

THE DIVERSE IMPACT OF VITAMIN D ON CHRONIC AILMENTS

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Abstract: The beneficial effects of vitamin D in humans are numerous and various, and include neuronal, immune and bone homeostasis, and regulation of cardiovascular function. Recent studies have related vitamin D levels to cancer cell proliferation, but meta-analyses on this subject have provided controversial results. This review deals with the antioxidant and anti-inflammatory function of Vitamin D in chronic diseases, focusing mainly on cancer, immune diseases, and cardiomyopathies. Vitamin D contributes significantly to reducing pro-oxidant biomarkers, both systemic and in specific tissues, involved in the development, progression, and recurrence of cancer, chronic and cardiometabolic diseases. The overall picture provided by this work highlights the need for new randomised controlled trials on oral Vitamin D supplementation in patients affected by cancer, or neurological and cardiovascular disorders, with the purpose of lowering risk factors for relapse of these diseases and improving patients' quality of life.

Keywords: Vitamin D, Calcium homeostasis, Cancer, Immune system.

INTRODUCTION

Vitamin D (Vit D) is part of the group of fat-soluble vitamins. Several forms are known, but the most important for our organism are ergocalciferol (Vit D₂) and cholecalciferol (Vit D₃) (Figures 1-2). Both forms are used to treat and/or prevent rickets¹. Vitamin D is sourced from various types of food. Apart from certain types of foods (especially fatty fish), the amount of Vitamin D in food is not very high². Other examples of sources are egg yolk (Vit D₃), mushrooms (Vit D₂), cereal and dairy products³. Concerning the synthesis of Vitamin D₃, ultraviolet (UV) rays have a very important role. 7-dehydrocholesterol (7-DHC), or Pro-Vit D, is transformed to Vit D, thanks to the action of ultraviolet rays in the spectral range of 290-320 nm UVB, in a thermosensitive way⁴, usually in dermis or epidermis⁵. Vit D is carried to the liver. Here the enzyme 25-hydroxylase leads to the synthesis of 25-OH Vit D. Then, in the kidneys, it is hydroxylated again by the action of the 1-hydroxylase, obtaining 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol, both addressed with the abbreviation 1,25(OH)₂D⁶. The rate of Vit D₃ formation varies with UVB power and the color of the skin⁷ because clothes, use of sunscreens and melanin can block UVB activity on the skin, leading to a lower production of Vit D. It acts not only as a vitamin, but also as a hormone, binding intracellular receptors, mostly situated in osteocytes and intestinal epithelial

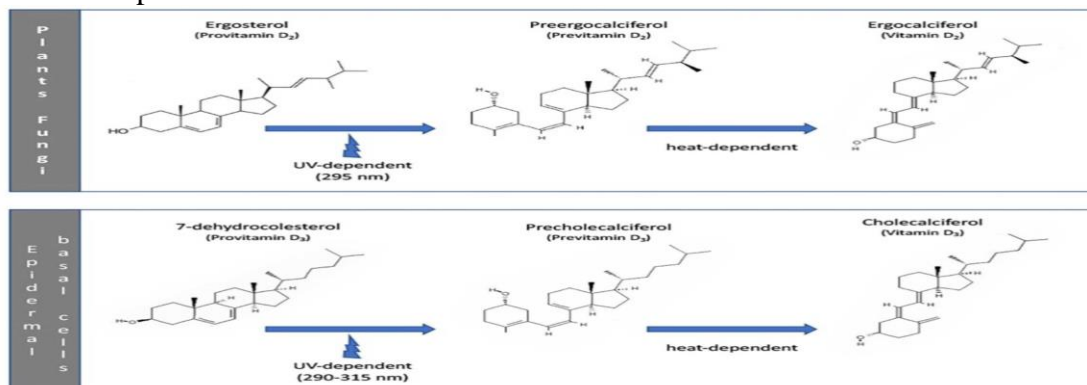


Figure 1. Synthesis of ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). Ergocalciferol is produced only in plants and fungi, while cholecalciferol in basal cells of the epidermis. Both processes occur via two steps, the former induced by the UV light radiation from sun, the latter in a heat-dependent process.

cells, but also in other tissues, like adipose, muscular and brain, or hematopoietic cells and hair follicles ⁸. After the bound with its nuclear receptors, 1,25(OH)₂D enters the nucleus, where a DNA interaction leads to gene expression modulation and calcium-uptake increase. Calcium assimilation and bone reabsorption represent two of the most relevant function of Vitamin D, even if other medical implications are not fully characterized yet ^{9,10}, especially in numerous human pathologies, like cancer, infections, osteoarticular and cardiovascular diseases ¹¹. Standard doses of Vitamin D are usually well tolerated and do not cause significant adverse effects (AEs), while high doses could be toxic, leading to many signs and symptoms ¹². Therefore, clinical studies, especially in oncological patients are necessary to obtain significant data about the therapeutic aspects of Vit D ¹³.

MATERIALS AND METHODS

A systematic research of EMBASE and Medline databases was conducted in order to find all relevant English-language papers on the health effects of vitamin D in human being. Full English-language texts with accessible abstracts and at least one of the following features were considered: clinical or preclinical studies about the importance of Vitamin D in immune system; cancer; cardiovascular diseases; pharmacological processes. Boolean operators AND/OR were used to combine search terms. The following strings were used in PubMed: “Vitamin D OR Vit D AND cancer” OR “Vitamin D OR Vit D AND cardiovascular” OR “Vitamin D OR Vit D AND immune system”. Concomitant research was executed on the Clinical Trial Register. A Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram ¹⁰, accessed, was created in September 2022 to summarize the systematic review process. The databases were last updated on 30 September 2023. Reports of the systematic review were performed in accordance with the PRISMA guidelines and are presented in Figure 3 ¹¹.

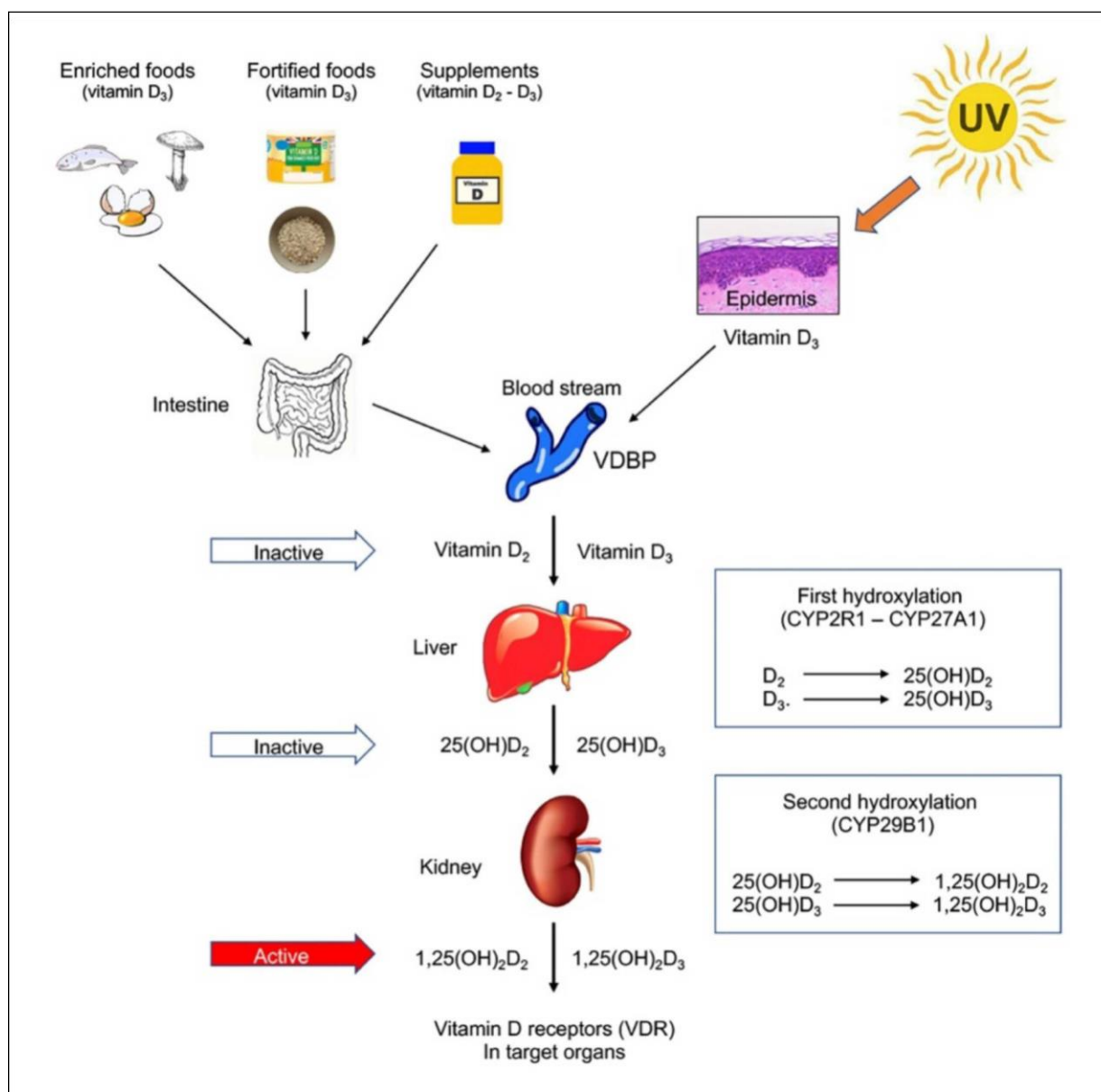


Figure 2. Metabolism of Vitamin D. Vitamin D₃ is present in dietary sources, while Vitamin D₂ is synthesized in the skin or can be provided through supplements. Once absorbed, it is converted in the liver into 25(OH)D and then in the kidney into the active 1,25(OH)₂D. Through the circulation, it is brought to the target organs possessing VDR.

METABOLISM OF VITAMIN D

Many cytochrome P450 oxidases (CYPs) enzymes have a role in the metabolism of Vit D. For example: CYP2R1, CYP24A1, CYP27B1, and CYP27A1 (in the mitochondria). They can manage Vit D metabolism through three main reactions: 25-hydroxylation, 1 α -hydroxylation, and 24-hydroxylation. Vit D formation mainly occurs in the liver, and studies on liver 25-hydroxylase showed that its activity is greater in microsomes and mitochondria. Published data have shown that some CYPs have a similar activity to 25-hydroxylase¹⁴. For example, CYP27A1 is well distributed, and it is contemplated that it is the only mitochondrial hydroxylase with a 25-hydroxylase-like function. Nevertheless, it cannot form 25hydroxylate Vit D₂. Another one with 25-hydroxylase-like activity is CYP2R1, founded in mouse livers¹⁵. This one can 25-hydroxylate Vit D₃ and Vit D₂ (Figure 2). Other enzymes

that have a relevant action in Vit D metabolism are 3-epimerase enzymes, because they can inactivate the main Vit D metabolites. They can convert 25(OH)D3 to 3-epi-25(OH)D3 in the liver. Moreover, CYP27B1 transform 25(OH)D3

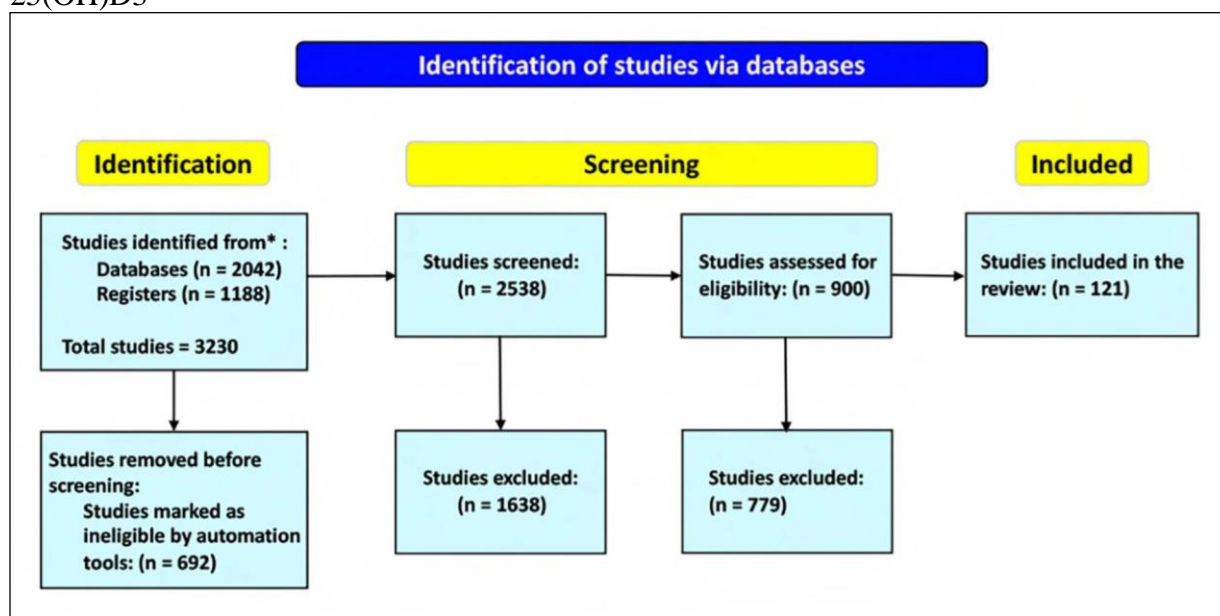


Figure 3. PRISMA diagram. The databases were last accessed on September 2023.

and 3-epi-25(OH)D3 to 1 α ,25(OH)2D3 in the kidneys (Figure 4). The epimeric forms 3-Epi-25(OH)D3 and 3-Epi-1 α ,25(OH)2D3 show low affinity with Vitamin D binding proteins (DBPs) and VDR. In human colon cancer cells, this conformational change causes a decreased calcium transport and a decreased gene expression^{16,17}. Another important enzyme in Vit D metabolism is CYP11A1, that hydroxylate Vit D3 and Vit D2, producing new metabolites: 20,22(OH)2D3 or 20,22(OH)2D2, and 20OHD3 or 20OHD2. The concentrations of 20,22(OH)2D3 and 22(OH)D3 are high in keratinocytes, suggesting that UVB exposure may activate CYP11A1¹⁸⁻²¹.

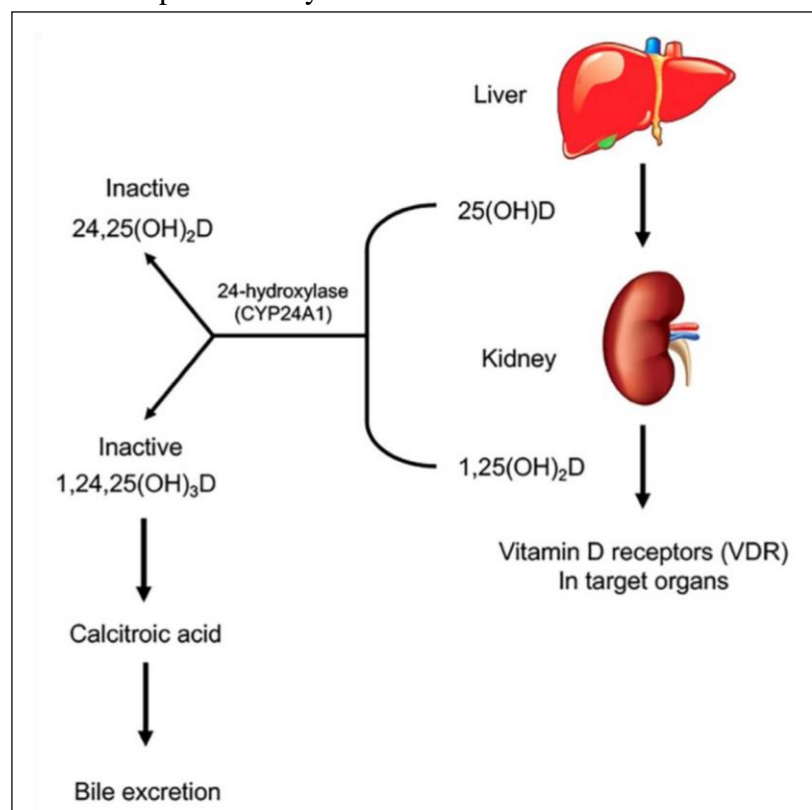


Figure 4. Vitamin D catabolism. Vitamin D is metabolized first to 25 hydroxyvitamin D (25(OH)D), then to 1,25-dihydroxyvitamin D (1,25(OH)2D). CYP27B1 is the key 1-hydroxylase. Both 25(OH) D and 1,25(OH)2D are catabolized by CYP24A1. Once inactive, 1,24,25(OH)3D is then converted in calcitric acid and secreted as bile into intestine.

VITAMIN D EFFECTS: FROM ANTIOXIDANT TO GENOMIC EFFECTS

Vit D action can be described in genomic and non-genomic terms. The genomic mechanism was studied by Pike et al²² and Haussler et al²³. An important role is played by the Vit D receptor (VDR), encoded by the *VDR* gene. It is a member of the nuclear hormone receptors.

VDR is composed by three main domains: *I*) a DNA-binding domain that with its two zinc fingers binds vitamin D response element (VDRE); *II*) a C- terminal ligand-binding domain; *III*) a connection region between these two domains ²⁴. VDR forms heterodimers with retinoid X receptor (RXR), binds to specific VDREs that is located near the target gene promoters, and mediates the recruitment of a huge number of coregulatory complexes that have an essential role in the level of expression of the target gene ²⁵. The features of VDR/RXR complex are: *I*) the number of binding sites for VDR depends on the cell type; *II*) this ligand-receptor complex is the most relevant active transcription unit, but it is not the only one; *III*) the VDR binding sites are for the most classical hexamer half-sites; *IV*) the enhancers of the gene encoding for VDR can be located proximally or distally, and several enhancers are grouped in clusters situated hundreds of kilobases ahead; *V*) Enhancers have different binding sites for each transcription factors; *VI*) these enhancers are dynamic and cell-type-specific. Vit D also shows non-genomic effect on different types of cells, through a membrane receptor. One of these kinds of effects is the increasing of calcium and phosphate reuptake from the intestine. This process is named transcalcification ²⁶, term coined to express the fast onset of calcium movement through the intestine in Vit D-fortified chicken nourished with 1,25(OH)2D ²⁶. Vit D also regulates the activity of chloride channel, the activation and distribution of protein kinase C, and the activity of phospholipase C in various cellular types, including osteoblasts, liver, and intestinal cells ²⁷⁻³¹. It also stimulates the reabsorption of phosphate in renal tubules and promotes the input of calcium from the bones into the blood. Another effect consists in the decreasing in pro-oxidative substances and lipid peroxidation ³⁰; for example, in patients affected by diabetes, Vit D could reduce the levels of glucose-related pro-inflammatory proteins and 4-hydroxynonenal, a marker of lipid-peroxidation ³¹. Another key role of this molecules in the homeostasis of neuronal functions. Recent meta-analyses correlated 25(OH)D low blood levels with a significant risk of cognitive decline, memory decline and with progression of Parkinson's disease ³²⁻³⁴. A meta-analysis on Vitamin D3 and neurodegenerative disorders states that improving Vitamin D levels at 75 nmol/l may improve cognitive functions, neuron survival and bone health ³⁵.

DRUG INTERACTIONS

The interaction between drugs and Vit D are numerous because of the host genetic variations in the CYP and VDR genes ^{36,37}. Pharmacological effects of Vitamin D equivalents can be reduced by their association with drugs that induces the CYP450, such as rifampicin, barbiturates, and some anticonvulsants (e.g., oxcarbazepine) ³⁸. These agents could activate the conversion of Vit D in its inactive metabolites, and the reducing of blood levels of Vit D, together with an increase of production of parathyroid hormone (PTH). Patients assuming long-term anticonvulsant therapy could sporadically develop osteomalacia ³⁹. Some patients also showed a poor response to Vit D analogues while treated with phenytoin and/ or primidone ⁴⁰. Examples of the most important interactions are provided in Table 1.

GENETIC FACTORS INFLUENCING VITAMIN D HOMEOSTASIS AND METABOLISM

DBPs transport Vitamin D and its products to the liver. The main actor of Vit D metabolism is CYP2R1, although several CYPs participate too ^{15,18}. Therefore, polymorphisms in genes encoding these enzymes can have an impact on Vitamin D metabolism, but it is not easy to find a significant relation between CYPs polymorphisms and blood levels of Vit D, because several substances can inhibit these enzymes. Patients show different reactions to Vit D3 administration, and are classified into high, moderate, and low responders ⁴¹⁻⁴³. Nonetheless, it has yet to be completely understood which genomic and epigenomic modifications influence Vit D homeostasis, although up until 700 genes encoding for Vit D targets have been identified through several genome-wide association studies (GWASs) ^{37,44}. For example, several Single Nucleotide Polymorphisms (SNPs) in the gene encoding for CYP2R1, can affect the expression and/or function of the enzyme, and they are associated with low levels of 25(OH)D, reduced sensitivity to Vit D analogues, and several diseases as rickets, obesity and tumors ⁴⁵⁻⁵¹. Other studies examine the VDR gene. It is associated with bone mass density and arthritis ⁵². Several sites in the VDR have been identified, that **Table 1. Drug interactions with vitamin D.**

Drug/ Action	Clinical	Interaction Substance	Action
Erdaftinib	Pharmacodynamic effects of	It is recommended to reduce	Major

(FGFR/aKlontho) inhibition by phosphate intake to erdafitinib can cause 600-800 mg per day hyperphosphatemia

Ergocalciferol and Additional toxicity, manifesting In case of hypercalcemia, vitamin D Major Vit D3 derivatives hypercalcemia, hypercalciuria and any Calcium supplements and hyperphosphatemia should be immediately avoided

Oxcarbazepine It Induces CYP450 inducers. It may Patients who metabolize CYP450 Moderate decrease the pharmacologic poorly must be supplemented effects of vitamin D analogues, with double doses of Vi D inducing the hepatic conversion of when receiving oxcarbazepine Vitamin D to inactive metabolites.

Magnesium salts Possible increases in plasma Patients on chronic dialysis Moderate hypermagnesemia, particularly treatment with a vitamin D in chronic renal dialysis patients, analogue should avoid due to potentially additive magnesium-containing pharmacologic effects. Chronic products hypermagnesemia may be one of the causes of adynamic bone disease in dialysis patients

Indapamide and Thiazide diuretics inhibit the renal Serum calcium should be Moderate others thiazide excretion of calcium and may monitored if patients experience diuretics also enhance the responsiveness sign of hypercalcemia.

of bone and renal tube to parathyroid hormone. Thus, the concurrent use of large amount of calcium or vitamin D can lead to excessively high levels of calcium.

can be recognized using restriction enzymes TaqI, BsmI, ApaI, and FokI. Basing on these sites, the alleles called T-t, B-b, A-a, and F-f. TaqI SNP (rs731236) cause a T>C substitution. The T nucleotide is also called allele T, the C nucleotide is known as allele t; this mutation results in methylation. An A>G nucleotide substitution is the result of BsmI (rs1544410) SNP, the A nucleotide corresponding to allele B and the G nucleotide corresponding to allele b. This mutation influences the transcription process. Moreover, FokI SNP (rs2228570) leads to a T>C substitution on the codon start (ATG[®] ACG)⁵³⁻⁵⁵ that cause the production of a shortened protein with more transcription activity because of its minor steric bulk⁵⁶. In this SNP, the T nucleotide is called allele f, while the C nucleotide is allele F. Lastly, ApaI (rs7975232) SNP causes a C>A substitution, known as A>a allele, but the impact of this last polymorphism has yet to be clearly described. These polymorphisms correlate with diseases onset and homeostasis processes^{52,53,55}. Two lesser-known polymorphisms in the 5' promoter region of the VDR gene has been described: Cdx2 (rs11568820) and GATA (rs4516035). The first one consists of an A>G substitution, provoking a deletion of the binding site. The G allele is accountable for a 70% reduction in the VDR transcriptional activity. Similarly, the T>C nucleotide substitution caused by GATA polymorphism results in a decreased VDR promoter activity. These SNPs are in linkage disequilibrium and are analyzed as haplotypes^{57,58}. They have also been correlated with an increased risk of prostate cancer. Example of medical conditions are provided in Table 2. The most used technology platforms for the genotyping of known SNPs include I) fluorescence-free PCR-based methods, such as allele-specific amplification and RFLP; II) sequencing methods, either as automated Sanger sequencing or high-throughput sequencing technologies called 'Next Generation Sequencing' (NGS).

Table 2. Vitamin D receptor gene polymorphisms' frequency and several clinical conditions linked.

SNP code	Genetic	Functional	MAF	Medical	variant	consequence
rs2228570	FokI T>C (Met1Pro) site	T>C eliminates translation start Vitamin D and parathyroid hormone levels ⁶⁰ Invasive ovarian carcinoma	0.35	T	Calcium absorption and calcium accretion to skeleton	and breast cancer risk ⁶¹
rs1544410	BsmII Intron 8	A>G nucleotide	0.26	A	Cutaneous malignant melanoma ⁶⁰	

rs731236	substitution	and colorectal carcinoma risk ⁶²	
	TaqIExon 9	T>C methylation	0.26 C Breast Cancer Prognosis
r7975232	nucleotide 352T>C	Psoriasis ⁶⁰	
	ApaI T>g	T>G nucleotide	0.50 T Renal Cancer Carcinoma risk ⁶³
rs11568820	substitution		
	CDx2 A >G eliminates	0.46 T Prostate cancer risk ⁶⁰	
rs4516035	Cdx binding site	Calcipotriol response	
	Growth defect and urinary calcium/		keratinise ⁶⁰ levels
	GATA T>C eliminates	0.18 C Growth defect and urinary calcium/	
	GATA binding site	keratinise levels	
	Fat gain, BMD and apparent BMD ⁶⁰		

MAF = Minimum Allele Frequency.

THE ROLE OF VITAMIN D IN OSTEOPOROSIS

Vit D can increase dietary calcium absorption by the action of PTH, to promote the maintenance of an adequate calcium homeostasis ⁶⁴. PTH stimulates the activity of 25(OH)D-1 α -hydroxylase, which is responsible for the transformation of 25(OH)D to 1,25(OH)2D, while this one is inhibited by 1,25(OH)2D itself ⁶⁵. Moreover, ViD3 inhibits parathyroid cells proliferation, leading to a decreasing in PTH secretion and activity. The calcium absorption occurs by the activity of a protein localized in the brush borders of the intestinal epithelial cells, that binds the ion and transports it to the cytoplasm. Furthermore, 1,25(OH)2D promotes calcium passive absorption by enhancing permeability “tight junctions” ⁶⁶. Calcium and phosphorus form hydroxyapatite, which gives strength to the bones. A deficiency in Vit D causes a compensatory raise in PTH, which induces bone turnover and calcium renal tubular reabsorption in order to maintain calcium levels ⁶⁷. So, lack of Vit D indirectly exerts its action on the bones, causing hypocalcemia and hypophosphatemia, leading to rickets or osteomalacia, depends on the age ⁶⁸ (Figure 5).

Both are caused by an impairment in bone mineralization due to a non-adequate calcium-phosphate product and to the effect of PTH on the kidneys, which cause phosphaturia ⁶⁹. Good blood levels of Vitamin D3 have a great impact on bone density ⁷⁰. Fracture risk is correlated to bone mineral density, Vit D is essential for the treatment of osteoporosis ⁷¹. Bone tissues are constantly transforming, through modelling and remodeling processes. Modelling is important to adapt the bone's structures to the stresses due to growth and age. Remodeling is useful to replace damaged or aged bone tissue ⁷². These processes are mediated by osteoblasts, osteoclasts, osteocytes, and lining cells. Osteoblasts regulate the formation, deposition, and mineralization of bone tissue ⁷³. They also mediate the differentiation and maturation of osteoclasts, involved in bone resorption. Osteoclasts express various factors that regulate osteoblast activity ⁷⁴. Osteocytes, act as mechano-sensors and regulate both osteoblasts and osteoclasts functions. Lining cells assist the other bone cells during bone remodeling ⁷⁵. The discovery of Osteoprotegerin (OPG), a receptor that can bind to Receptor Activator of Nuclear factor kappa-B Ligand (RANKL), derived from osteoblasts, has permitted to improve comprehension on the mechanism of cross-communication between osteoblasts and osteoclasts. RANKL is situated on the surface of osteoblasts, while RANK, its own receptor, is localized on osteoclasts ⁷⁶. This interaction, in addition with the

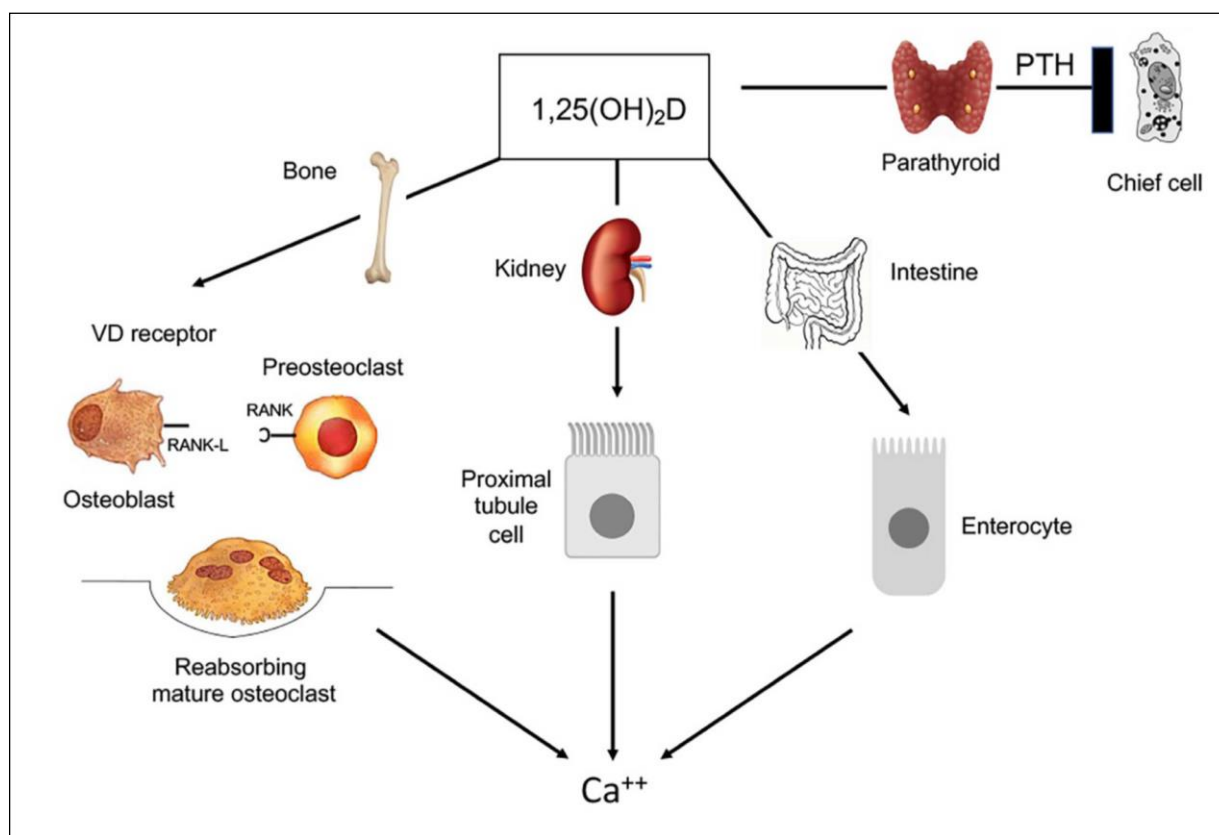


Figure 5. Calcium homeostasis regulation by vitamin D in bone, kidney, intestine and parathyroid glands. action of macrophage colony-stimulating factor (m-CSF), stimulates the precursor cells to differentiate into osteoclasts, also increasing their activity⁷⁶. $1,25(\text{OH})_2\text{D}$ mediates this process by binding to the VDR expressed on osteoblasts surface so as to induce RANKL's production⁷⁷.

Osteoporosis consists in a progressive bone mass reduction associated with skeletal microarchitecture alteration, causing bone strength loss, and increasing the risk of pathological fractures even after some very mild traumas; the osteoporotic fractures principally occur on the vertebral bodies and the femoral neck⁷⁸. It can be classified in primary and secondary. Primary osteoporosis can be also divided into Type 1, postmenopausal osteoporosis, and Type 2 or age-related osteoporosis. The first one occurs in women almost 15–20 years after the onset of menopause, and it is related to the estrogen deficiency⁷⁹. The second one affects people over 75 years of age, more directly related to the aging. On the other hands secondary osteoporosis refers to a huge range of conditions and is the result of diseases and pharmacological treatments⁷⁹. Sufficient Vitamin D levels and a good calcium intake promote the maintenance of an adequate bone mineral density (BMD) and thus help to compensate for the decreasing of calcium caused by the bone turnover during menopause or in older age⁸⁰.

Moreover, the muscle weakness observed in hypovitaminosis D enhances the risk of falling, and indirectly also the risk of pathological fractures⁸¹. $25\text{OH}\text{D}$ serum levels represent a valuable indicator of Vit D status. According to most experts, Vit D deficiency occurs when serum levels are $<50 \text{ nmol/L}$ ($<20 \text{ ng/mL}$), while other societies, such as the Endocrine Society, advocate larger ranges. $25(\text{OH})\text{D}$ serum levels $>75 \text{ nmol/L}$ ($>30 \text{ ng/mL}$) are considered normal overall, while levels between $50\text{--}75 \text{ nmol/L}$ ($20\text{--}30 \text{ ng/mL}$) are considered as Vit D insufficiency⁸².

VITAMIN D AND MUSCLE HOMEOSTASIS

Persistent Vitamin D deficiency could lead to proximal myopathy and unsteady gait⁸⁴. Moreover, typical characteristics of rickets and osteomalacia are muscular aches and hypotonia. Muscle protein production is stimulated by $1,25(\text{OH})_2\text{D}$, which is responsible of calcium transport in the sarcoplasmic reticulum, contributing

to muscle contraction⁸⁵. Based on VDR's expression in muscles, it has been suggested that Vit D could exert influence on this tissue. Studies in mice knockout for the skeletal muscle specific VDR showed a decreased muscle type 2 fiber diameter⁸⁶. Another study suggests the possibility of a Vit D modulation on myostatin, that negatively regulate muscle mass⁸⁷. Based on a decrease Vit D production in the skin during aging, with a reduction in the renal action of 25(OH)D and in the VDR concentrations in muscle tissue, all these effects may make the muscle more sensitive to Vit D3 deficiency and enhanced the risk of falls.

A proper sunlight exposure represents the more efficient method to maintain good Vit D levels, since its content in natural sources is very low⁸⁸. Whole-body sun exposure during summer provides specifically likely 10,000 IU Vit D, while every 100 IU of Vit D supplement administered increases 25(OH) D levels by 0.5 to 1 ng/mL⁸⁹. Obese people or people with malabsorption probably require higher doses⁹⁰. Moreover, older age, higher BMI and darker skin increase the risk of suffering from Vit D deficiency.

VITAMIN D SUPPLEMENTATION AND MODULATION OF IMMUNE FUNCTIONS: PUTATIVE IMPLICATIONS FOR CANCER PATIENTS

The immune system is composed of different cell types, for example monocytes, B and T-type lymphocytes and so on. Their activity can be modulated by Vit D⁹¹. Indeed, it can control the expression of the genes involved in immune responses. In fact, in various epidemiological studies, a correlation between autoimmune disease and risk of infections with low serum levels of 25(OH)D has been⁹². Some interventional studies, aimed to improve the levels of 25(OH)D in patients suffering from immune-related disorders, have produced contrasting results⁹³.

Some reports from the mid-18th to the early 19th century, have provided evidence for the correlation between Vitamin D and innate immune response, when tuberculosis was treated with cod liver oil, a rich source of Vit D3, and exposition to sunlight⁹³. During an infective process, proinflammatory substances and growth, stimulate CYP27B1 which induces the transformation of 25(OH)D to 1,25(OH)2D. The latter, through autocrine mechanism, increases the production of cathelicidin⁹⁴, which has antiviral and antibacterial functions on different microorganism. Furthermore 1,25(OH)2D has a paracrine activity, stimulating macrophages, reaching serum concentrations of 30 ng/mL, provoking hypercalcemia, a marker of infection⁹⁵. 1,25(OH)2D can also maintain immune tolerance in Antigen-Presenting Cell (APC) and manages the production of cytokines and co-stimulation molecules and the surface expression of MHC class II⁹⁶ (Figure 6). The modulation of the immunogenic cytokine profile has an important role in immune homeostasis; for instance, Vitamin D enhances IL-10 levels, that has an anti-inflammatory activity⁹⁶. On the other side, 1,25(OH)2D decreases the production of cytokines that have pro-inflammatory and atherogenic effects, which led to immune hyperactivation, as IL-6 and IL-17⁹⁷. Finally, the stimulate the activity of NK cells can be modulated by 1,25 (OH)2D, because it may activate NK cells and could offer a new potential use in cancer patients treated with immune check-point inhibitors⁹⁸.

VITAMIN D AND CANCER

Vitamin D Association with Cancer Risk and its Prevention

Vit D3 is commonly used in various lines of therapy, with regard to the patients' comorbidities⁹⁹. Based on pre-clinical studies both *in vitro* and *in vivo*, different pathways have been suggested, through which Vit D may impede carcinogenesis and slow tumor progression. Moreover, observational studies hypothesize that Vitamin D3 may provide additional protection against cancer mortality rather than cancer occurrence, regardless of a reduction in both¹⁰⁰⁻¹⁰². Oncological patients develop one or more comorbidities, such as cardiopathy, hypertension, diabetes, osteoporosis, apparently not related to the concomitant neoplasia¹⁰³. Vit D3 deficiency represents one of these medical conditions, typically discovered while executing routinary blood tests and widely related to osteoporosis, fractures and in general bone disorders. Rusińska et al¹², suggested that patients should be classified according to comorbidity, age and blood level of Vitamin D. According to these authors, in adults with serum levels <50 nmol/L (<20 ng/mL) it could be sufficient behavioral strategies such as sunbathing at least 15 minutes between 10.00-15.00 h, without sunscreen, from May to September. However, this is imprudent for people over 65 or African people due to a decreased efficacy of Vit D skin synthesis. Oral supplementation is furthermore recommended, specifically with a dosage from 800 to 4000 UI/day, based on age, body weight and

Vit D3 food intake¹⁰⁴. Oncologists and General Practitioners (GP) should therefore focus to their patients' blood test results and, in cases of low level of Vitamin D, act consequently, in order to avoid Vit-D3-related symptoms¹⁰⁵.

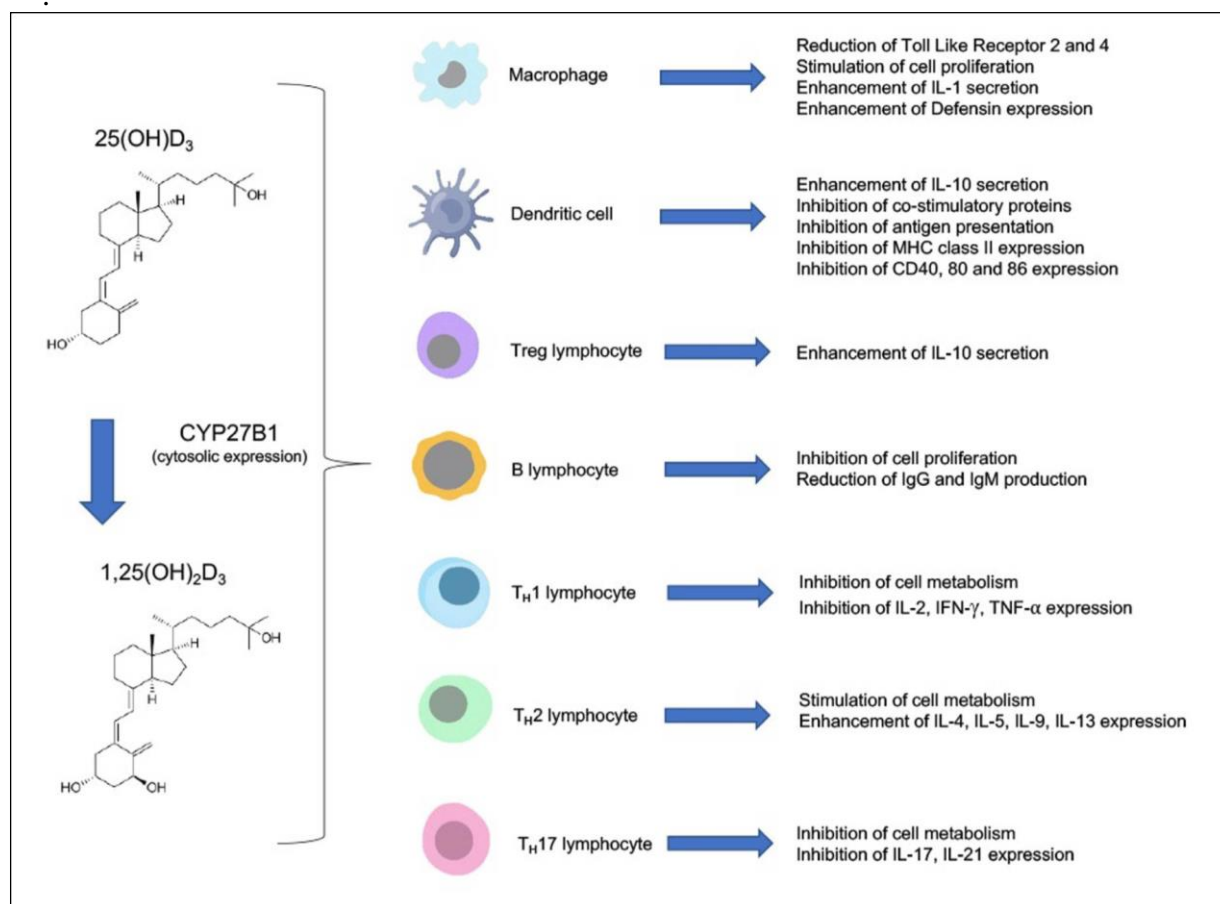


Figure 6. Schematic representation of Vitamin D functions on cells of the innate and adaptive immune system.

Vitamin D Pathophysiology in Cancer Prevention

Observational studies have investigated the role of Vit D3 in cancer development in order to evaluate if VitD3 can play a protective role. However, these studies have not found a correlation between low levels of Vit D in the blood and an increased cancer risk; so, its role remains uncertain¹⁰⁶. Manson et al¹⁰⁷ conducted a randomized, double-blind, placebo-controlled, in order to evaluate risks and benefits of Vitamin D3 and marine omega-3 fatty acids for the prevention of cancer amongst 28.871 subjects (men ≥ 50 y.o. and women ≥ 55 y.o.). Patients were randomized in four homogeneous groups, according to age, sex, and ethnic group. The four groups were: Vitamin D supplement, Omega 3 fatty acid supplement, and both agents and placebo. Any patients had a history of cancer (except for non-melanoma skin cancer) or cardiac disease at the time of study inclusion¹⁰⁷. A total of 1617 participants achieved the primary endpoint of invasive cancer, with analogous events in the Vitamin D group and placebo group, and the two groups did not significantly differ in the incidence of site-specific cancer (prostate, breast, colorectum). During the follow-up, 154 in the Vitamin D group and 187 in the placebo one died from cancer¹⁰⁸. Although this study has adequate size and duration (>5 years), there is no evidence that oral Vit D3 supplementation has an impact on cancer incidence in healthy adults, but it suggested to take in consideration BMI (Body Mass Index), since the normal-weight participants showed decreased cancer incidence, likely associated with the treatment.

Vitamin D Levels and Breast Cancer

The presence of the same enzymes responsible for Vit D metabolism in epithelial breast cells, as the kidneys, suggest an influence of Vit D on breast cancer: 1,25(OH)₂D has a chemo-preventive action that support the control on the cells cycle. According to preclinical studies, the supplementation of Vit D₃ promotes differentiation and apoptosis, and inhibits cell proliferation^{109,110}. To support this hypothesis, a preclinical study was carried out: human mammary cells were incubated with 25(OH)D physiological concentrations, and it was observed that these cells produced 1,25(OH)₂D enough to suppress cell proliferation¹¹¹. It was suggested that, in breast cells, Vit D core receptor and metabolic complexes may exert their action in an autocrine or paracrine way¹¹¹. In a meta-analysis based on 9 studies aimed to evaluate the interactions between Vit D level and postmenopausal breast cancer on 5206 women and 6450 controls, it was proved that there is a non-linear inverse association between blood levels of 25(OH)D and postmenopausal risk of breast cancer¹¹². These findings were explained through physical and hormonal changes experienced by women in menopause, including weight gain and obesity, which induce an augmented circulating estrogen level, and so an augmented risk of hormone-dependent breast cancer¹¹³. Therefore, Vit D supplementation might lower the risk of this kind of cancer as it can downregulate estrogen receptors expression and then reduce their synthesis and signaling¹¹⁴.

Prostate Cancer and Vitamin D

There are numerous studies about how Vit D could influence the clinical history of prostate cancer. Chen et al¹¹⁵ evaluated calcitriol, 1alpha-hydroxyVit D₂ (doxercalciferol), and 19-nor-1alpha-25-dihydroxyVit D₂ (paricalcitol) as single agents in patients suffering from castration-resistant prostate cancer (CRPC) and castration-sensitive disease. Despite authors observed a reduction of the prostate specific antigen (PSA) levels in castration-sensitive disease and few evidence of activity in CRPC (19% PSA response rate), strong evidence convincing about the clinically important single-agent activity was not confirmed by any of these studies¹¹⁶. However, these results could be influenced by the associated use of Vitamin D analogues and dexamethasone, given its control on the hypercalcemic effects of calcitriol and its antineoplastic activity¹¹⁷. In large clinical trials that compared analogues to single-agent glucocorticoids, reported PSA response rates were in the range of 3–10%. Moreover, single agent doxercalciferol was investigated in 26 patients with CRPC, but there was not a substantial reduction of PSA. Paricalcitol was assessed on a 3-times-a-week schedule, and it did not correlate with a reduction in serum PSA^{117,118}. Two randomized trials studied the association of Vitamin D₃ and cytotoxic agents. In the first one (ASCENT I)¹¹⁵, 250 patients were randomized to receive either standard therapy for castration resistant prostate cancer (docetaxel 36 mg/m² weekly, every 4 weeks, and every 6 weeks) or the same therapy adding calcitriol (DN-101), at 45 mcg per os/die. The authors reported a significant difference in the DN-101 arm, although patients did not meet the primary endpoint, and there also was a longer median survival rate in the patients receiving calcitriol (24.5 months vs. 16.4 months). The second study (ASCENT II)¹²⁰ was a larger trial started to confirm the better survival of DN-101 plus docetaxel group. However, the results didn't demonstrate improvement in the antineoplastic efficacy of Docetaxel in CRPC. Therefore, after an interim analysis demonstrated a statistically inferior survival in the DN-101 group, the study was interrupted^{118,119}.

Vitamin D and Melanoma

Vit D levels and alterations in its metabolism can be instinctively related to skin cancer. 1,25(OH)₂D₃ anti-melanoma activity and its influence on differentiation, cell-death, cancer cell invasion and metastasis were already known 30 years ago^{121,122}. Many studies have proved that the same above-mentioned mechanisms (the VDR expression in cancer cells and its effect on the cell cycle), can take part in melanoma carcinogenesis¹²¹. A study conducted to evaluate the *in vivo* activity demonstrate that the growth of human-melanoma-derived xenografts in immunosuppressed mice was inhibited by Vit D₃¹²². Moreover, the activity of Vitamin D₃ on melanoma, have been investigated by several studies, but with discordant results. In fact, some studies suggested a protective effect of high Vitamin D₃ levels at the time of diagnosis, while other authors have shown that this effect is ascribed to the fluctuation in 25(OH)D₃ levels during follow-up, rather than to levels at the time of diagnosis^{123,124}.

Vitamin D and Colorectal Cancer

Several studies trying to find a correlation between Vitamin D3 and the colorectal cancer development (CRC) have proposed an inverse relationship between blood 25(OH)D levels and the risk of CRC ¹²⁵. Four meta-analyses showed inverse correlation between the risk of CRC development and serum 25(OH)D levels. Lee et al ¹²⁶ demonstrated an increased influence of these levels on CRC, while two other papers by Gandini et al ¹²⁷ and Touvier et al ¹²⁸ reported a decrease in cancer incidence for each increase of 100 IU/L and 25 nmol/L of circulating Vit D3, respectively. Finally, Maalmi et al ¹²⁹ examined five cohort studies from three distinct geographical regions (United States, Europe and Japan) and they found robust results with the previous three studies, observing a considerable decrease in cancer mortality (up to 35%). Even though the trial sample size was limited, the results were statistically significant in patients with higher level of Vitamin D3: from a population of 2330, only one achieved 1202 included patients. Maalmi et al ¹²⁹ in a recent update, included 11 prospective cohorts and achieved the same results as done before. In a subgroup analysis of a European studies with larger sample size including stage I-IV, it was found a stronger association between Vit D levels and overall survival (OS) ¹²⁹. A randomized double-blind phase II clinical trial, enrolled patients from April 2012 to November 2016 with diagnose of metastatic CRC previously untreated. They were randomized to FOLFOX-bevacizumab plus supplementation of high dose of Vit D3 (8000 IU/day for 2 weeks followed by 4000 IU/day) vs. standard-dose FOLFOX-bevacizumab plus Vitamin D3 (400 IU/day) ¹³⁰. The results, although not reaching statistical significance, showed improved PFS in patients assigned to the high-dose Vitamin D3 arm. A recent meta-analysis investigated the correlation between serum Vit D levels and impact on survival and risk of recurrence in stage III colorectal cancer (CRC) patients. Ottaiano et al ¹³¹ demonstrated that patients with lower levels of Vitamin D had a 38% and 13% increased risk of death and recurrence, respectively. These findings indicate that a low Vit D concentration negatively impacts the time-to-outcome in stage III CRC ¹³¹.

Vitamin D and Head-and-Neck Cancer

Head-and-neck cancer (HNC) predominantly affects the older population with metabolism disruptions, due to comorbidities or intrinsic frailty. A higher prevalence of Vitamin D3 deficiency in HNC patients was shown in a recent publication ¹³². In a meta-analysis, Pu et al ¹³³ describe an inverse association between HNC incidence, mortality, Vit D3 exposure or dietary or supplemental intake, with an improvement in prognosis.

Vitamin D Levels and Bladder Cancer

Recent studies have investigated the association between bladder cancer (BLC) and Vit D3 serum levels. Baykan et al ¹³⁴ conducted a genetic analysis to prove a connection between VDR polymorphisms and the developing risk of BLC. It was found a statistically significant difference in the genotype distribution of FokI polymorphism, which was, however, lost when adjusting the odds ratio by smoking history. Two different meta-analyses ^{135,136} highlighted that low 25(OH)D serum levels increased the risk of BLC development. Zhang et al ¹³⁵ demonstrate that patients with low Vit D level had an increased risk of BLC development than patients with higher level of serum 25(OH)D. Moreover, Zhao et al ¹³⁶ demonstrated that high 25(OH)D serum concentrations reduced BLC risk by 60%.

Vitamin D and Onco-Hematological Cancer

Sunlight exposure has a potential protective role in various hematologic pathologies ¹³⁷; consequently, Vit D3 also has an impact on prevention. A recent meta-analysis that includes 30 between case-control and cohort studies demonstrated that the possibility of use Vitamin D3 supplementation content in food or their surrogates (sun and UV rays' exposure) is a good protective factor in non-Hodgkin lymphoma (NHL) ¹³⁸. Results showed that UVR exposure may have a protective effect on NHL; however, a higher risk of come down with NHL seems possible when Vitamin D3 serum levels < 25 nmol/L, although these results seem not significant. Drake et al ¹³⁹ conducted a retrospective, observational study where they proved worse prognosis in newly diagnosed Non-Hodgkin Lymphoma patients with Vit D3 deficiency. In addition, in some histotype (like T-cell lymphomas), even with normal Vit D levels, supplementation was necessary. However, this work did not establish a strong relationship between low Vit D3 serum levels and a worse prognosis.

VITAMIN D AND HEART DISEASES

In human body the receptors for vitamin D are highly expressed. It has recently been discovered that Vitamin D receptors are located in endothelial cells and cardiac cells, regulating their metabolism, calcium homeostasis and metalloproteases endocardial production¹⁴⁰. In a recent published article, authors demonstrated that low serum level of 25(OH)D increased the risk of cardiovascular disorders, and in general cardiovascular mortality¹⁴¹. Recently, a meta-analysis showed that the supplementation of Vit D doesn't lower cardiac mortality, heart attack, MACE (major adverse cardiovascular events), or myocardial infarction, either in old or in young patients¹⁴². Anyway, it is suggested that in pediatric patients the supplementation of Vit D may have good impact in cardiac mortality in adulthood, maybe because of epigenetic modifications Vit D induced. In addition, observational studies have shown, in their secondary purposes, an inverse correlation between serum Vitamin D levels and heart disease incidence, even though several confounding factors can alter the data's interpretation and a conclusion can't be clearly established^{143,144}. The primary endpoints, however, concerned with the relationship between Vit D and the risk of postmenopausal osteoporosis in women and dialysis in patients with renal failure. It is notable that these studies included elderly people or at least non-premenopausal women. Therefore, long-term benefits of Vitamin D for cardiovascular disease events were not taken into account as a primary endpoint. Consequently, it is useful to conduct clinical studies on the inverse association between high doses of Vit D and cardiac events as a primary result in a larger population including young subjects. Another recent study showed that early administration of high-dose enteral vitamin D offered no advantage compared to placebo in terms of mortality in critical patients with vitamin D deficiency¹⁴⁵. By contrast, other studies showed that improvements in endothelial function and reduction in the expression of oxLDL and ICAM1 can be provided by daily vitamin D supplementation at 2000 IU for three months in patients suffering from high blood pressure and diabetes¹⁴⁶. Another, similar trial, showed that the everyday administration of 2000 IU and 800 IU of Vit D for two years sensibly lowered systolic blood pressure¹⁴⁷.

VITAMIN D AND HUMAN MICROBIOTA

The human microbiota consists of the population of commensal, symbiotic and pathogenic microorganisms that houses human body. It is composed of around 900 or 1000 different species of microorganism of bacteria, bacteriophage, protozoa, fungi and small protists¹⁴⁸. The gut microbiota is the most varied, vast, and well investigated, but the epidermis' microbiota, lung, buccal cavity, and genitourinary system is also becoming relevant in human pathophysiology¹⁴⁹. The gut microbiota is being considered as an organ given its importance¹⁵⁰. Both genetic and non-genetic factors and in particular diet dynamically influence the gut microbiota, although eating habits are the main cause of these changes^{151,152}. The human microbiota, as demonstrated by several clinical studies, is involved in numerous physiological mechanisms such as the production and degradation of several human nutrients and metabolites, including vitamin D^{139,153-157}. VDR is widely found in normal intestinal epithelial cells, in particular in the crypts. Vitamin D/VDR signaling pathway plays a role in immunomodulation and intestinal barrier homeostasis by regulation tight junctions and adherent junction elements, but also by releasing antimicrobial peptides, like defensins^{159,160}. In this scenario, a dynamic interaction has been observed between active metabolites of Vitamin D and butyrate producers such as Firmicutes¹⁶¹⁻¹⁶³: butyrate-producing intestinal microbiota promote the local production of 1,25(OH)₂D by colon resident immune cells. It is demonstrated that VRD signaling is also influenced by Firmicutes, with other butyrate-producing bacteria (*Coprococcus* and *Faecalibacterum*), further promoting anti-inflammatory function¹⁶⁴. Furthermore, the modulation of bacteria like Firmicutes engages genes that control mucus and butyrate enhances gut healing processes¹⁵⁵. An observational study of 567 elderly men showed an association between high serum Vit D levels and an increment in butyrate-producing bacteria¹⁶¹. In two interventional studies conducted on patients with Intestinal Bowel Disease (IBD), it was found that after administration of vitamin D intestinal microbiota significant changes^{165,166}. In human cell cultures, an increase in VDR expression was observed following the introduction of Lactobacilli¹⁶⁷. A GWAS evaluation of the microbiota showed changes in VDR according to diet and non-genetic factors from 1812 subjects¹⁶⁸. About the axis gut microbiota-Vit-D, an intact Vit D signaling is important for the health of gut microbiota. In fact, it is reported that in mice the disruption of Vit D metabolism

causes intestinal dysbiosis¹⁵⁴, while thanks to a supplementation of Vit D in adults suffering from cystic fibrosis it has been identify a clear change in their intestinal and airway microbiota, with an enrichment of *Lactococcus*, which is linked to better intestinal health¹⁶⁹. It has also been observed that vitamin D supplementation can restore gut dysbiosis and reduce liver damage induced by a high-fat diet by increasing the production of *Lactobacilli*¹⁵⁹. On the contrary, high doses of Vitamin D administered to healthy humans do not modify the stool microbiome composition¹⁷⁰. These studies on humans suggest that the effects on the gut microbiota derived from vitamin D supplementation are expressed in case of physiological reduction of its levels whereas benefits are not providing in humans with normal ones.

CONCLUSIONS

Vit D works as a steroid hormone. Its main source is the conversion of 7-dehydrocholesterol to Vitamin D in the skin induced by UVB. Additional sources are foods that contain Vit D and dietary supplements^{2,3}. Whatever the main source, several hydroxylation reactions are needed to get to its active form, 1,25-dihydroxyvitamin D, which is responsible of its biological effects. Vitamin D takes part in several physiological processes, all involved in calcium homeostasis. Vit D biological activities are mediated by its binding to VDR, a nuclear receptor for steroid hormones that has a transcription factor-activity that ligand-activated, so regulating genes' expression. Although Vit D receptor is expressed mostly in organs with high sensitivity to Vit D because of their role in homeostasis of calcium, such as the bones, kidneys, and small intestine. VDR can also be found in the skin, and in certain cells immune system cells, suggesting that Vit D influences the immune response to numerous pathologic conditions⁸⁶. It is commonly known that rickets in children is directly caused by a diet with severe deficiency of Vit D. On the other hand, the association between osteomalacia in adults and low serum level of Vit D is more controversial. It has been suggested that rickets and osteomalacia may be prevented by a supplementation of 400 IU of Vit D per day, when serum 25(OH) D levels rise above 30 nmol/L¹⁷¹. Nonetheless, supplementation with only Vit D does not seem to be the remedy for limiting fracture risks. On the other hand, the incidence of hip and other fractures in adults can be reduced up to 20% thanks to the combination of calcium and Vit D orally implementation (1000 mg and 800 UI/die, respectively), due to both an increase in 25(OH)D serum levels by 25 nmol/L and an improvement of BMD and bone quality¹⁷²⁻¹⁷⁴. Vit D also regulates muscle homeostasis, affecting strength and development of the muscles. In fact, muscle weakness is common in subjects with chronic kidney disease because of the depletion of 1,25(OH)₂D, and in individuals with genetic mutations in CYP27B1 and Vitamin D Receptor^{37,44}. Low level of Vitamin D is also associated with an augmented risk of autoimmune diseases, multiple sclerosis as an example. Given the role that 1,25(OH)₂D has in downregulating the adaptive immune system, it's understandable how Vit D deficiency may lead to autoimmune diseases, like type 1 diabetes, multiple sclerosis, and inflammatory bowel disease¹⁰. Recent evidence on Vitamin D status and cardiovascular disease's risk suggest that there is no clear advantage from Vitamin D supplementation in patients with heart failure risk. Anyway, the available data are not enough to draw definitive conclusions, and specific trials are required to better clarify if vitamin D supplementation in individuals with cardiovascular disorders adds some benefits. As to type 2 diabetes mellitus and metabolic syndrome, their association with low Vit D serum levels is supported by numerous studies, especially the relationship between Vitamin D supplementation and the slowing in progressing from prediabetes to T2DM¹⁷⁵. Recently, a great and increasingly importance has been given to the importance of the microbiota in the balance of human health, and numerous studies are underway to better clarify the relationship between the gut microbiota composition and the development of diseases. The role of Vitamin D supplementation in improving gut microbiota composition has been supported by some studies, although some questions persist about the adequate 25(OH)D serum level require to improve the microbiota-Vit-D axis^{170,176}. During COVID-19 pandemic, observational studies and meta-analyses explored the connection between Vit D levels and severity of SARS-CoV-2 disease. Results correlate low Vit D serum levels with high COVID-19 mortality and morbidity; however, there are many factors that should be considered, such as a similarity between the risk factors for Vit D deficiency and for COVID-19^{177,178}. Nevertheless, it has been suggested by recent studies that hospitalized patients with COVID-19 had no benefit from Vitamin D oral integration and no association has been found between serum

25(OH)D levels and hospitalization risk in COVID-19 patients^{179,180}. Therefore, drawing definitive conclusions on how Vitamin D can decrease the risk of more severe SARS-CoV-2 infection remain difficult. Concerning cancer patients, preclinical and epidemiological trial correlated Vitamin D to the risk of developing cancer, of cell proliferation, and with prognosis. Vit D has multiple effects on carcinogenesis, that's because it takes part in controlling several cellular processes, like inflammation, angiogenesis, differentiation, invasion, and apoptosis. Overall, epidemiological studies are discordant about the real role of Vit D on cancer developing risk and patient outcomes^{181,182}, showing that new and adequately designed randomized clinical trials are needed. Nonetheless, it can be affirmed that supplementation with Vitamin D is a good strategy for both cancers preventing and therapies. Furthermore, using exogen Vitamin D in a particular subgroup of patients, for examples the ones with HIV infection and cancer, should be part of the standard treatment, with the purpose of decreasing the opportunistic infections' risk. In fact, adequate serum values of Vitamin D should reduce cancer's risk and immunity deficiency¹⁸³⁻¹⁸⁵. Most significantly, in a recent meta-analysis it was shown a reduction in the plasma levels of malondialdehyde, a marker for lipid peroxidation, when Vitamin D is administered orally at doses of 100,000 and 200,000 IU every month. Its antioxidant mechanisms are explained with its scavenger activities for membrane and lipoprotein, which can decrease ROS production, iron damage and ferroptosis¹⁸²⁻¹⁸⁴.

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