Vitamin D and Diseases

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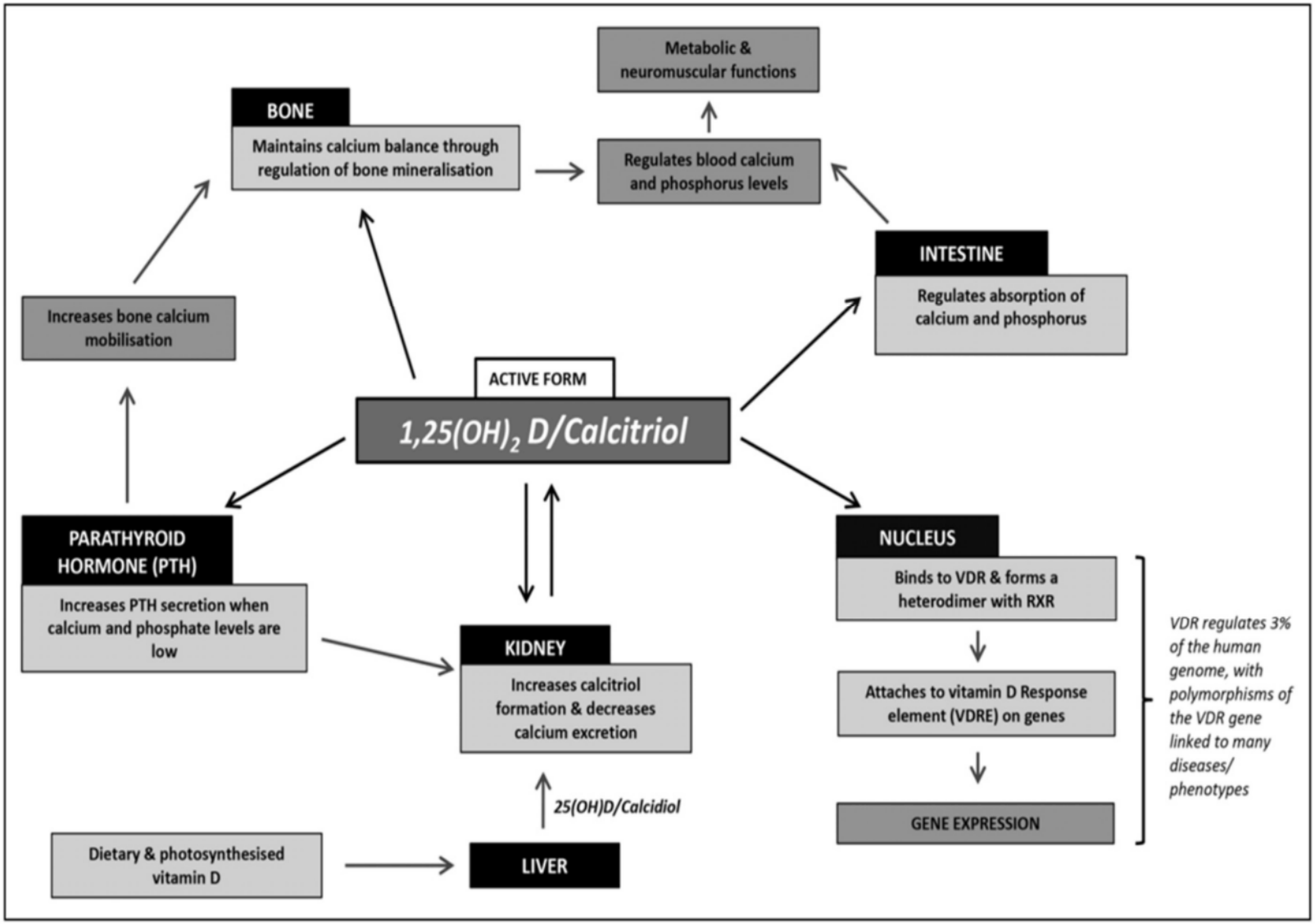
- The first proof of the existence of vitamin D was demonstrated by **Elmer McCollum in 1922** who discovered that cod liver oil was efficacious in preventing rickets in children.
- Nobel Prize awardee in **1928, Adolf Windousin** had this honor for the discovery of vitamin D hormone.
- Vitamin D deficiency has been associated with serious consequences, including an increased risk of common cancers and autoimmune, infectious, and cardiovascular diseases (CVDs).
- Vitamin D – also known as the 'sunshine vitamin' is an extremely important vitamin that serves many important bodily functions, like absorption of calcium and phosphorous, and ensuring a healthy immune system.

- Low vitamin D levels have become an epidemic across the continent irrespective of amount of sunshine during different seasons.
- The epidemiological studies estimate that currently at least 1 billion people suffer from low vitamin D levels.
- In spite of our ability to synthesize vitamin D3, majority of the population requires additional amounts through our diet or health supplements to maintain the optimum levels that are relevant to chemopreventive or therapeutic in nature.
- Vitamin D3 is physiologically converted into its active form called 1α,25-dihydroxyvitamin D3 [1α,25(OH)2D3 or calcitriol] which is responsible for binding to VDR and exerting its critical functions.
- Because vitamin D is not active in its native form and a specific receptor is present for its functions, it is also referred as a prohormone rather than a vitamin.

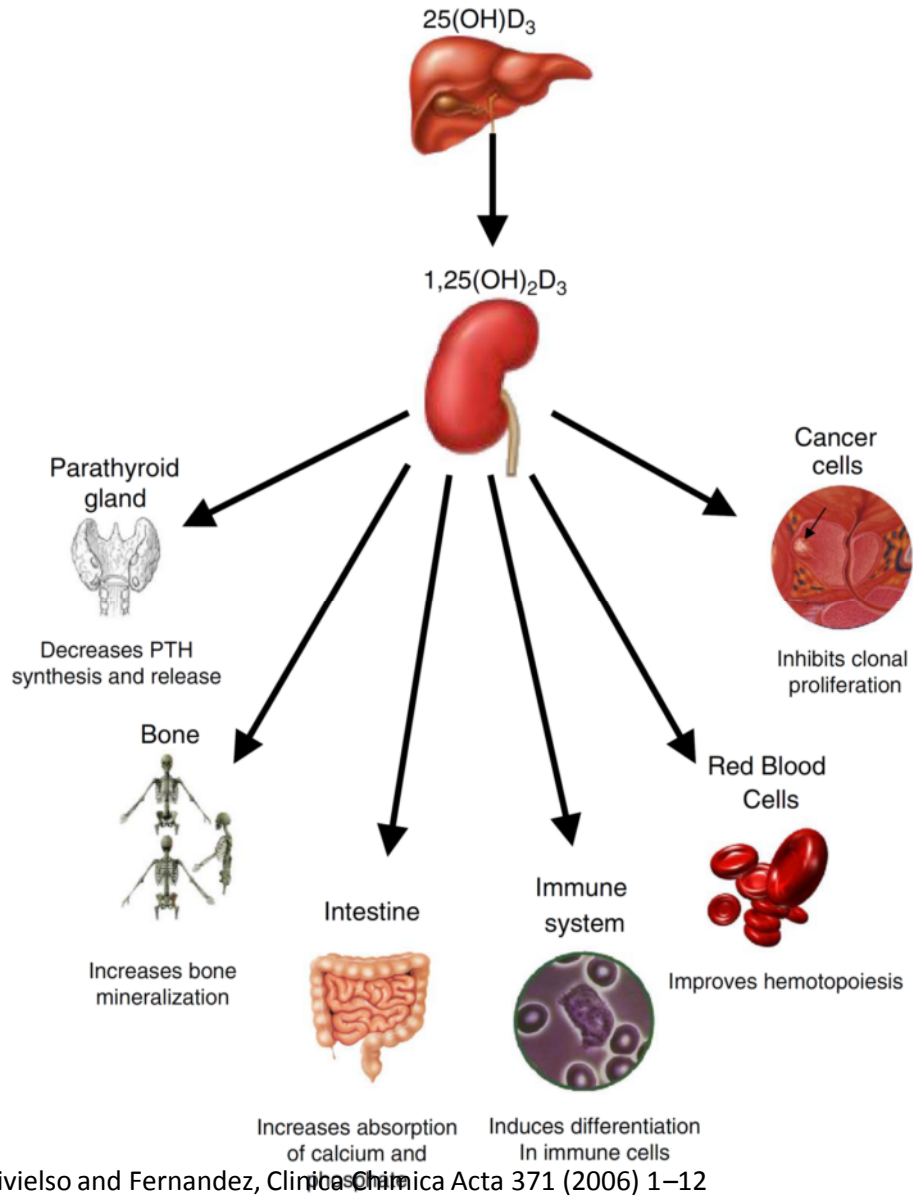
Sakharkar et alJ Basic Clin Pharma 2017;8:S06-S10.

Simple overview of the vitamin D endocrine system



Lucock et al., Journal of Evidence-Based Complementary & Alternative Medicine 2015, 20,310-322.

Effects of vitamin D on target cells



Valdivielso and Fernandez, Clinica Chimica Acta 371 (2006) 1–12

Deficiency symptoms

1. Muscle weakness or spasm
2. Body pain
3. Pain in muscle or bones
4. Not able to climb stairs or getting up from the floor
5. Stress fractures
6. Tiredness
7. High blood pressure
8. Feeling depressed
9. Weight gain
10. Head sweating
11. Gut trouble

Benefits of Vitamin D

- Vitamin D – also known as the ‘sunshine vitamin’ is an extremely important vitamin that serves many important bodily functions, like absorption of calcium and phosphorous, and ensuring a healthy immune system.

Synthesis of Vitamin D

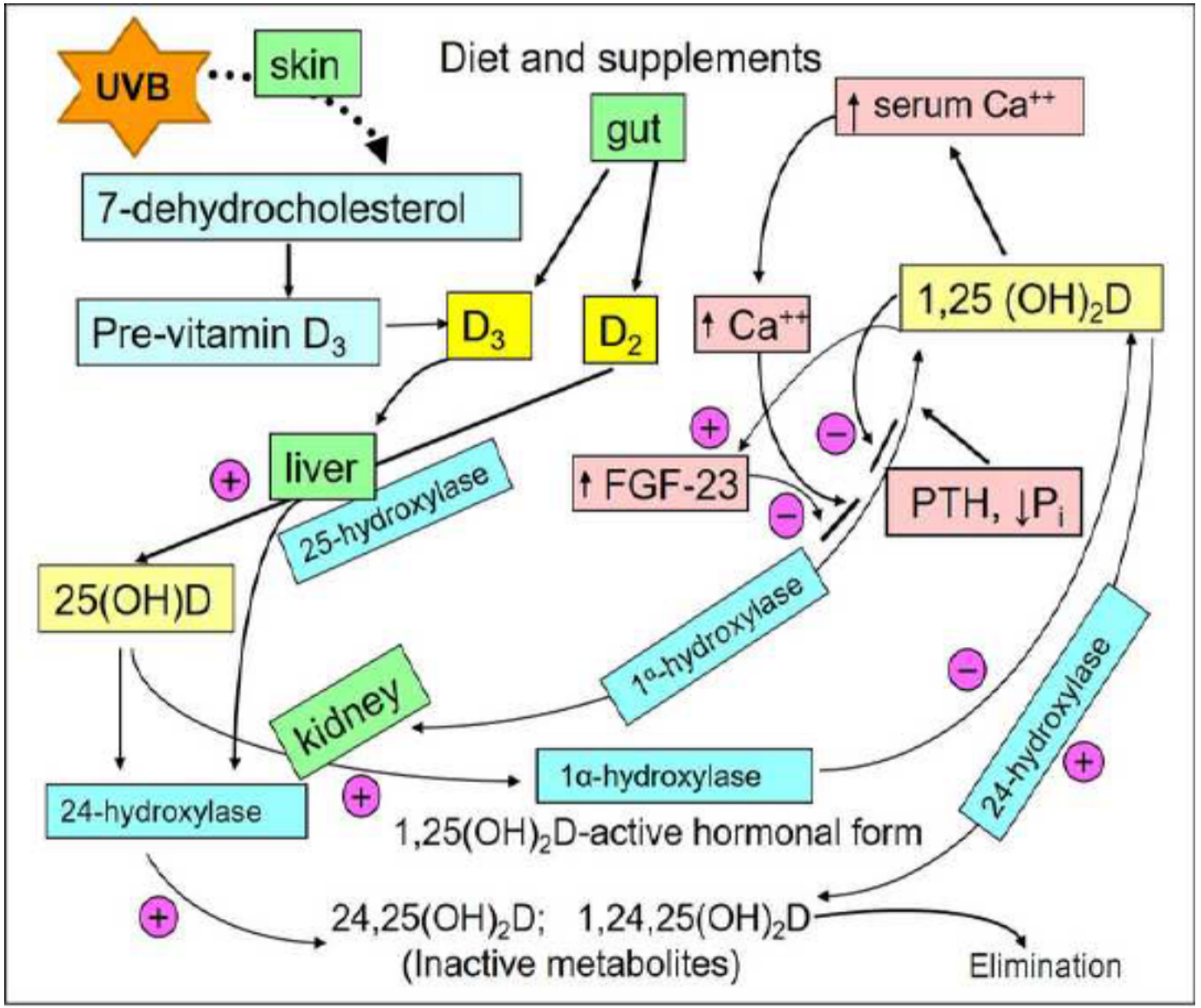
Pre-vitamin D in the skin is synthesized from the precursor 7-dehydrocholesterol,followingskin exposure to UVB.

Pre-vitamin D together with the vitamin D absorbed via the gastrointestinal tract are transported to the liver, where 25-hydroxylase enzyme (CYP24A1) converts it to 25(OH)D, the body's storage form of vitamin D.

1α- hydroxylase enzyme (CYP27B1) is predominantly located in renal tubules (also present in other cells, such as in macrophage); converts 25(OH)D into its active hormonal form, **1,25(OH)D**.

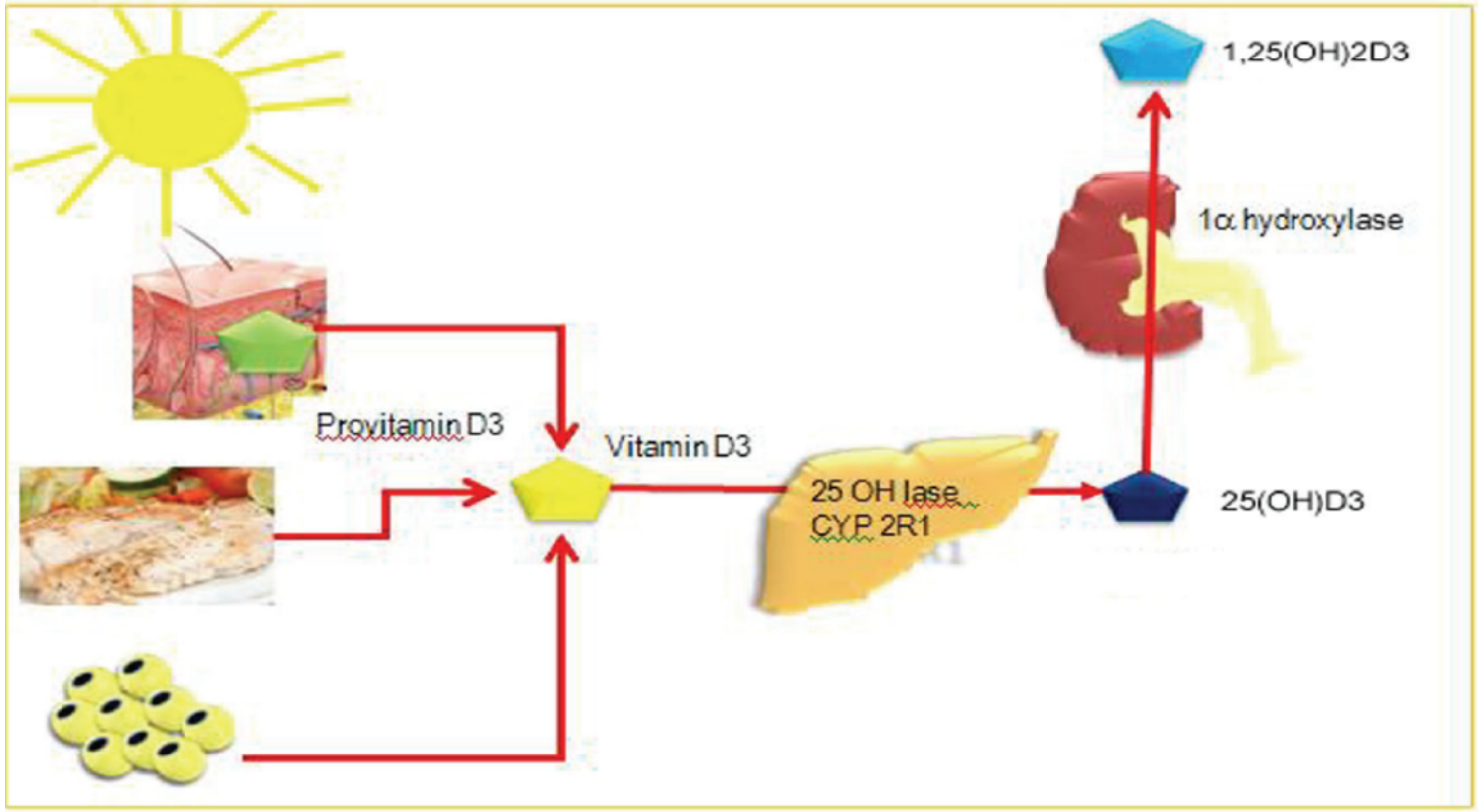
Any excess vitamin D is converted to an inactive metabolite through 24-hydroxylation.

Wimalawansa, *Journal of Steroid Biochemistry & Molecular Biology,2016*



Wimalawansa, Journal of Steroid Biochemistry & Molecular Biology,2016

Synthesis of Vitamin D



Synthesis and metabolism of vitamin D. Vitamin D can be obtained from food (vitamin D2 and D3) or by photobiogenesis in the skin (vitamin D3). In the blood, all vitamin D metabolites are bound to vitamin D-binding protein (DBP). Vitamin D3 is converted by two successive hydroxylations in the liver (25-hydroxylases) and kidney (1α-hydroxylase) into its active hormonal form, 1,25(OH)2D3.

Seshadri et al., Endocrinol Metab,2011;1(2):47-56

The epidemiological studies estimate that more than 1 billion people suffer from low vitamin D levels.

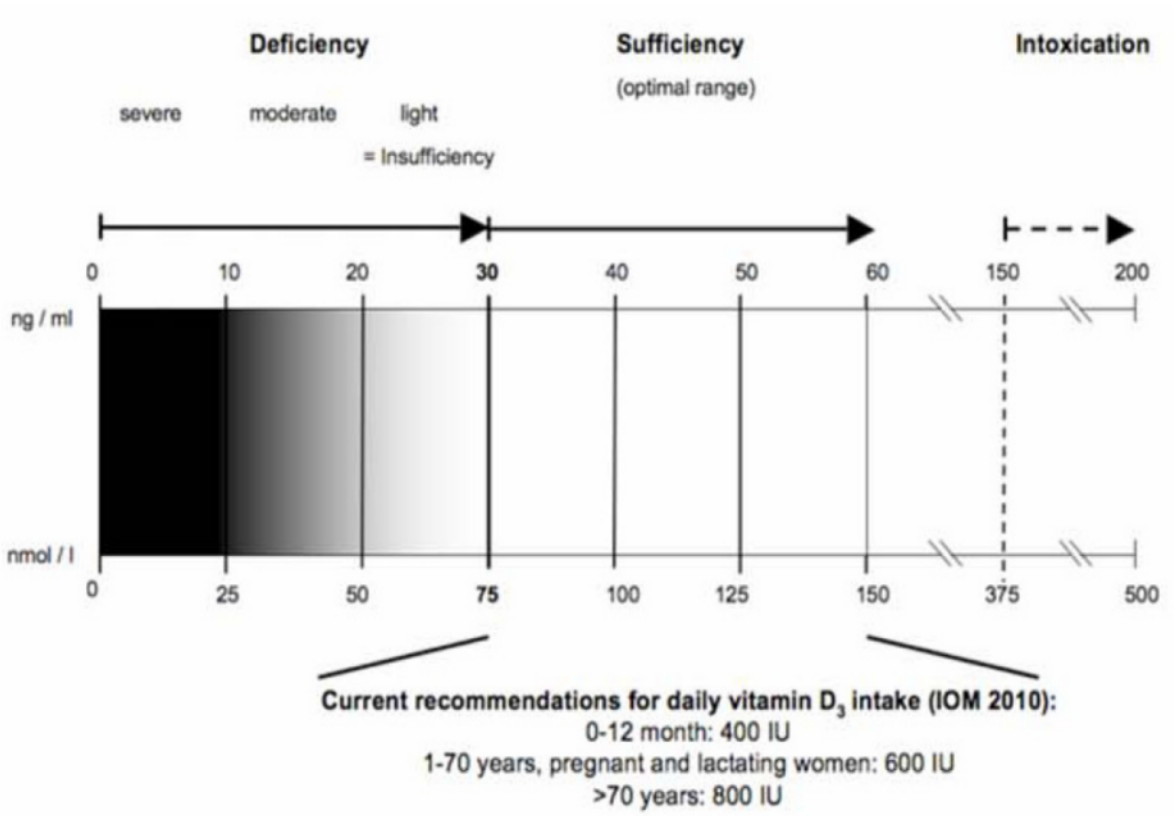


Figure 2 Classification of vitamin D status and recommendations for substitution.

Grundmann and von Versen-Höynck Reproductive Biology and Endocrinology 2011, 9:146

Vitamin D in Health

Humans obtain vitamin D in two forms; vitamin D2 (ergocalciferol, derived from plant ergosterols) and vitamin D3 (cholecalciferol), which differ in the number/location of double carbon–carbon bonds.

Vitamin D2 has only two C=C bonds, whilst vitamin D3 has three, affording D2 a lower affinity for vitamin D-binding protein (DBP), increasing clearance and reduced bioavailability; thus, **vitamin D3 is the main form of vitamin D used by humans**.

Generation of active, hormonal, vitamin D3 involves a series of non-enzymatic and enzymatic processes.

Firstly, **7-dehydrocholesterol** is converted to **vitamin D3** when exposed to UVB light in the dermis.

Vitamin D3 is then converted to **25-hydroxycholecalciferol(25-OHD3)** by the enzyme 25-hydroxylase (CYP2R1) located predominantly in the live.

Harrison et al.,Calcified Tissue International (2020) 106:58 –75.

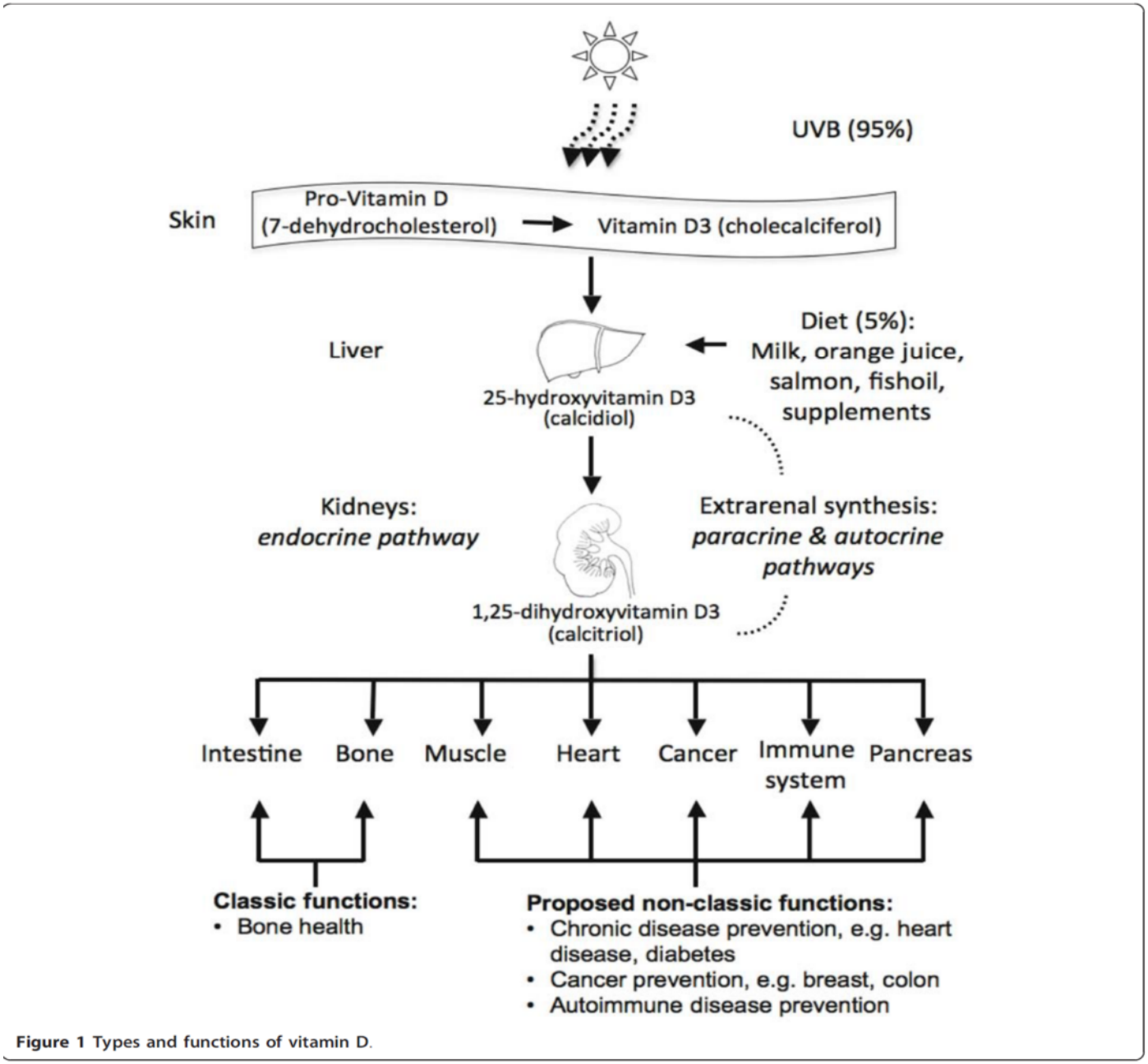
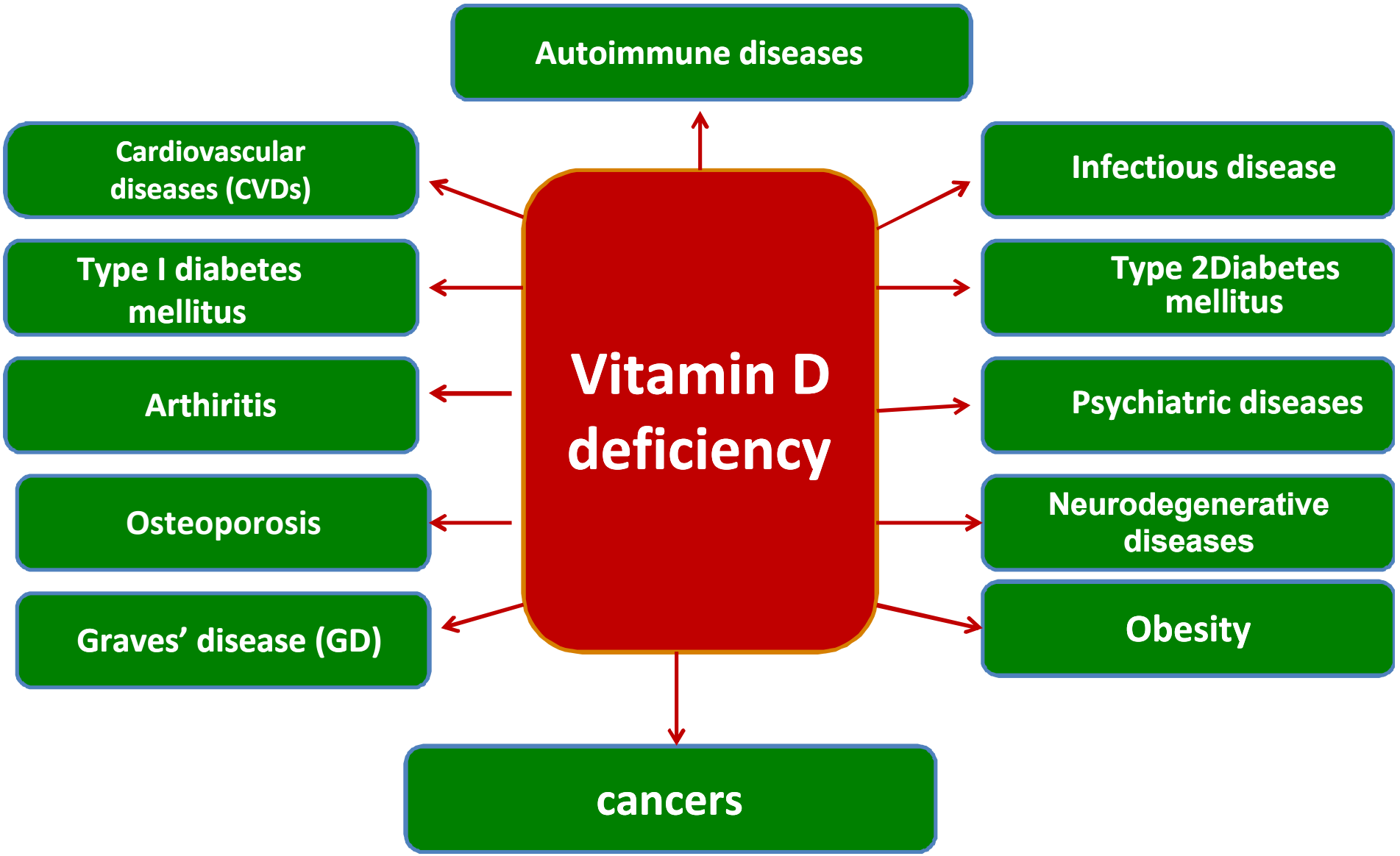


Figure 1 Types and functions of vitamin D.

Grundmann and von Versen-Höynck Reproductive Biology and Endocrinology 2011, 9:146

Vitamin D in Health

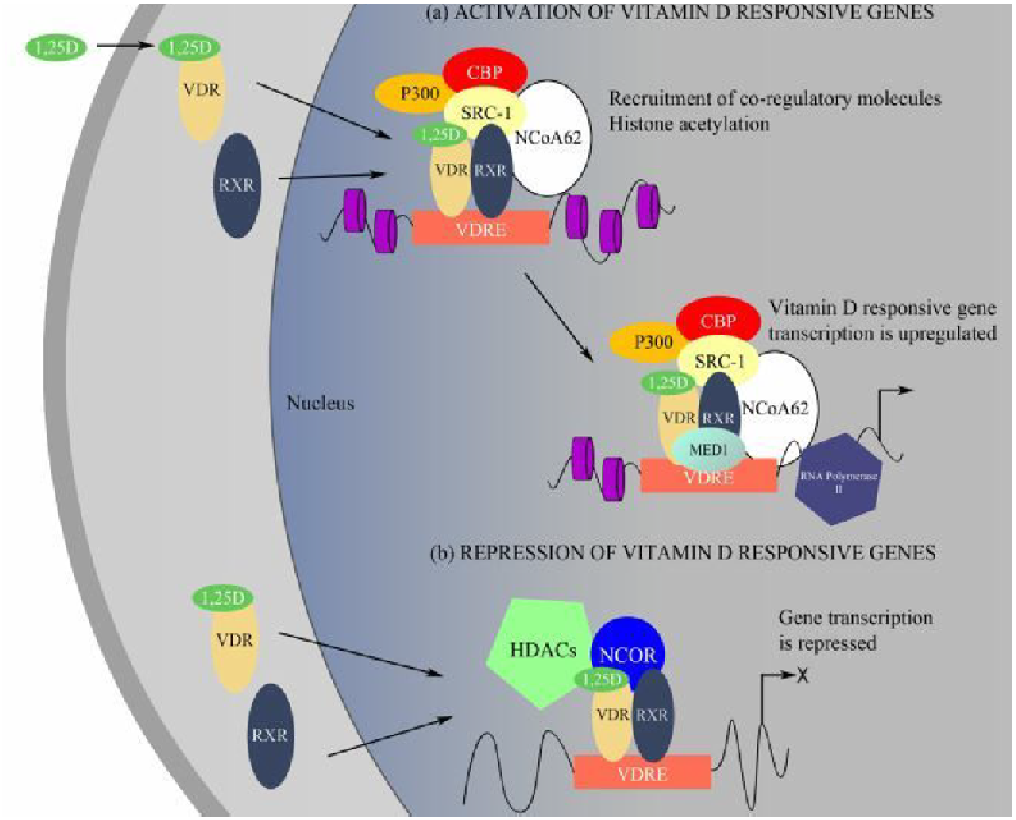


Vitamin D deficiency

- Vitamin D deficiency has been associated with other serious consequences, including an increased risk of common cancers and autoimmune, infectious, and cardiovascular diseases (CVDs).
- Vitamin D deficiency is also associated with higher circulating concentrations of the inflammatogenic matrix metalloproteinase-9.
- The paracrine and autocrine biological activities of vitamin D are exerted by binding to its intracellular receptor known as vitamin D receptor (VDR).

- 7-Dehydrocholesterol undergoes specific alterations in the skin, liver and kidney. As a result calcitriol is formed and enters the cell cytosol through specific channels together with vitamin D receptor (VDR).
- After heterodimerization, the complex enters the nucleus and as a result, a multi-component complex is formed (phosphorylated calcitriol-VDR complex, retinol X receptor, 9cRa transcription factor) which subsequently binds to DNA. In the presence of HDAC complexes and other transcription factors, CYP27B1 gene responsible for parathormone production is repressed.
- However, in the presence of PBA/SWI/SNF complex other compounds are added (regulators of interaction, transcriptional factor IIB and most important of all, RNA polymerase II).
- As a consequence, CYP27B1 transcription occurs. The protein encoded by this gene localizes to the inner mitochondrial membrane where it hydroxylates 25-hydroxyvitamin D3 at the 1α position. This reaction synthesizes 1α,25-dihydroxyvitamin D3, the active form of vitamin D3, which binds to the VDR.

Khan et al., International Journal Of Oncology 44: 349-363, 2014



Ryan et al.,Clin Biochem Rev. 2015 May; 36(2): 53–61.

Effects of Vitamin D in the intestine

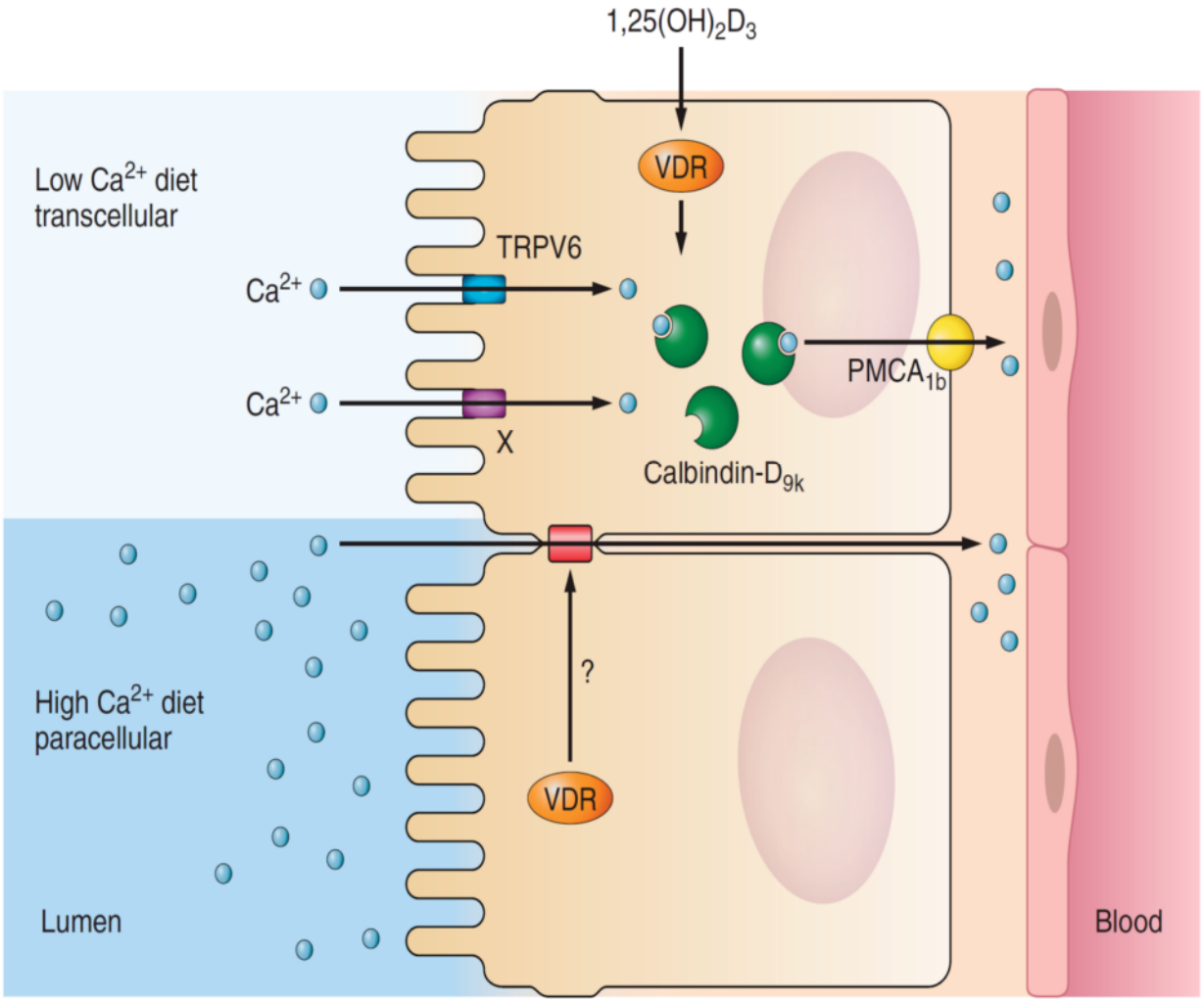
Effects of 1,25(OH)2D3 in the intestine. An important function of 1,25(OH)2D3 is the stimulation of transcellular intestinal calcium transport by increasing the expression of the apical membrane calcium channel TRPV6 and calcium binding protein calbindin-D9k.

The extrusion of calcium is across the basolateral membrane by PMCA1b. This process is especially enhanced when dietary calcium intake is low.

Mouse genetic studies however suggest that other calcium transporters (X) are likely involved.

When calcium intake is high, the paracellular calcium transport prevails, but studies suggest that this pathway may also be regulated by 1,25(OH)2D3.

Christakos et al.,*Physiol Rev 96: 365–408, 2016*



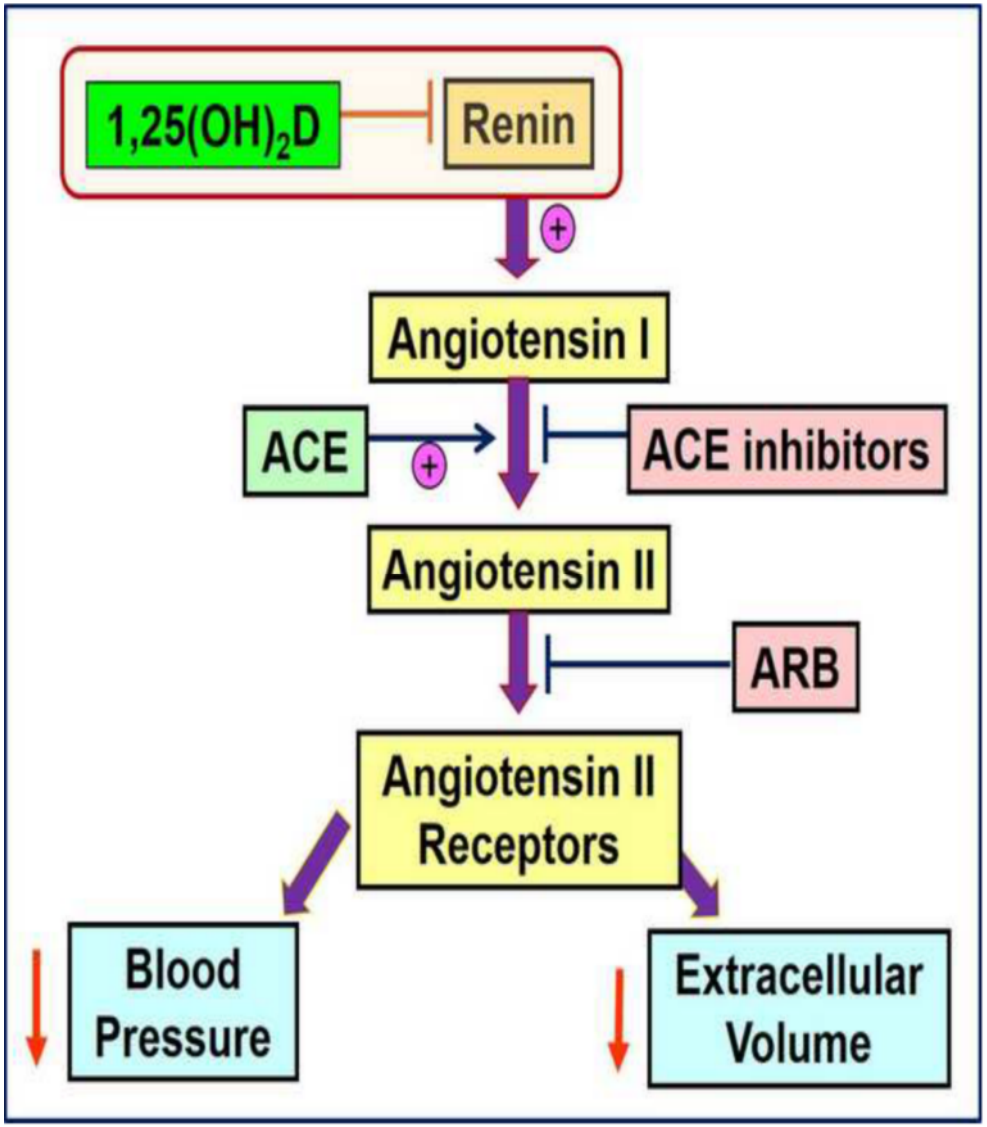
Christakos et al.,Physiol Rev 96: 365–408, 2016

Metabolic syndrome

- Metabolic syndrome is a cluster of conditions such as high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels that occur together thereby increasing the risk of developing cardiovascular disease and type 2 diabetes mellitus (T2DM).

Vitamin D deficiency and CVD risk

Physiological levels of vitamin D, decrease blood pressure and improve vascular functions: Interactions of vitamin D metabolite with the renin–angiotensin system (RAS), leading to control of blood pressure and intravascular volume distributions



Wimalawansa, *Journal of Steroid Biochemistry & Molecular Biology,2016*

Vitamin D and Type 2 Diabetes

- Type 2 diabetes is characterized by insulin resistance and altered insulin secretion.
- The role of vitamin D in type 2 diabetes is suggested by a seasonal variation in glycemic control reported in patients with type 2 diabetes being worse in the winter , which may be due to prevalent hypovitaminosis D as a result of reduced sunlight in winter.
- Several studies have demonstrated a link between vitamin D and the incidence of type 2 diabetes.

Vitamin D and the beta-cell

There are several lines of evidence supporting a role for vitamin D in pancreatic beta-cell function .

I.A high prevalence of hypovitaminosis D was noted among women with type 2 diabetes.

II.Hyper responsive insulin secretion after a glucose challenge has been found in older men with hypovitaminosis D.

III.Vitamin D may act in two possible pathways; vitamin D may act directly to induce beta-cell insulin secretion by increasing the intracellular calcium concentration via non-selective voltage-dependent calcium channels or it may

Insulin resistance

- Insulin resistance is a recognized precursor for the development of type 2 diabetes. Vitamin D may have a beneficial effect on insulin action either directly, by stimulating the expression of insulin receptors thereby enhancing insulin responsiveness for glucose transport, or indirectly via its role in regulating extracellular calcium ensuring normal calcium influx through cell membranes and adequate intracellular cytosolic calcium [Ca2+]i pool.
- Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue with a very narrow range of [Ca2+]i needed for optimal insulin-mediated functions.

Inflammation

Type 2 Diabetes is associated with systemic inflammation.

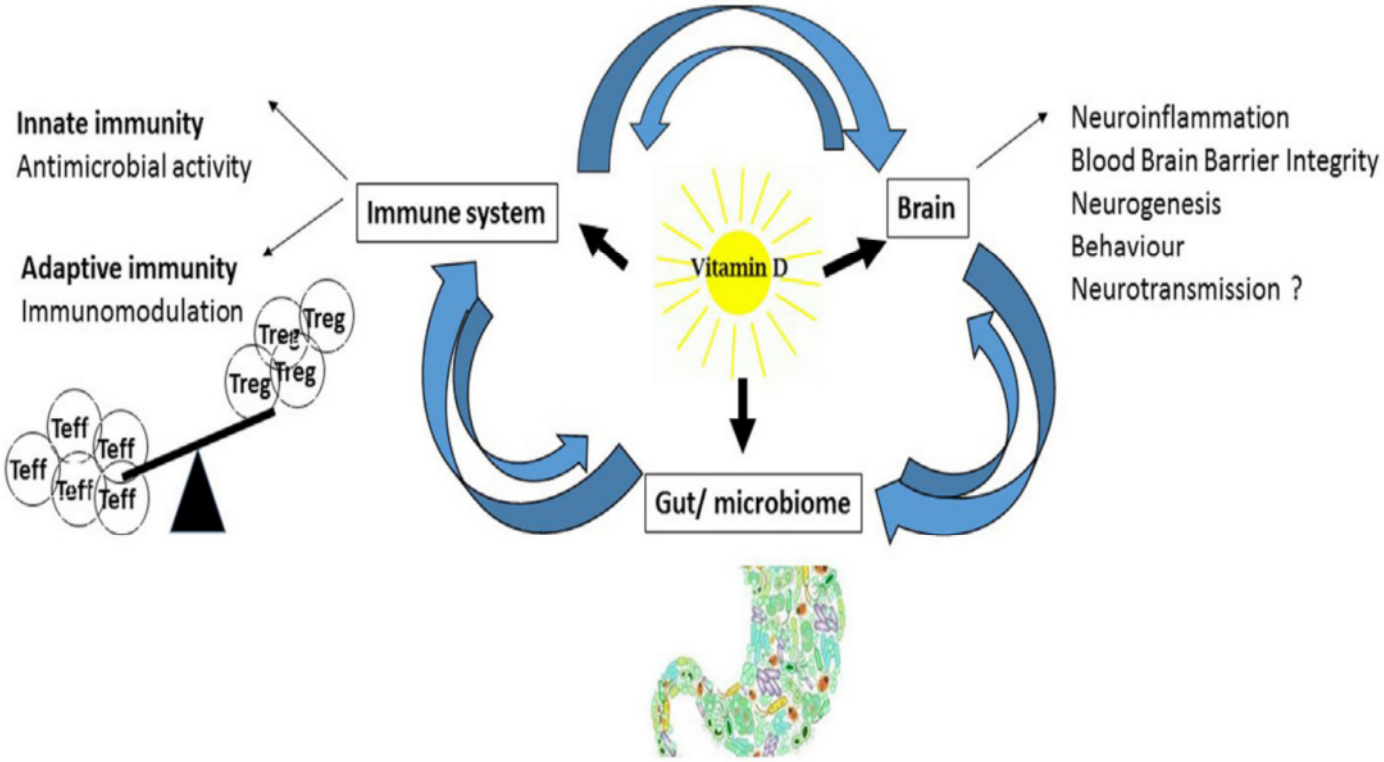
- Systemic inflammation has been linked primarily to insulin resistance but elevated cytokines may also play a role in beta-cell dysfunction by triggering beta-cell apoptosis.
- Vitamin D may improve insulin sensitivity and promote beta-cell survival by directly modulating the generation and effects of cytokines.

Seshadri et al., Endocrinol Metab,2011;1(2):47-56

Involvement of Vitamin D in brain health and diseases

- Eyles et.al have meticulously reported the evidence that vitamin D differentiates brain cells, regulates axonal growth and calcium signaling directly in the brain, modulates the production of brain-derived reactive oxygen species and stimulates the production of neurotrophic factors which are relevant to the variety of neuropsychiatric conditions and also neurodegenerative disorders.
- Vitamin D is widely recognized to play a crucial role in the nervous system health and disease conditions.
- Vitamin D contributes to neurotrophic support, neurotransmission, neuroprotection, and neuroplasticity.
- **Neurotrophic:** The neurotrophic role of vitamin D was first demonstrated from in vitro studies which indicated that vitamin D3 is involved in the synthesis of nerve growth factor (NGF).
- In an experiment where vitamin D was added to the cultured embryonic hippocampal cells enhanced neurite outgrowth and NGF production were observed.

Sampat, et al., Int J Nutrition, Pharmacology, Neurological Diseases, 9, 2019.



Effects of vitamin-D: schematic diagram of vitamin-D effects on the immune system, brain, and gut.

Kocovská et al., Frontiers in Psychiatry , 2017, 8 , 47

- **Neurotransmission:** Vitamin D3 and its metabolites are responsible for mediating the synthesis of various neurotransmitters like dopamine, serotonin, catecholamine, and acetylcholine. Several studies have suggested that vitamin D3 affect changes in neurotransmitters level an that this influence have a transgenerational impact.
- **Neuroprotection:** 1, 25(OH)2D3 is described to have neuroprotective role because of its ability to regulate certain neurotrophic factors and influence inflammation. Pretreatment with 1, 25(OH)2D3 displays pleiotropic effect. It causes plummet in glutamate-mediated cell death in cortical[53], hippocampal, and mesencephalic neurons cultures decreased L-type calcium channel expression and increased VDR levels.
- In addition, it causes reduction in reactive oxygen species (ROS) induced cell death through controlling proteins that either decrease the levels or inhibit the toxicity of ROS, or that increase antioxidant species in glia and neurons

Sampat, et al., Int J Nutrition, Pharmacology, Neurological Diseases, 9, 2019.

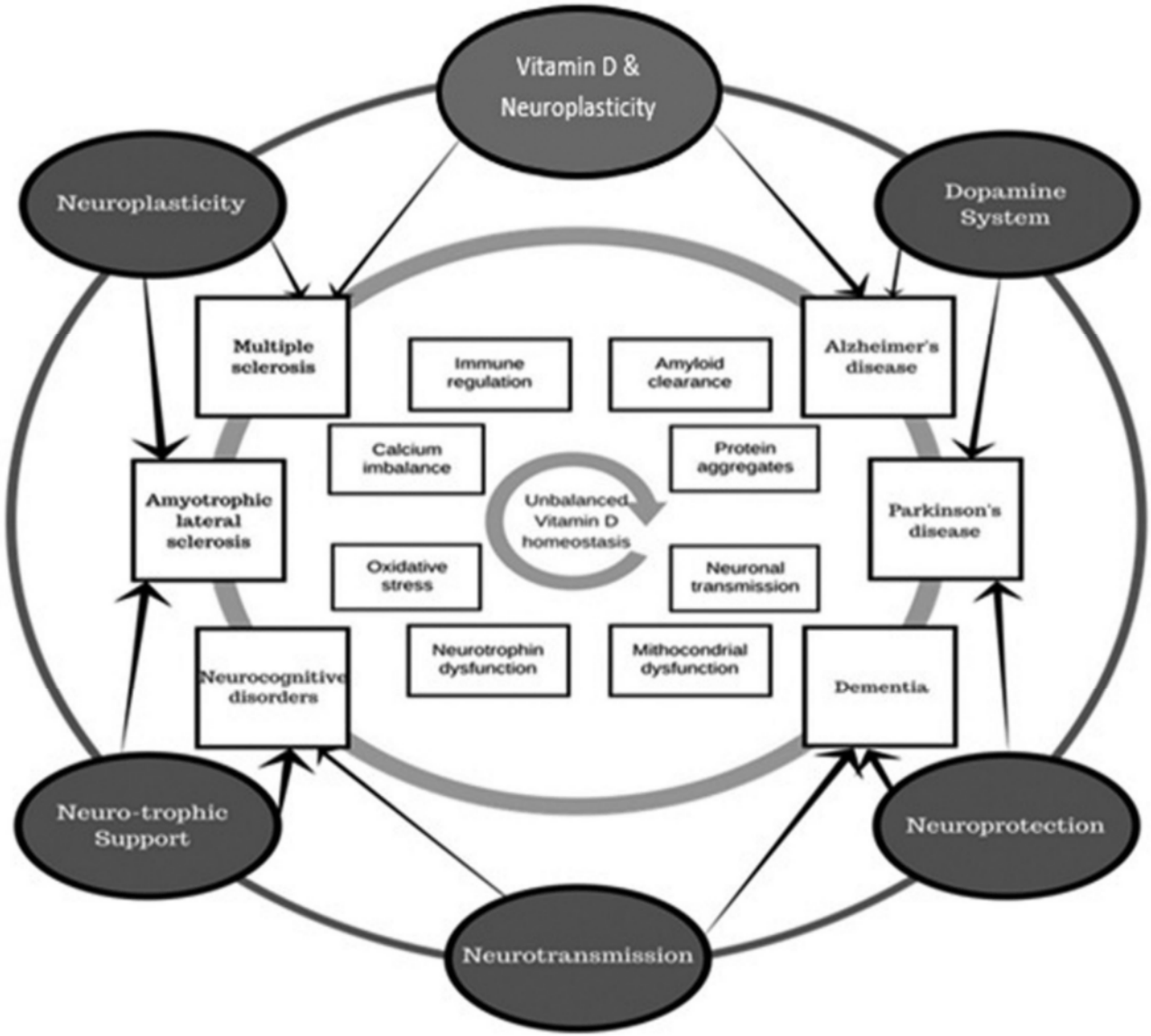
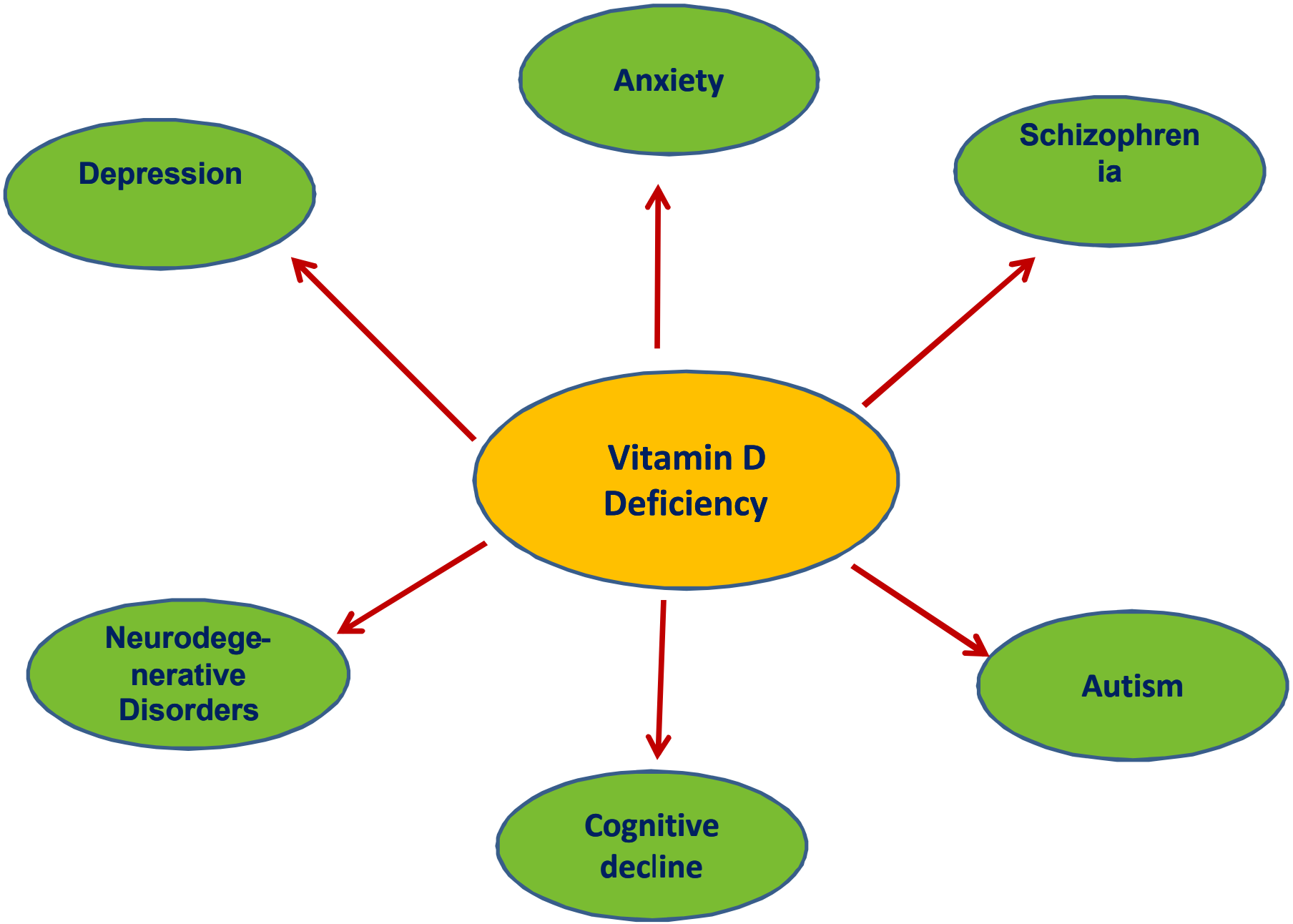


Diagram showing vitamin D crucial role in the nervous system health and disease conditions. Vitamin D contributes to neurotrophic support, neurotransmission, neuroprotection, and neuroplasticity.


Anxiety
Depression
Schizophrenia
Vitamin D Deficiency
Neurodege-nerative Disorders
Autism
Cognitive decline

Vitamin D prevents depression

- Vitamin D functions normally to maintain low intracellular Ca2+ levels, but when vitamin D levels decline the levels of Ca2+ begin to rise within the cell and this may enhance the onset of depression.
- This elevation of Ca2+ is enhanced by the fact that vitamin D plays an important role in maintain normal mitochondrial respiration.
- In addition, vitamin D acts to reduce inflammation, it maintains the synthesis of serotonin, and it induces the expression of DNA demethylases that controls the epigenetic landscape, thus enabling gene transcription to continue to maintain normal neuronal activity and to prevent depression.

Berridge, Pharmacol Rev 69:80–92, April 2017

Vitamin D prevents the onset of depression

Vitamin D prevents the onset of depression by activating a number of processes that are critical to maintain normal healthy neurons.

Vitamin D enters the nucleus where it associates with the retinoid X receptor (RXR) and then binds to the vitamin D response element (VDRE), which is located on a large number of genes.

It maintains Ca2+ homeostasis by inducing the expression of calbindin, parvalbumin, Na+/Ca2+ exchanger 1 (NCX1), and the plasma membrane Ca2+-ATPase(PMCA) pump.

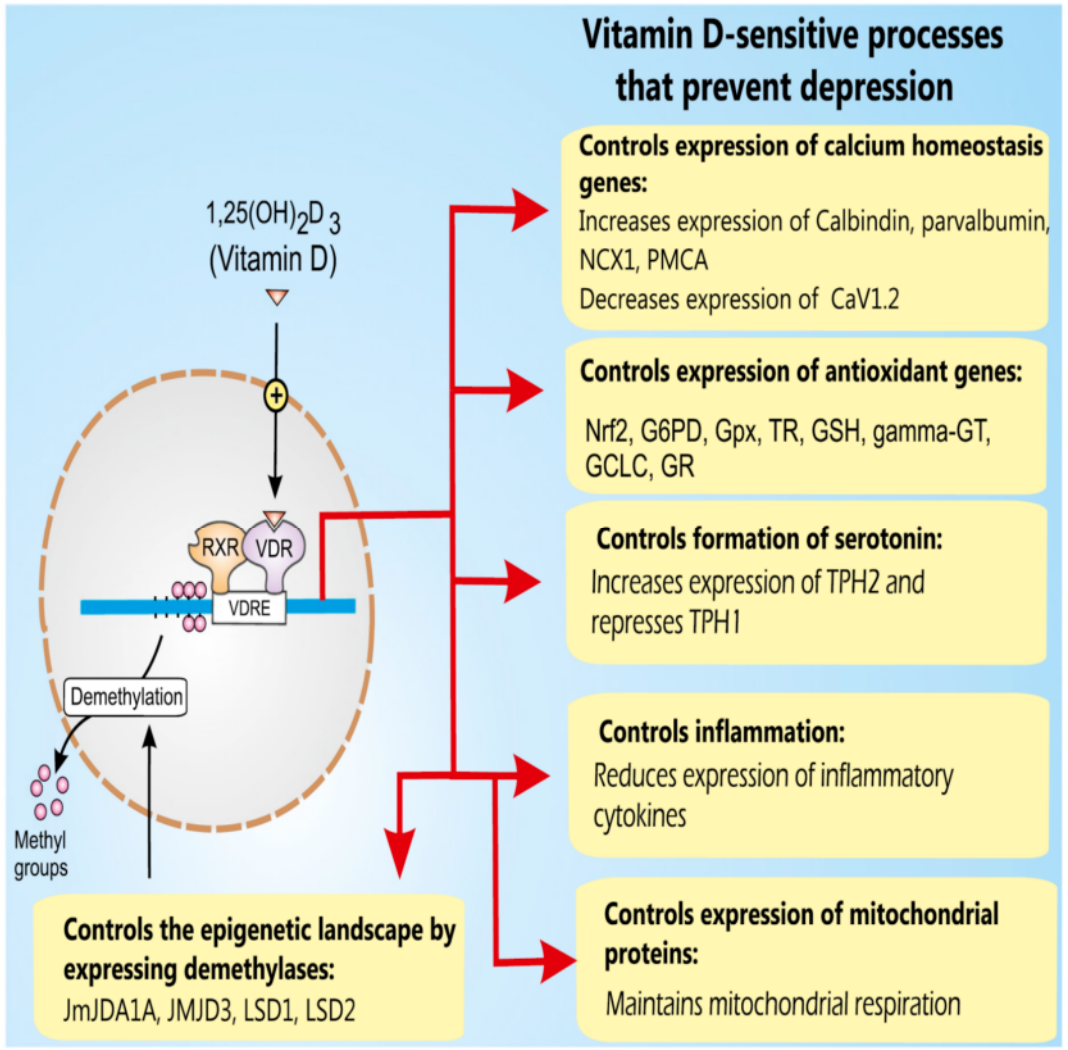
It also regulates Ca2+ by reducing the expression of the CaV1.2 calcium channel.

It activates expression of many antioxidant genes such as the nuclear factor-erythroid-2-related factor 2 (NRF2), g-glutamyl transpeptidase (g-GT), glutamate cysteine ligase (GCLC), glutathione reductase (GR), glutathione peroxidase (Gpx).

It controls the formation of serotonin by increasing the level of tryptophan hydroxylase 2 (TPH2) while repressing tryptophan hydroxylase1 (TPH1).

It reduces inflammation by reducing the expression of inflammatory cytokines.

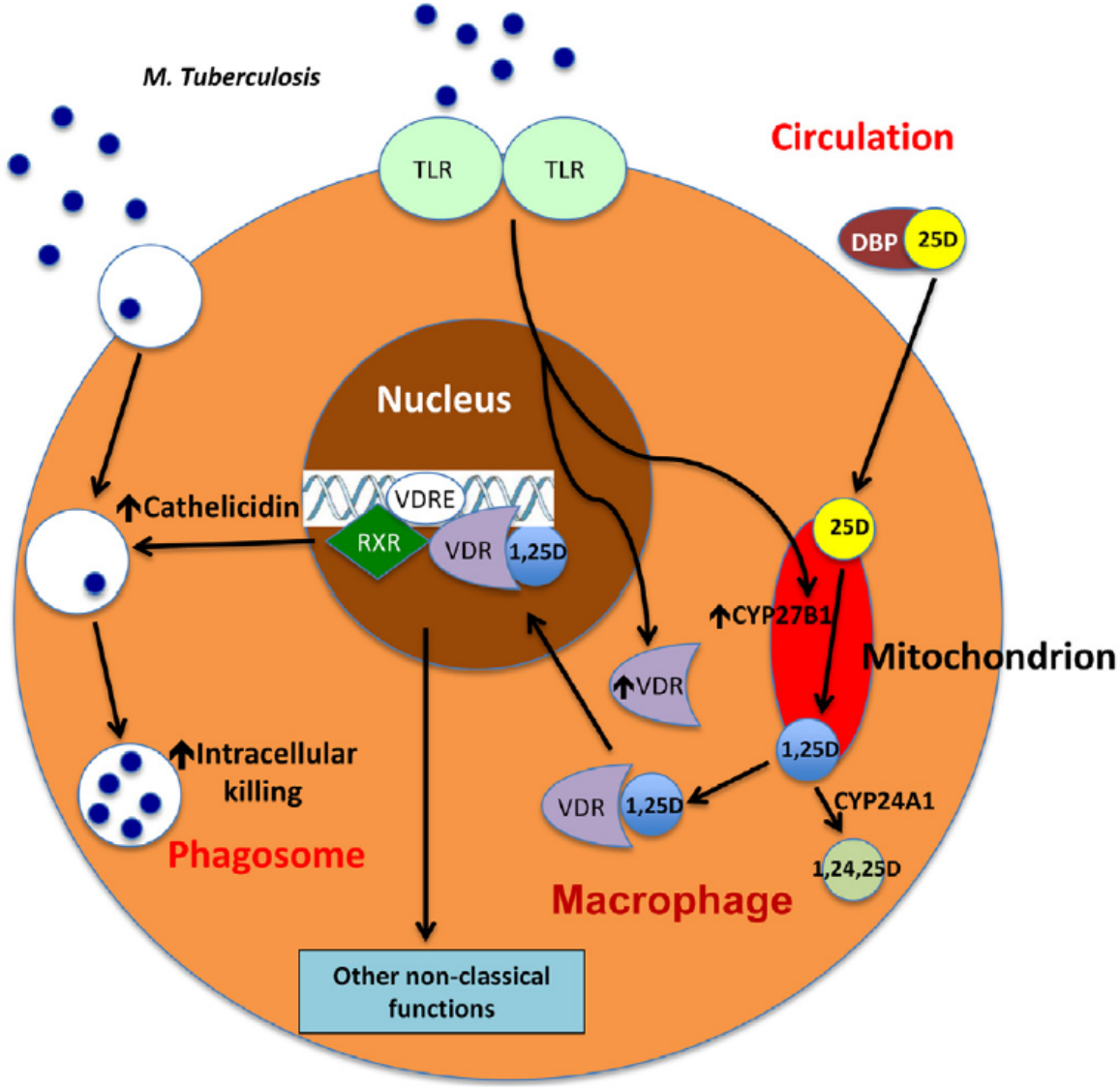
It regulates the expression of many mitochondrial proteins that maintain normal



Berridge, Pharmacol Rev 69:80–92, April 2017

Vitamin D and immune system

- The Vitamin D Receptor is a ligand-dependent transcription factor that forms a complex with hormonally active vitamin D and regulates the expression of genes associated with inflammation and immune modulation.
- The complex is expressed in immune cells, neuronal cells and glial cells.
- Vitamin D and the cytokine gamma interferon (IFN-γ) are the activators of macrophage immune function.
- IFN-γ induces vitamin D synthesis by macrophages and inhibits vitamin D induction of 24-hydroxylase, a key enzyme in vitamin D inactivation, causing high levels of vitamin D in serum leading to hypercalcemia in conditions such as sarcoidosis, tuberculosis, and several granulomatoses.
- Excessive vitamin D which results into hypercalcemia has also receiving much attention from the renal transplant community, since it has been associated with the



Vitamin D-mediated activation of the innate immune system in macrophages. Innate immune systems provide the first line of defense against pathogen infection. Upon pathogen detection, toll-like receptors (TLR) on the macrophage membrane are activated to induce transcriptional up-regulation of the vitamin D receptor (VDR) and enhance CYP27B1 expression, leading to the increased synthesis of 1,25D and VDR, two essential components responsible for the VDR-dependent regulation of a variety of genes including the up-regulation of cathelidicin expression. Incorporation of cathelidicin into phagosomes containing internalized pathogen enables the peptide to function as an antimicrobial agent to kill the invading pathogen. Shtaya et al., Journal of Clinical & Translational Endocrinology 1 (2014) 151e160.