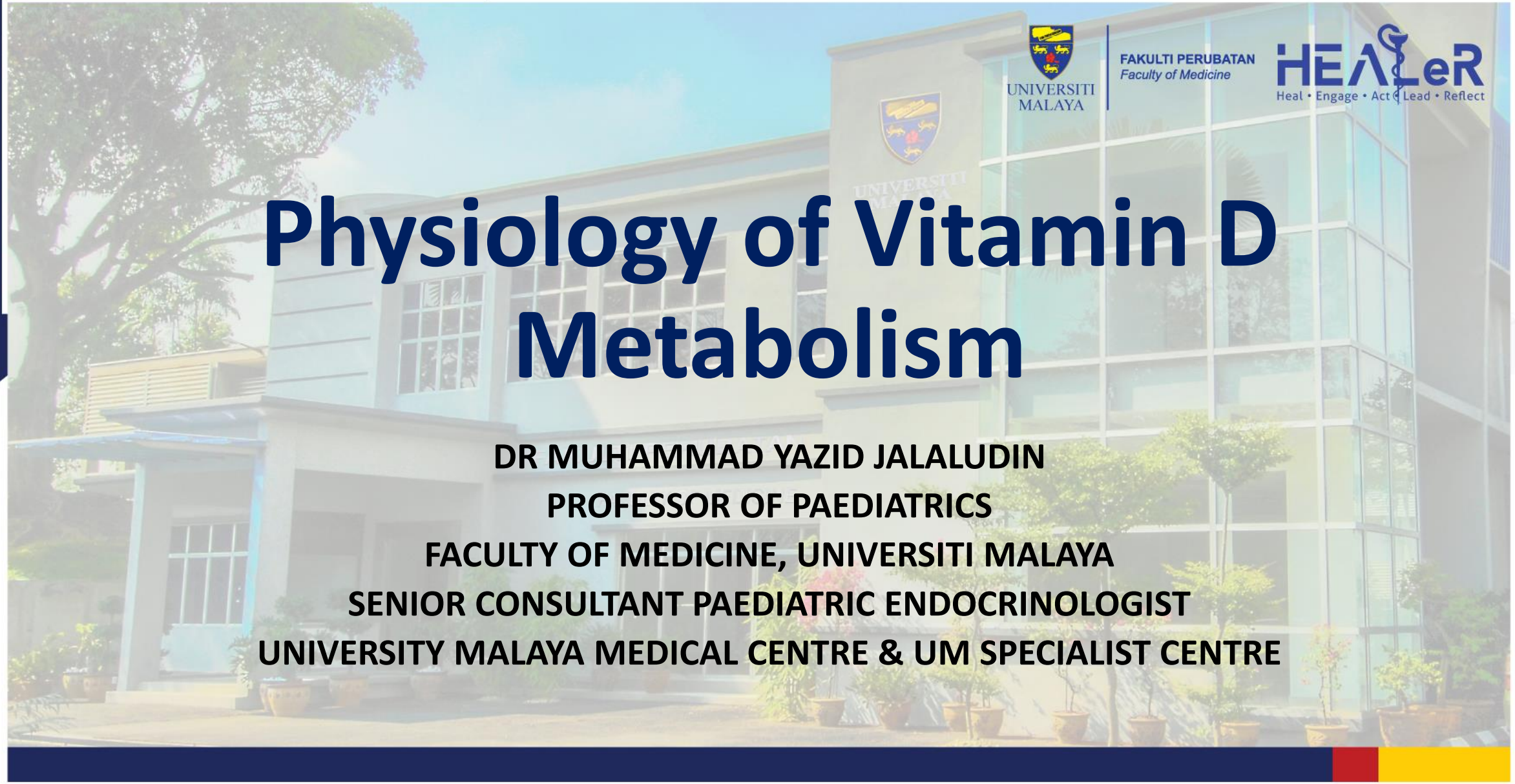

UNIVERSITI MALAYA | FAKULTI PERUBATAN *Faculty of Medicine*

HEALeR
Heal • Engage • Act • Lead • Reflect

Physiology of Vitamin D Metabolism

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Outlines

Vitamin D: Physiology and Metabolism

- Types of Vitamin D
- Vitamin D: Sources, Synthesis and Metabolism
- Vitamin D Physiology
- Vitamin D: Skeletal & Non-Skeletal Functions
- Vitamin D Status: Insufficiency vs Deficiency
- Risk factors
- Daily Recommendation

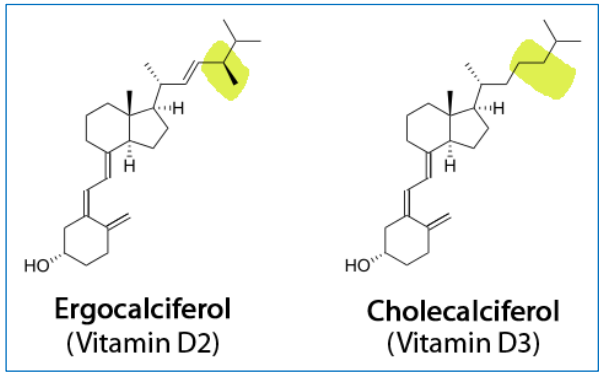
The Types of Vitamin D

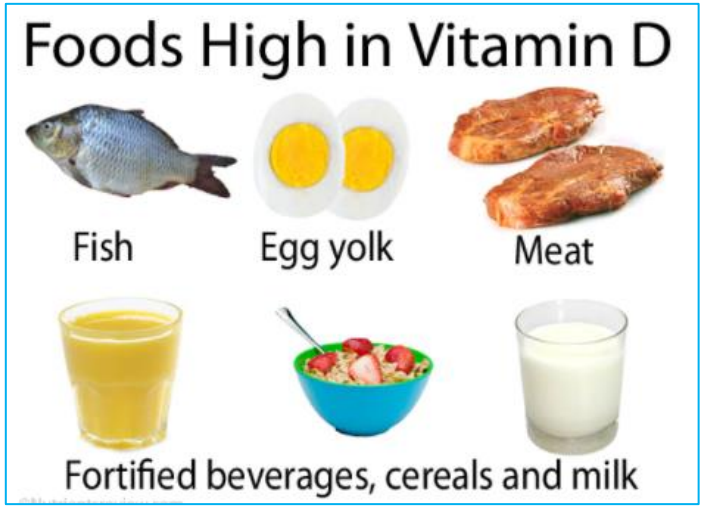
Food with Vitamin D3 (Animal)

- Fish (Salmon), egg yolk, beef, liver etc

Food with Vitamin D2 (Plant)

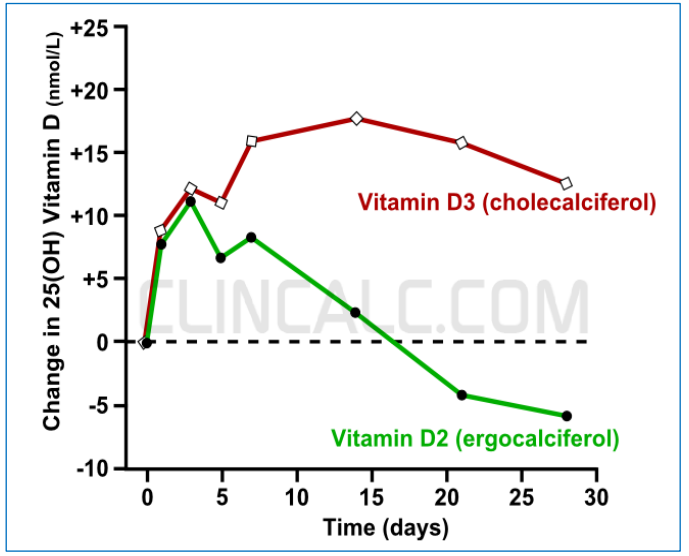
- Mushroom, milk, cereal etc





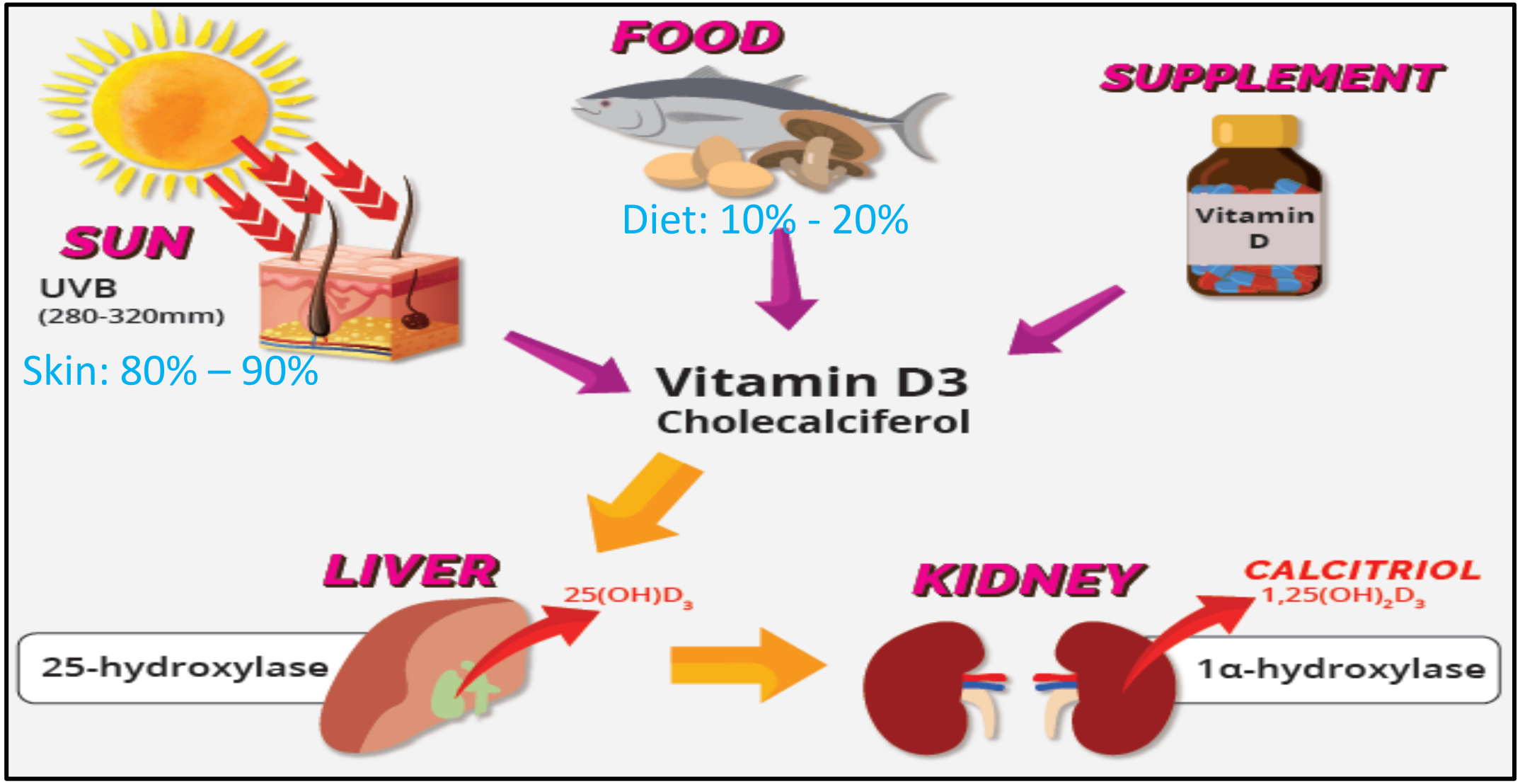
Vitamin D3 appears to be more potent and x3 as effective as vitamin D2.

(D2 is easily broken down and has a shorter shelf life)

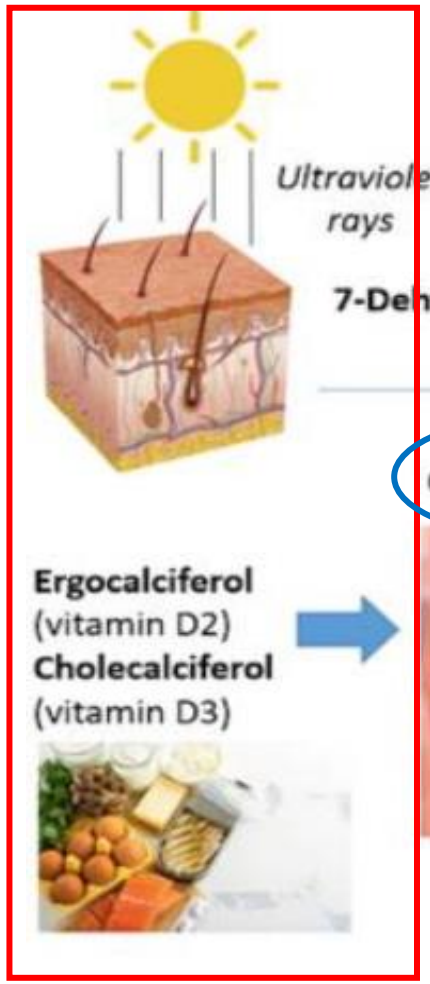


Francesca Ramelli et al. Nutrients. 2019 Dec; 11(12): 2861

Vitamin D: Sources, Synthesis & Metabolism



The Physiology of Vitamin D



1. Vit D produced from our skin or diet - biologically inactive form **(Cholecalciferol)**

2. With the regulation of **parathyroid gland (PTH hormones),** Vit D will be either:

- Stored in adipose cell (if sufficient)
- Undergo hydroxylation by liver - kidney

3. The 1st hydroxylation in **LIVER** to form **25(OH)D** is the major circulating form of Vit. D – **best indicator for blood test**

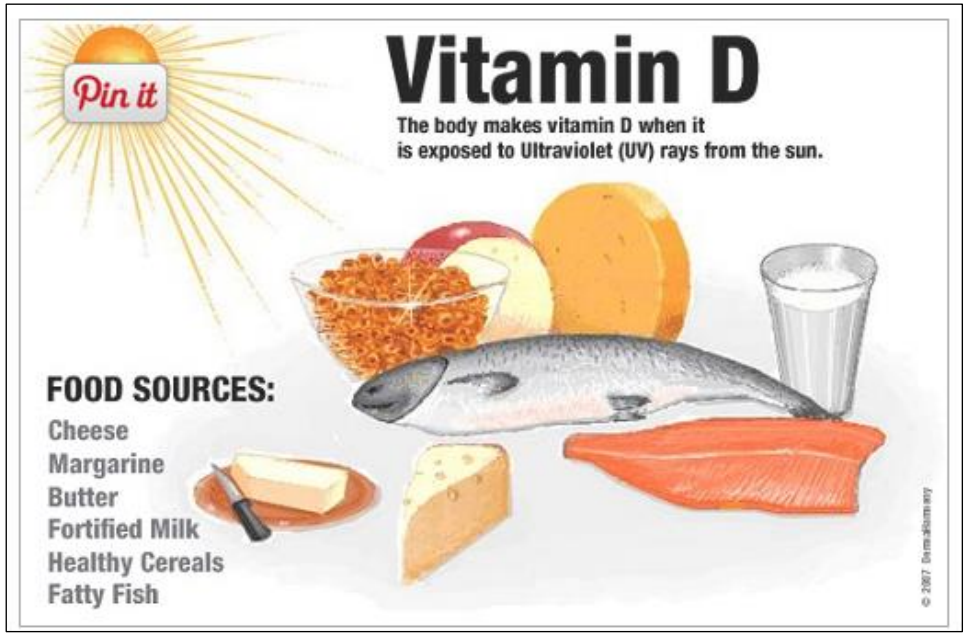
4. The 2nd hydroxylation in **KIDNEY** to form **1,25(OH)D** – active form, ready to interact with VDR present in various organs

Parathyroid gland is an auto-regulation of PTH

Wherever low in Ca2+ / Vit D, 25(OH)D will be hydroxylated by kidney.

Role of Vitamin D

Vitamin D is well recognized as a hormone that affects many of our body's important function.

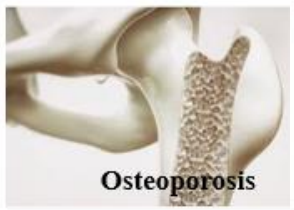


The Essential role of Vitamin D

1. Musculoskeletal

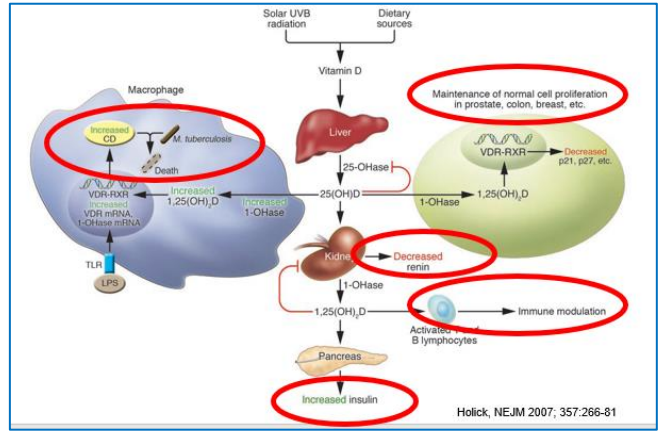
(bone and muscle health)

- To maintain calcium and phosphate homeostasis



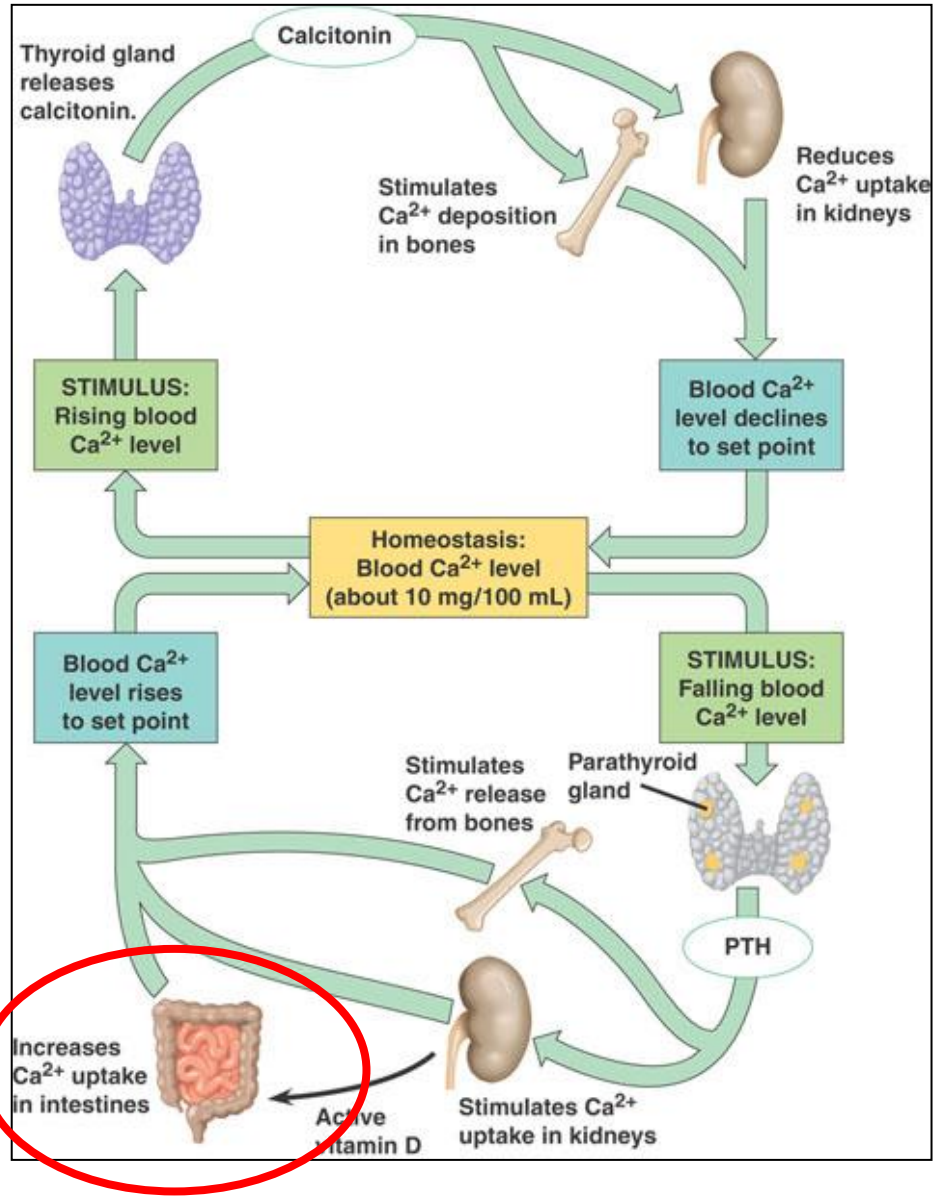
2. Non-skeletal role

- Immunomodulation
- Cellular proliferation
- Cancer prevention
- Hypertension and CVD
- Insulin production



Francesca Ramelli et al. Nutrients. 2019 Dec; 11(12): 2861

Significance of Vitamin D: Skeletal Effects



Vitamin D is essential in:

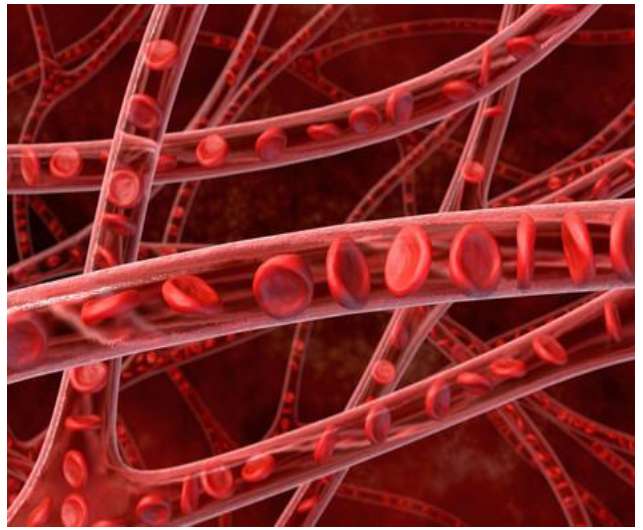
- Promoting calcium and phosphorus absorption in the gut
  - Without vitamin D:
    - **10-15%** of dietary calcium
    - **40-60%** of phosphorus is absorbed
  - **Vitamin D double** the efficiency of intestinal **calcium** and **phosphorus** absorption.
    - **Calcium up to 30-40%**
    - **Phosphorus up to 80%**
- Maintaining adequate circulating serum calcium and phosphate concentrations.

Inter-relation between Vitamin D, Calcium & Bone Health

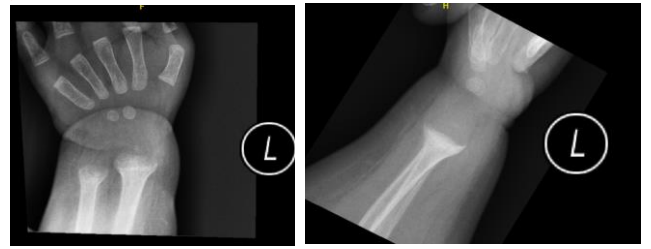
1,25(OH)2 D ↑ absorption of dietary calcium is by 2-4 times

Serum calcium maintained at 2.20-2.62 mmol/L

Bones as reservoir for calcium that provides calcium for bood when serum calcium is low



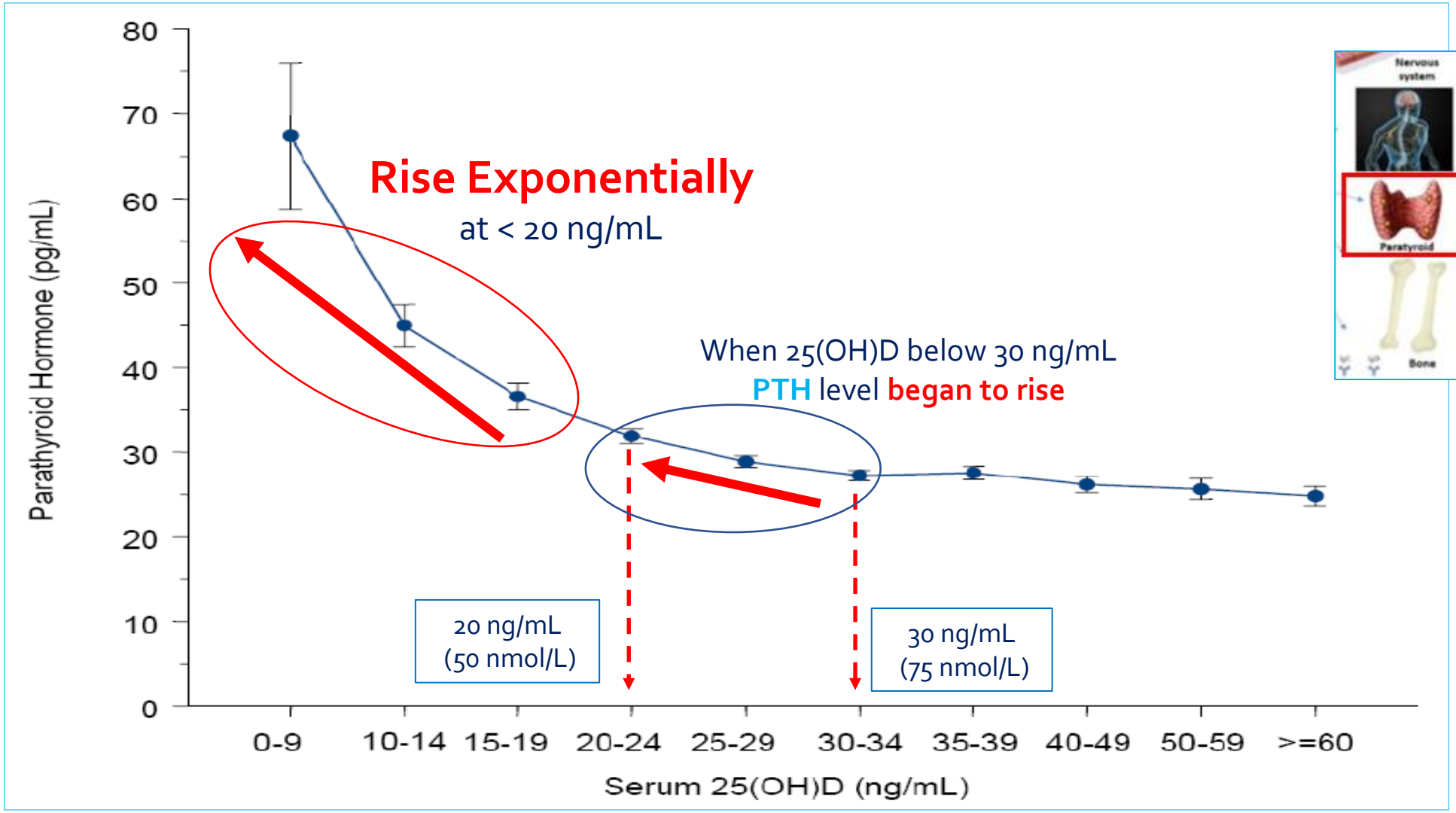
Bone weakness
Rickets / osteomalacia
(softening of bones)

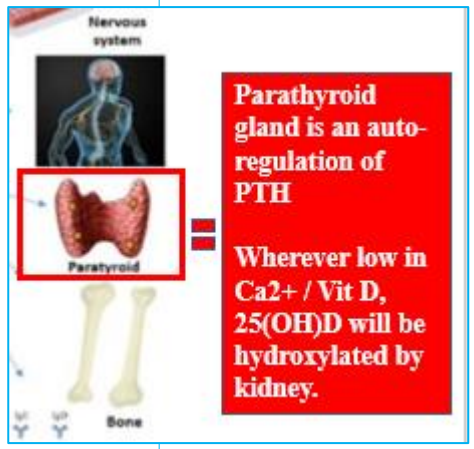


1,25(OH)2D = 1,25-dihydroxyvitamin D (Active Form of Vit D)

Sufficiency = above 30 ng/mL (75 nmol/L)
Insufficiency = between 20 - 30 ng/mL (50-75 nmol/L)
Deficiency = below 20 ng/mL (<50 nmol/L)

The important relationship between PTH and Serum 25(OH)D





Holick MF. *Ann Epidemiol* 2009; 19: 73-8.

Pathophysiology of Vitamin D Deficiency in Bone Health

(Ca^{2+}, calcium; PTH, parathyroid hormone; BMD, bone mineral density; PO4, phosphate)

Vitamin D Deficiency

↓ intestinal absorption of dietary Ca^{2+}

↓ serum Ca^{2+} in blood

Parathyroid gland ↑ PTH production

↑ Ca^{2+} resorption from bones into blood to maintain normal serum Ca^{2+} level

Low BMD

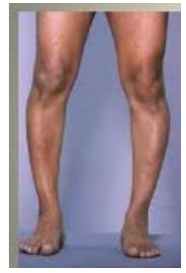
↑ PO4 wasting from kidney

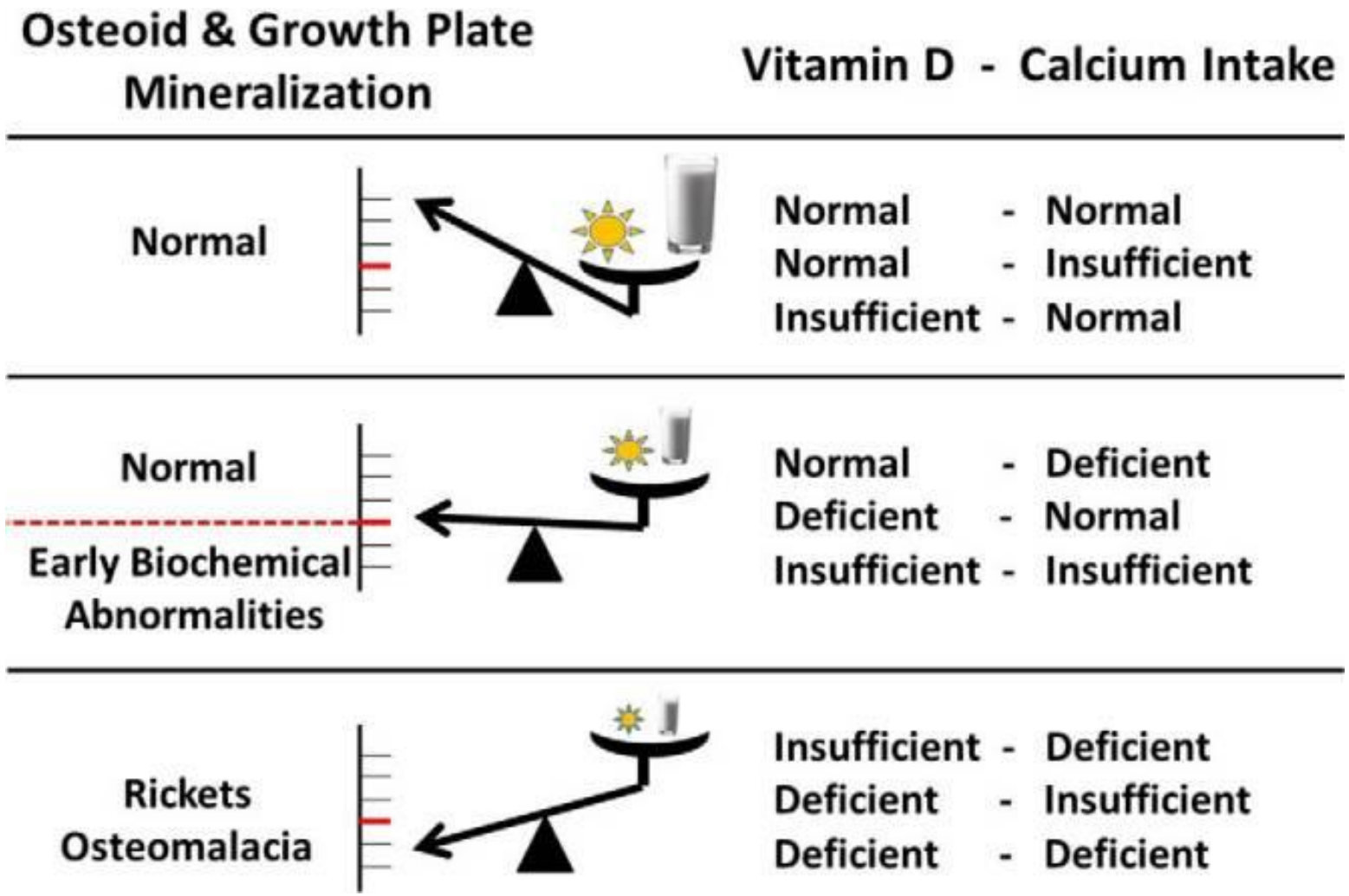
Bone mineralisation defect

Muscle weakness

Falls

Fragile bones that easily fracture or deformed (rickets, osteomalacia, osteoporosis)





Biochemical disturbances in rickets pathogenesis based on a three-stage classification of vitamin D status (symbolized by the sun) and calcium intake (symbolized by a glass of milk).

Högler W. Best Pract Res Clin Endocrinol Metab. 2015;29(3):385–398.(246)

Vitamin D Status

Vit D Status	Vit D Levels (nmol/L)[1]	Vit D Levels (nmol/L)[2]	Vit D Levels (nmol/L)[3]
Severe deficiency	<25	<12.5	-
Deficient	<50	< 37.5	<30
Insufficient	50-75	37.5-50	30-50
Sufficient	75-250	50-250	>50
Preferred	75-150	75-150	-
Toxic	>375	>375	>250

1. Holick M et al. NEJM 2007; 357:266-81
2. Misra M et al. Pediatrics 2008;122;398-417
3. Munns C et al JCEM 2016

These are the Contributing Factors

Why?

Inadequate Sunlight Exposure

Female (due to clothing styles & sunblock lotion)

Dark Skin Tone (high melanin inhibit Vitamin D synthesis)

Obesity

Elderly 70% ↓ in vit. D production

Bariatric Surgery

Where do we usually get Vitamin D?

5 - 30 minutes of sunlight exposure between 10.00am to 3.00pm at least twice a week

FUN FACT

Using sunscreen with SPF30 **reduces Vitamin D synthesis in the skin** by **more than 95%**

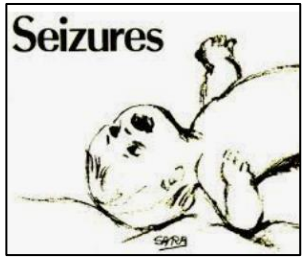
Michael F. Holick, N. C.-F. (2011). Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 20.

Children might be at risk of Vitamin D Deficiency if they

- Low sunlight exposure
- Inadequate dietary intake of **Vitamin D**
- Spend more time indoor
- Overweight / darker skin tone
- Cultural factors - clothing practices

Implication of Low Vitamin D

During Infancy → **Hypocalcemia seizure** → **Rickets** → **Gross motor delay**



Early Childhood* (*potential development of) → **Type I diabetes** → **Multiple sclerosis** → **Allergies** → **Respiratory tract infection**

Table 2. Recent Pediatric Recommendations of Vitamin D Intake

Maintenance Vitamin D Doses

Age	AAP and PES	IOM		Endocrine Society for Patients at Risk for Vitamin D Deficiency[b]		EFSA and ESPGHAN[d]	
	Daily Requirement, IU[a]	Recommended Dietary Allowance, IU	Upper Level Intake, IU	Daily Requirement, IU	Upper Level Intake, IU	Recommended Daily Supplementation, IU	Upper Level Intake, IU
0–6 mo	400	[c]	1000	400–1000	2000	400	1000
6–12 mo	400	[c]	1500	400–1000	2000	400	1000
1–3 y	400	600	2500	600–1000	4000	None	2000
4–8 y	400	600	3000	600–1000	4000	None	2000
9–10 y	400	600	4000	600–1000	4000	None	2000
11–18 y	400	600	4000	600–1000	4000	None	4000

Treatment of vitamin D deficiency or insufficiency

Age	PES	Endocrine Society[b]
0–1 mo	1000 IU/d for 2–4 wk	2000 IU/d or 50 000 IU/wk for 6 wk
1–12 mo	1000–5000 IU/d for 2–4 wk	
>12 mo	>5000 IU/d for 2–4 wk	

Abbreviations: AAP, American Academy of Pediatrics; PES, Pediatric Endocrine Society; IOM, Institute of Medicine; EFSA, European Food Safety Authority; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

Ministry of Health Malaysia

RNI

RECOMMENDED NUTRIENT INTAKES *for* MALAYSIA

National Coordinating Committee on Food and Nutrition
Ministry of Health Malaysia
2017

0 - 12 months
400 IU per day

1 - 9 Years
600 IU per day

Not achieveing RNI
(0.5 – 12.9 years)

Vit D: 94.8%

1mg = 40IU

Appendix 14.2. Comparison of recommended intake for Vitamin D: RNI Malaysia (2017), RNI Malaysia (2005), and IOM (2011)

Malaysia (2017)		Malaysia (2005)		IOM (2011)	
Age group	RNI (µg/day)	Age group	RNI (µg/day)	Age group	RNI (µg/day)
Infants		**Infants**		**Infants**	
0 - 6 months	10	0 - 5 months	5	0 - 6 months	10
7 - 12 months	10	6 - 12 months	5	7 - 12 months	10
Children		**Children**		**Children**	
1 - 3 years	15	1 - 3 years	5	1 - 3 years	15
4 - 6 years	15	4 - 6 years	5	4 - 8 years	15
7 - 9 years	15	7 - 9 years	5		
Boys		**Boys**		**Boys**	
10 - 18 years	15	10 - 18 years	5	9 - 13 years	15
		-		14 - 18 years	15
		-			
Girls		**Girls**		**Girls**	
10 - 18 years	15	10 - 18 years	5	9 - 13 years	15
	-			14 - 18 years	15
	-				-
Men		**Men**		**Men**	
19 - 50 years	15	19 - 65 years	5	19 - 30 years	15
51 - 65 years	15	51 - 65 years	10	31 - 50 years	15
> 65 years	20	> 65 years	15	51 - 70 years	15
				> 70 years	20

Poh BK, Wong JE, Lee ST, Chia JSM, Yeo GS, Sharif R, et al. SEANUTS II Malaysia. Public Health Nutrition. 2023;1–36. doi:10.1017/S1368980023002239

Can we get sufficient amount of vitamin D from diet?

Source	Vitamin D content IU = 25 nanograms
Natural sources	
Salmon, fresh wild caught	~600-1000 IU/100 g vitamin D_3
Salmon, fresh farmed	~100-250 IU/100 g vitamin D_3, vitamin D_2
Salmon, canned	~300-600 IU/100 g vitamin D_3
Sardines, canned	~300 IU/100 g vitamin D_3
Mackerel, canned	~250 IU/100 g vitamin D_3
Tuna, canned	236 IU/100 g vitamin D_3
Cod liver oil	~400-1000 IU/5 mL vitamin D_3
Shiitake mushrooms, fresh	~100 IU/100 g vitamin D_2
Shiitake mushrooms, sun dried	~1600 IU/100 g vitamin D_2
Egg yolk	~20 IU/yolk vitamin D_3 or D_2

100g of fresh salmon

600-1000 IU Vit. D3

14g of sun dried shiitake mushroom

7 packets → 1600 IU Vit. D3

500 IU Vitamin D_3
is equivalent to

=

Cheese slice (35 IU)

Salmon (600 to 1,000 IU)

Egg yolk (20 IU)

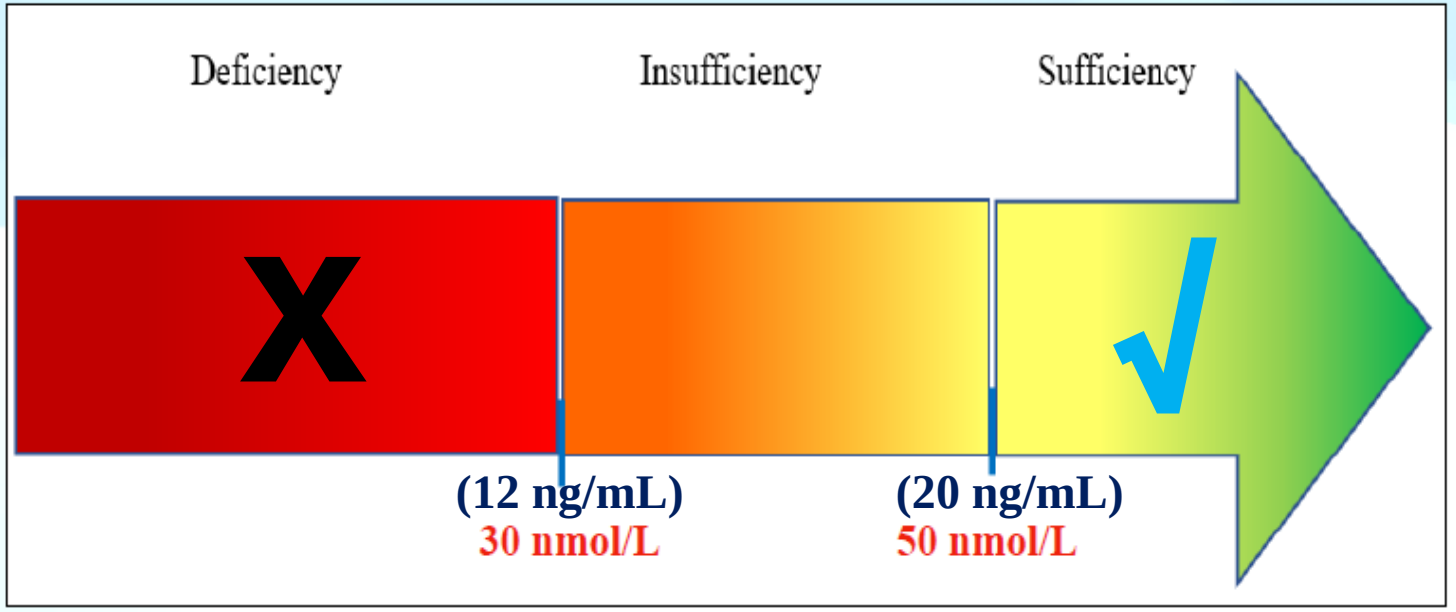
Fortified milk (100 IU)

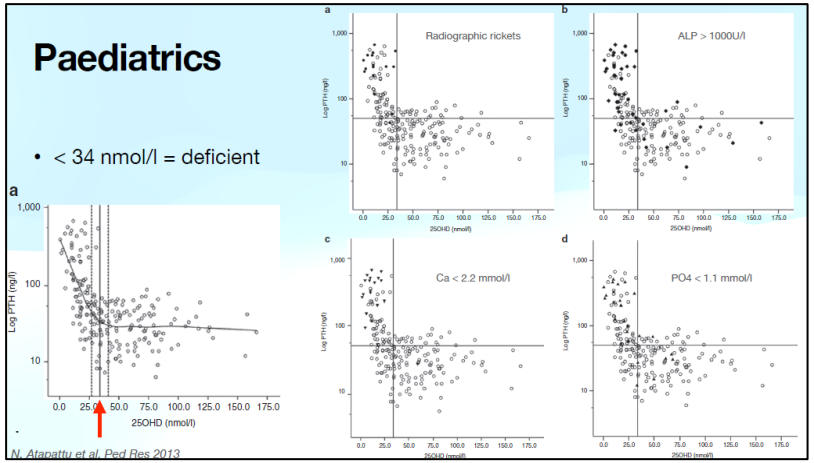
Michael F. Holick, N. C.-F. (2011). Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 20.

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets – JCEM 2016

Global Consensus Recommendations on Prevention and Management of Nutritional Rickets

Craig F. Munns, Nick Shaw, Mairead Kiely, Bonny L. Specker, Tom D. Thacher, Keiichi Ozono, Toshimi Michigami, Dov Tiosano, M. Zulf Mughal, Outi Mäkitie, Lorna Ramos-Abad, Leanne Ward, Linda A. DiMeglio, Navoda Atapattu, Hamilton Cassinelli, Christian Braegger, John M. Pettifor, Anju Seth, Hafsatu Wasagu Idris, Vijayalakshmi Bhatia, Junfen Fu, Gail Goldberg, Lars Sävendahl, Rajesh Khadgawat, Pawel Pludowski, Jane Maddock, Elina Hyppönen, Abiola Oduwole, Emma Frew, Magda Aguiar, Ted Tulchinsky, Gary Butler, and Wolfgang Högler*

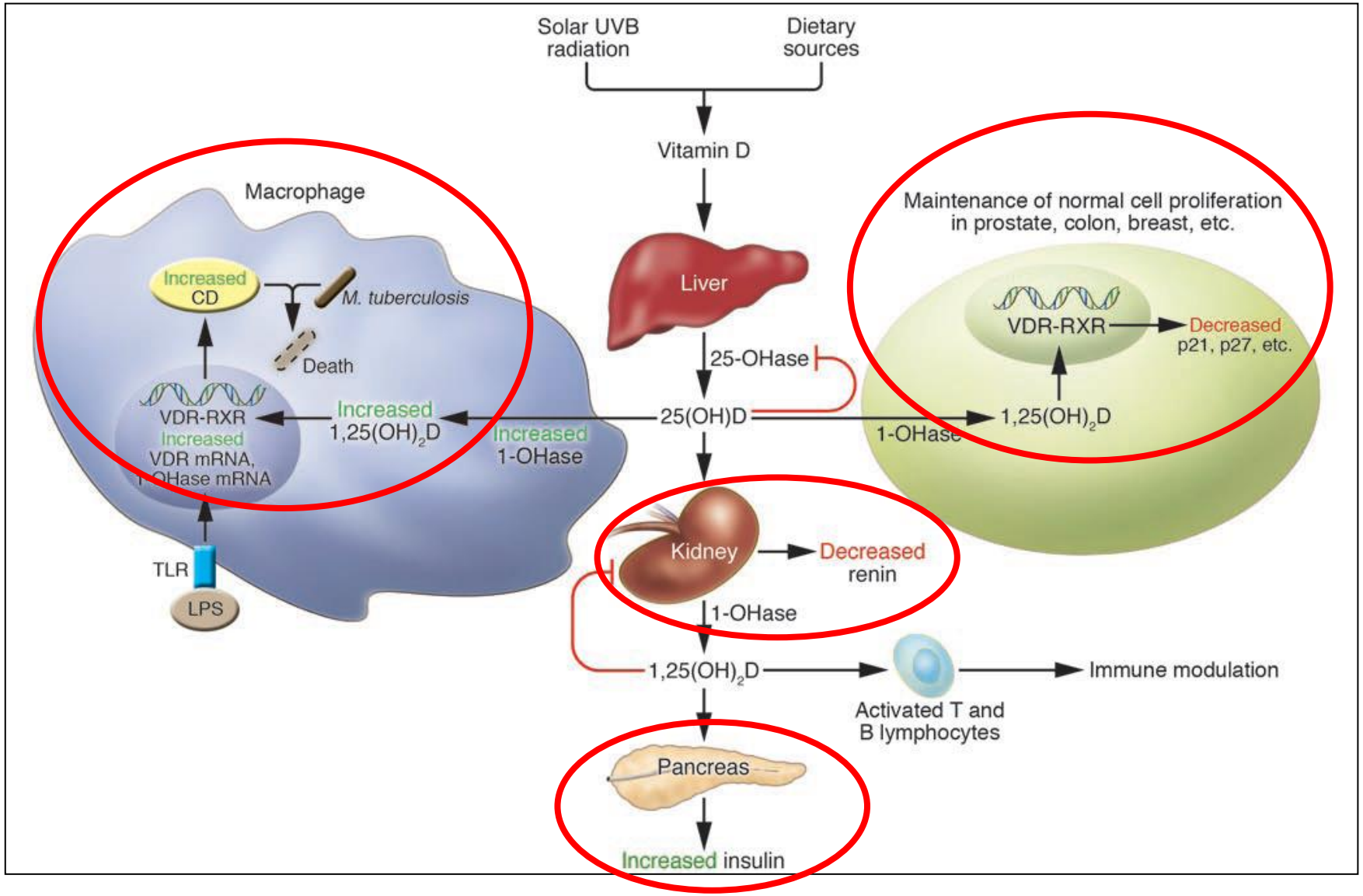




Toxicity :
>250 nmol/L
(100ng/mL)

C.F. Munns et al, JCEM 2016

Vitamin D: Non-Skeletal Roles



Vitamin D Effects

1. Immunomodulation
2. Cellular proliferation
3. Cancer prevention
4. Hypertension & CVD
5. Insulin production

Holick, NEJM 2007; 357:266-81

nutrients

MDPI

Systematic Review

Preventive Vitamin D Supplementation and Risk for COVID-19 Infection: A Systematic Review and Meta-Analysis

Marina Sartini [1,2,*,†], Filippo Del Puente [3,*,†], Martino Oliva [1], Alessio Carbone [1], Nicoletta Bobbio [3], Elisa Schinca [1,2], Luana Giribone [1] and Maria Luisa Cristina [1,2]

Vitamin D supplementation has a protective effect against:

1. the incidence of COVID-19 in RCT studies (OR 0.403, 95% IC 0.218, 0.747)
2. the incidence of COVID-19 in analytical studies (OR = 0.592, 95% IC 0.476–0.736) and
3. in ICU admission (OR 0.317, 95% IC 0.147–0.680).

The doses of vitamin D (cholecalciferol) administered as:

1. IU/daily were 5000, 4000, 3200, <1000 and 400;
2. IU/weekly were 50,000 and 5600;
3. IU/monthly were 100,000, 90,000, 80,000, 52,000, 50,000, 25,000 and 10,000.

Meta-analysis suggests a definitive and significant association between the protective role of vitamin D and COVID-19 **incidence and ICU admission**.

Sartini M et al, Nutrients Feb 2024

Conclusions

- Two types of Vitamin D: Vitamin D3 and D2
  - (D3 is more potent and effective than D2)
- Two main sources of Vitamin D
  - Sun (UVB 280-320 nm)
  - Food (animal or plant).
- Vitamin D undergoes 2 hydroxylation in the liver and kidney to form active Vitamin D (1,25(OH)2 Vit D).
- 1,25(OH)2 Vit D doubles the absorption of calcium and phosphates.
- Various levels used as cut-off values for Vitamin D Deficiency.
- Risk factors: low sun exposure, inadequate dietary intake.
- Malaysia RNI: 400 unit for infants, 600 unit for children and adults.