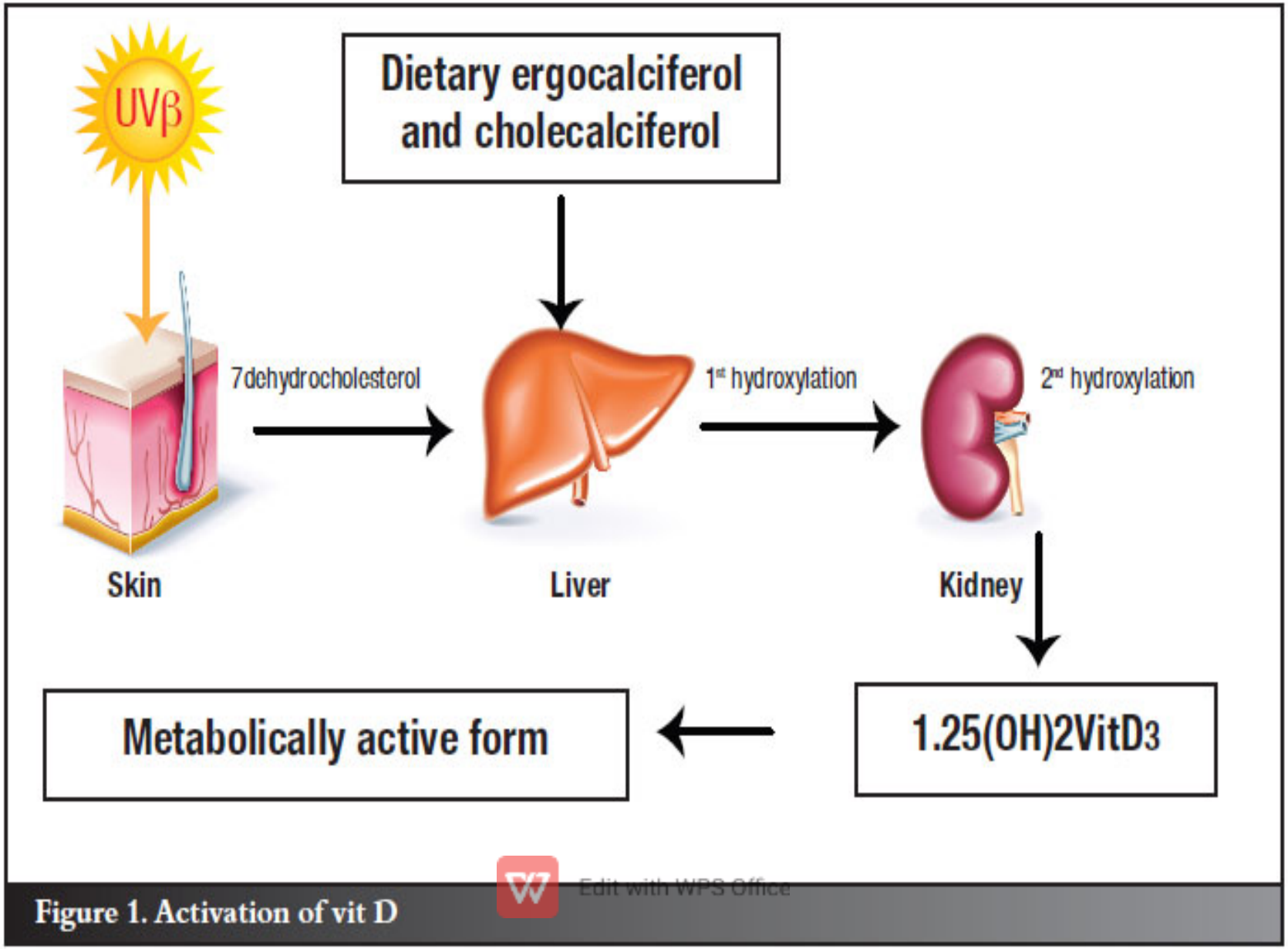





Figure 1. Activation of vit D

- Vitamin D3
  - absorbed from micelles in upper small intestine
  -Absorption requires bile salts
  - transported in lymphatics
  - circulate in the blood bound to - vitamin D binding protein
  - taken up by the liver

# Regulation of Calcitriol formation

## Reg. enz: renal 1 α – Hydroxylase

A. Factors ↑ Calcitriol synthesis

1. Low calcium diet & hypocalcemia
2. Secretion of PTH (+)
3. Hypophosphatemia

# B. Factors ↓ Calcitriol synthesis

1. **Calcitriol – feed back control**
2. Hypercalcemia
3. Low PTH stimulates synthesis of **inactive 24,25 - DHCC** by kidney.

# SOURCES

Skin- provitamin D

Cheese, butter, fortified milk,

Fish

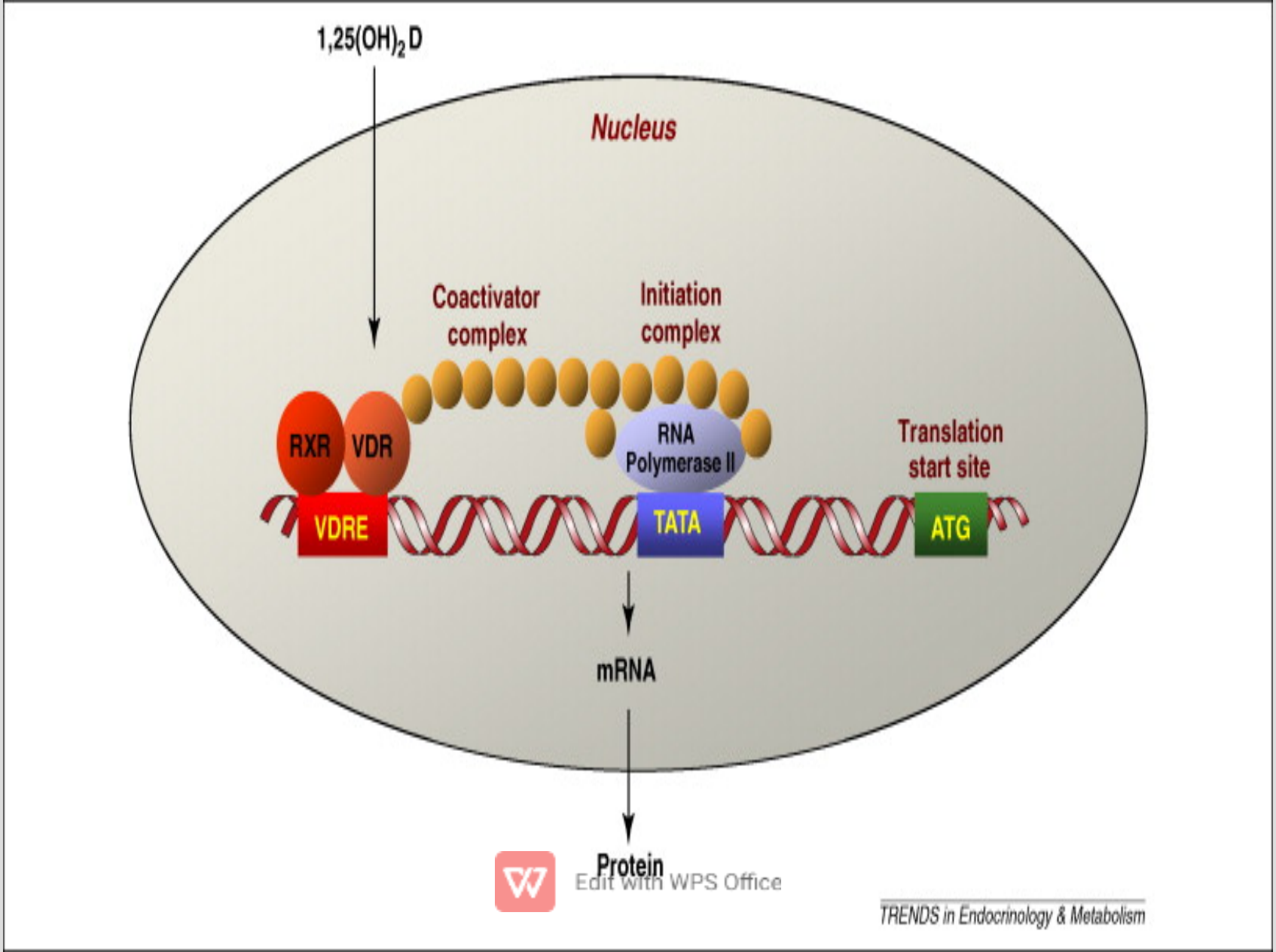
fortified cereals

# RDA

- Children - 10µgm / day
- Adults - 5 – 10µgm/day
- Pregnancy , Lactation - 10µgm / day
- Above 60 yrs age - 15µgm / day

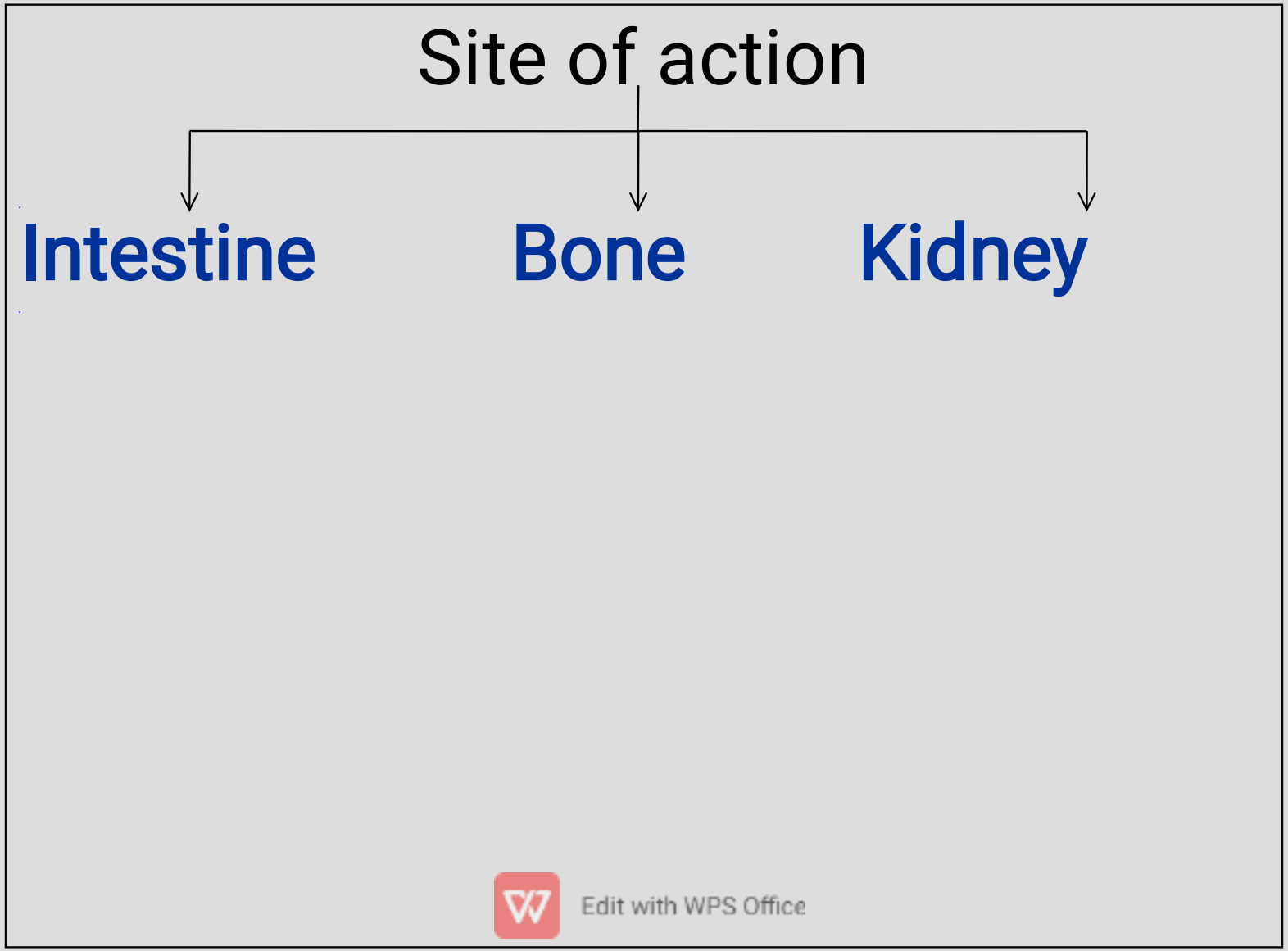
# Mechanism of action of Calcitriol (CT)

- binds to specific nuclear receptor – VDR (**CT-VDR**)
- Then binds to RXR (**CT-VDR-RXR**)
- Then binds to Vitamin D Response Elements (VDRE) on DNA
- Regulates gene expression


1,25(OH)2 D
Nucleus
Coactivator complex
Initiation complex
RXR
VDR
RNA Polymerase II
Translation start site
VDRE
TATA
ATG
mRNA
Protein
Edit with WPS Office
TRENDS in Endocrinology & Metabolism

# BIOCHEMICAL ROLE

**Maintains Blood Calcium & Phosphate levels**



# a. Effect in intestine

Promotes absorption of Calcium & Phosphorus from intestine

↑ blood calcium & Phosphorus level

- Cacitriol binds to receptor - VDR
- CT-VDR-RXR complex binds to VDRE on DNA

- Stimulates transcription → mRNA → **Calbindin** – calcium binding protein

- Calbindin promotes calcium uptake across intestinal cell.

- On the brush border calcium is absorbed passively
- Absorption from intestinal cell to blood is by sodium calcium exchange mechanism or by Ca – calbindin complex

- **Ca absorption increased.**
- **So blood calcium level increased**

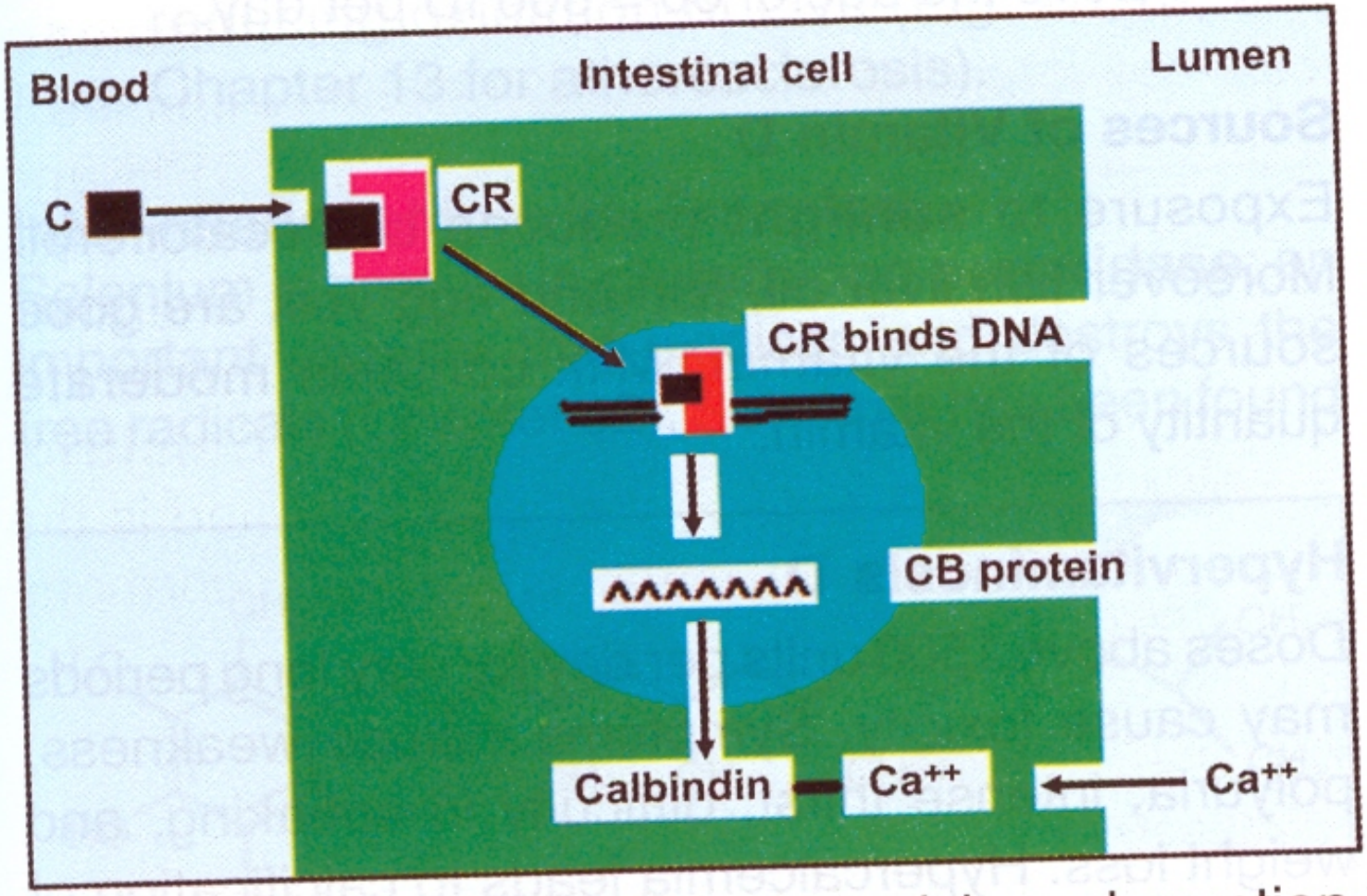



**Fig. 26.10.** Calcitriol increases calcium absorption. C = calcitriol; R = receptor; CR = calcitriol receptor complex; CB = calbindin.

# b.Effect in bone

| Osteoblasts | osteoclasts |
| --- | --- |
| - Uptake of calcium | - promote bone resorption |
| - ALP secretion | |
| - Deposit as Ca P OH apatite | |
| - Bone mineralization | - demineralization |

- ↑ production of bone matrix proteins - osteocalcein & osteopontin
- Coordinates bone remodeling

# c. EFFECT IN RENAL TUBULES

↑ *reabsorption of*
*calcium &*
*phosphorus by DCT*

Note: Calcitriol conserves both minerals while PTH conserves only Calcium

# Vitamin D deficiency

- Rickets in children
- Osteomalacia in adults

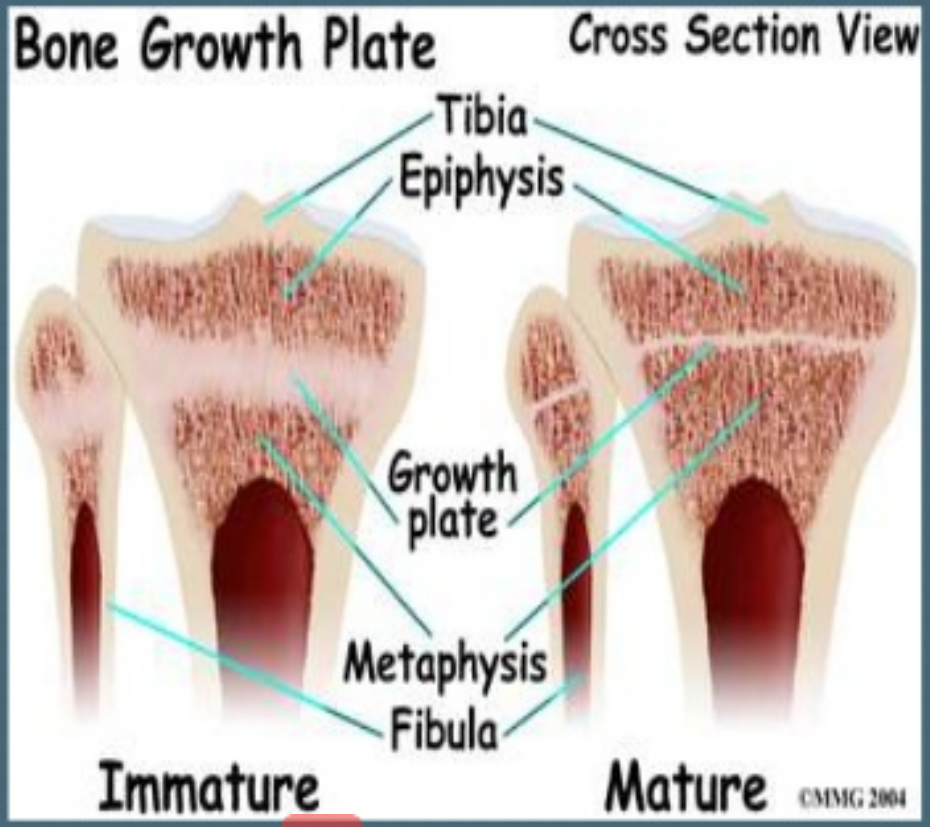
# Causes

- ↓/ no exposure to sunlight
- ↑ phytate  in diet ↓ absorption
- Obstructive Jaundice
- Abnormality in  Vit.D activation (liver & kidney diseases)

# Rickets

- Rickets is a disease of growing bone in children where bone mineralization is improper

# Growth plate in normal bone



# Radiological Manifestations

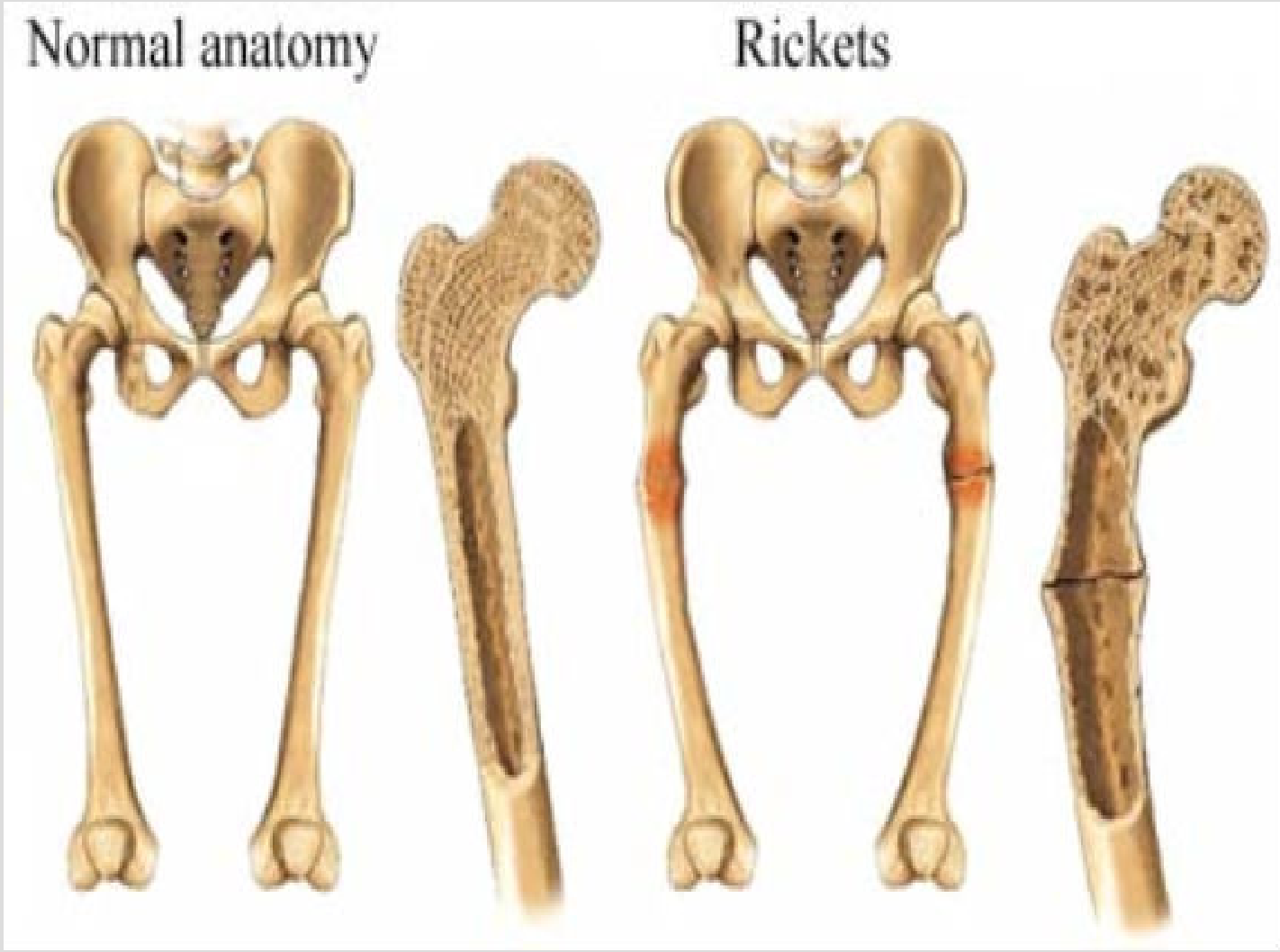
Fraying Cupping Widening of Growth plate

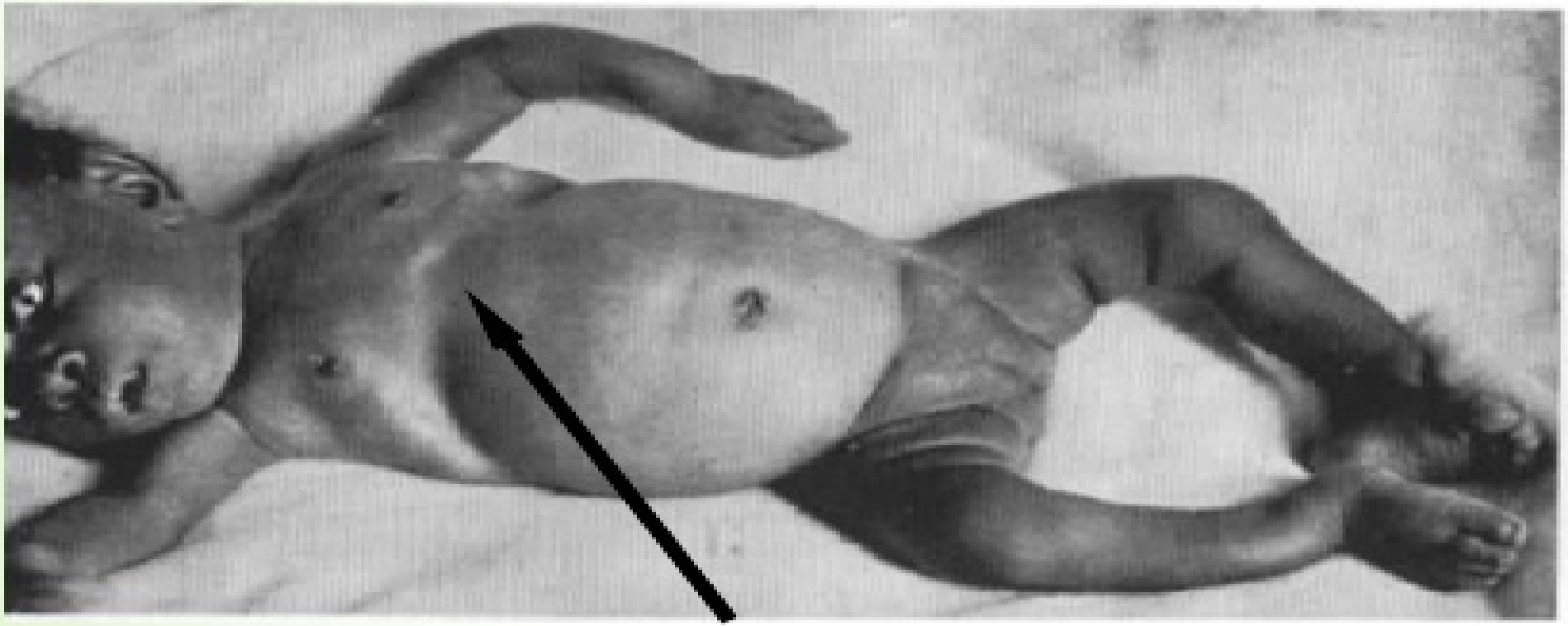
Normal

# Clinical Features

1. General :

- Bone deformities – soft & pliable bones
- Fractures
- Protruding abdomen



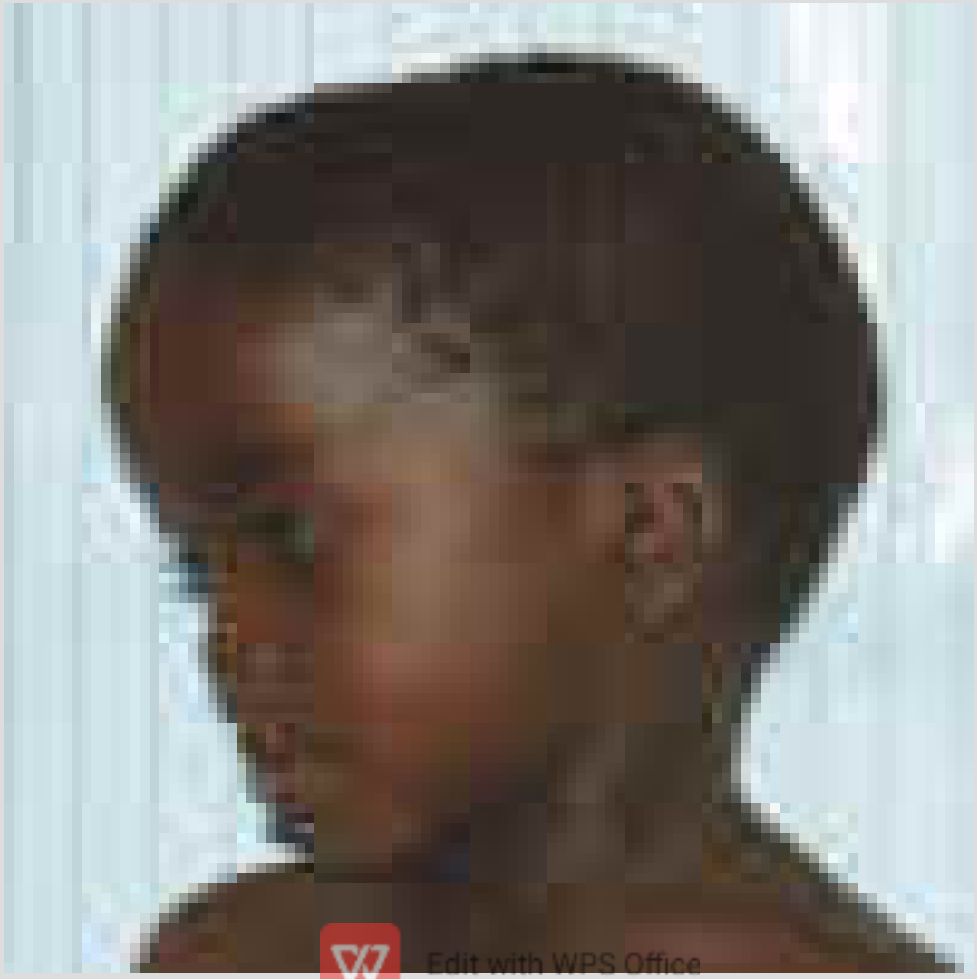


Harrison’s groove

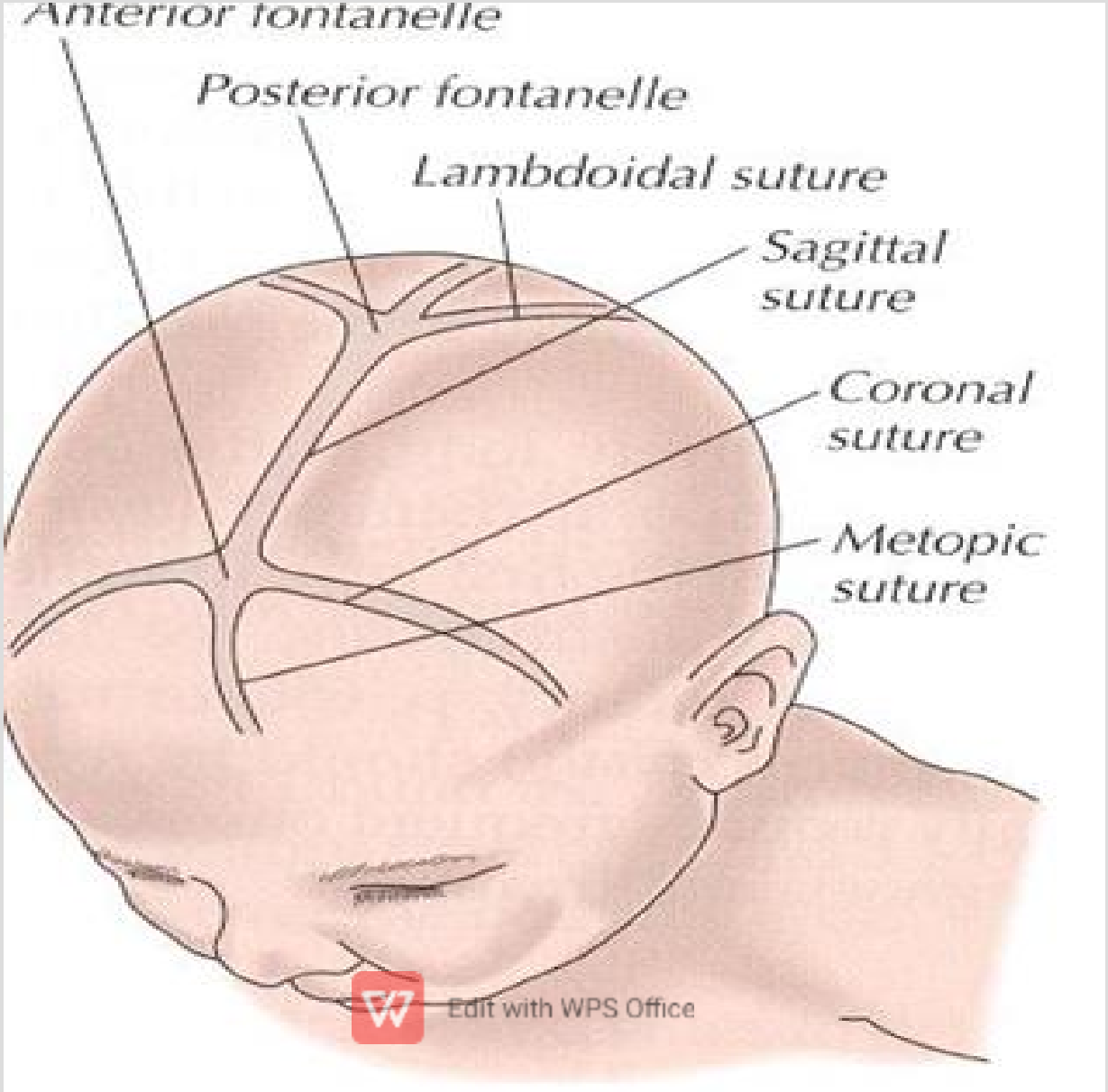
## 2. Head:

- Craniotabes – softening of cranial bones
- Frontal bossing
- Delayed fontanelle closure
- Delayed dentition
- caries

# Craniotabes



- **Delayed Fontanelle Closure**

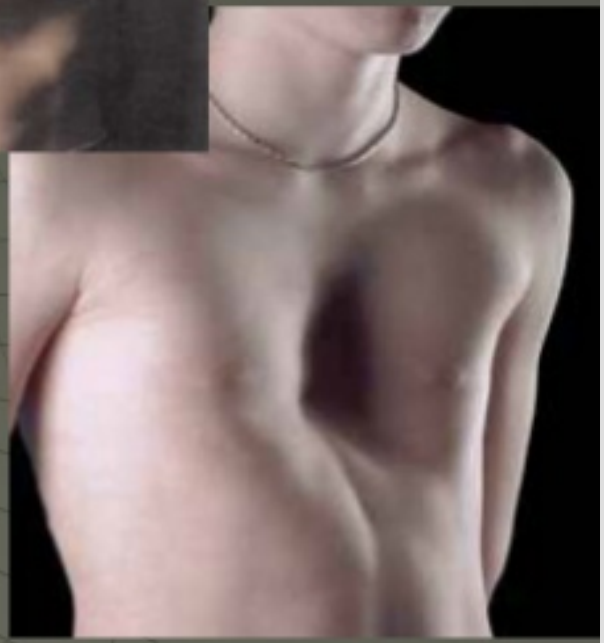


# 3. Chest:

- **Pigeon chest -** anterior protrusion of sternum
- **Rickety rosary –** widening & beading of ribs at costochondral junctions
- **Harrison's groove -** horizontal depression along the lower anterior chest, occurs due to pulling of the softened ribs by diaphragm during inspiration

# PHYSICAL EXAMINATION: Chest

- pigeon-breast deformity

# 4. Extremities:

- **Bow legs -** anterior bowing of tibia & femur
- **Knock knee -** due to enlarged ends of femur, tibia & fibula
- **Enlargement of wrists & ankles**

Bowing of the long bones

bulky physeal plates and irregularity ("fraying"), disorganization, and splaying ("cupping") of the bone at the junction of the metaphysis and physis

# Different types of rickets

- Vit. D deficiency rickets – cured by Vit. D
- Hypo phosphatemic rickets – renal tubular reabsorption of phosphate defective – supplementation of vit.D + Phosphate
- Vit. D resistant rickets – associated with Fanconi syndrome – reabsorption of bicarbonate, phosphate, a.as, glucose defective

- **Renal Rickets –** Calcitriol synthesis defective – supplement Calcitriol

- **End organ resistance to 1,25 DHCC -** ↓ in number / structural abnormality of VDR

# OSTEOMALACIA (soft bone)

Impairment of bone mineralization resulting in softening of bones

C/F:

- Vague bony pains
- muscular weakness
- prone to get fractures

# OSTEOMALACIA

## Causes-

- Vitamin- D deficiency from inadequate intake
- Chronic renal failure
- Malabsorption

# Lab findings in Rickets

- Slightly low Serum calcium (no Tetany)
- Low Serum  Phosphate
- Raised Serum ALP (bone form)

# Other actions of Vitamin D

- Modulatory effect on immune system
- ↓ the risk of cancer & CAD
- Low Vitamin D associated with risk for Metabolic Syndrome (MS)
- It has antibacterial role
- It has anti inflammatory role

# HYPERVITAMINOSIS D

- Immediate effects
- Anorexia, nausea, thirst, polyuria, hypertension, wt. loss

- **Delayed effects**

calcification of soft tissues-

renal tubules, arteries, myocardium, lungs & stomach.