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THE MULTIPLE EFFECTS OF VITAMIN D ON CHRONIC DISEASES

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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, 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 rickets [1]. 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 high [2]. Other examples of sources are egg yolk (Vit D3), mushrooms (Vit D2), cereal and dairy products[3]. 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 way [4], usually in dermis or epidermis[5]. 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 $1,25(OH)_2D$ [6]. The rate of Vit D3 formation varies with UVB power and the color of the skin [7] 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

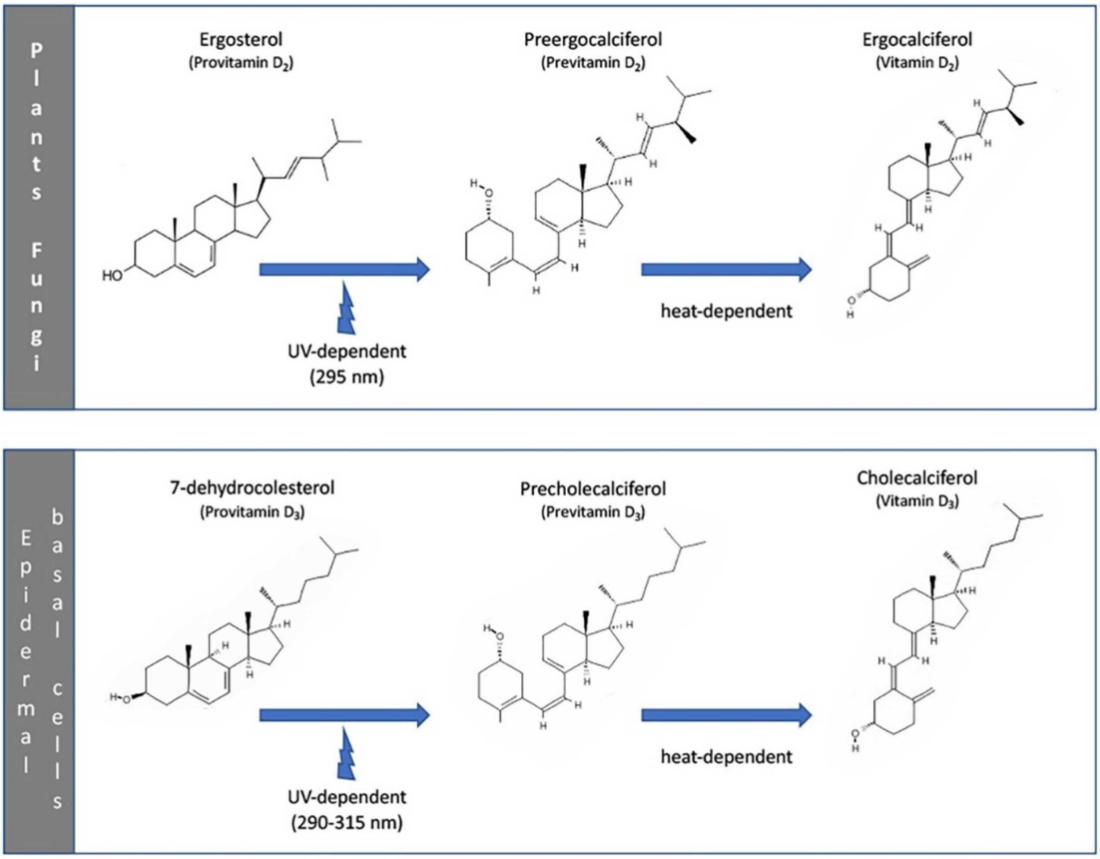

Figure 1. Synthesis of ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). Ergocalciferol is produced only in plants and fungi, while cholecalciferol in basal cells of the epidermis. Both processes occur via two steps, the former induced by the UV light radiation from sun, the latter in a heat-dependent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

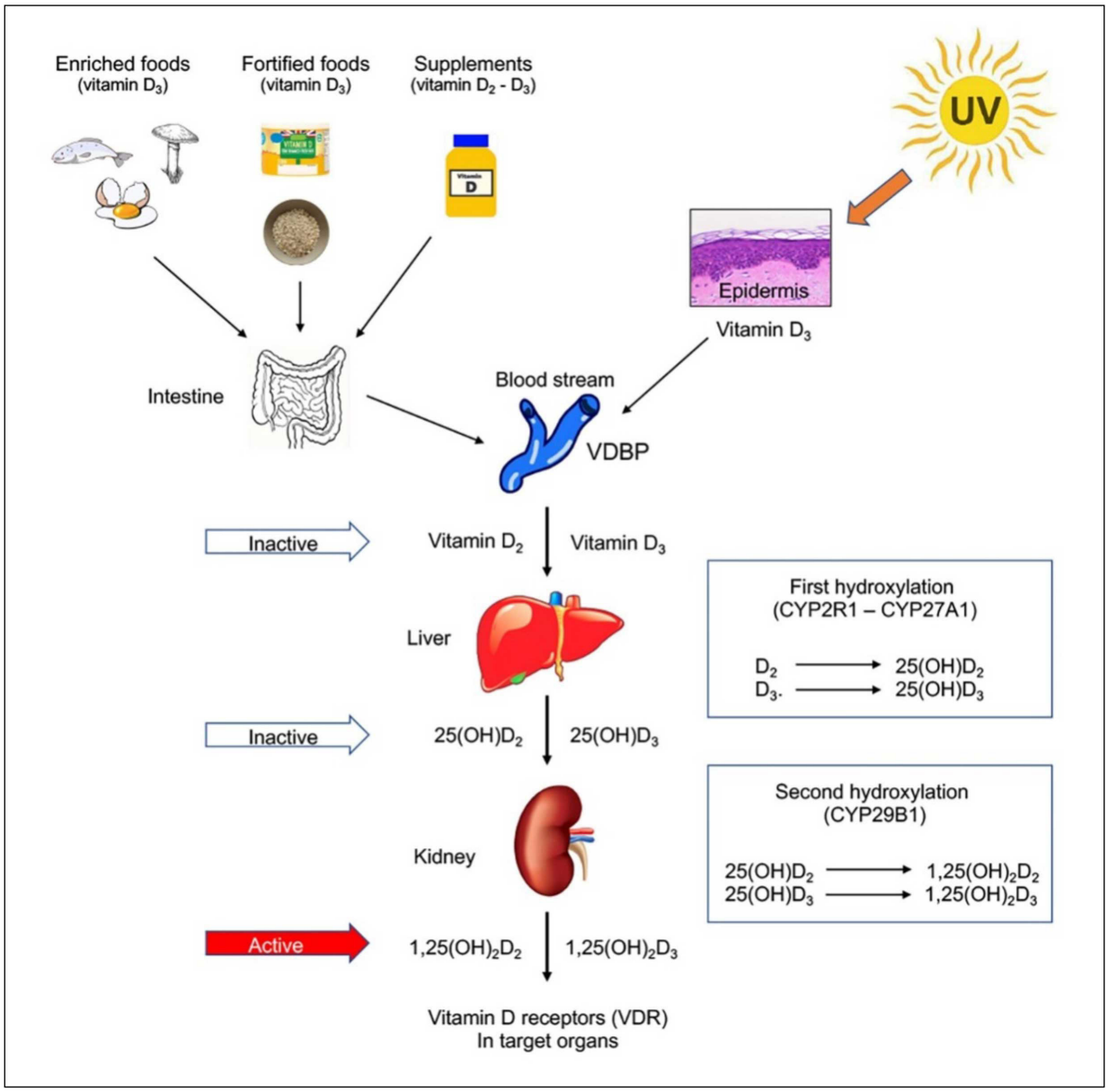

Figure 2. Metabolism of Vitamin D. Vitamin D3 is present in dietary sources, while Vitamin D2 is synthesized in the skin or can be provided through supplements. Once absorbed, it is converted in the liver into 25(OH)D and then in the kidney into the active 1,25(OH)2D. Through the circulation, it is brought 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, 1α- hydroxylation, and 24-hydroxylation. Vit D formation mainly occurs in the liver, and studies on liver 25-hydroxlase showed that its activity is greater in microsomes and mitochondria. Published data have shown that some CYPs have a similar activity to 25-hydroxylase [14]. For example, CYP27A1 is well distributed, and it is contemplated that it is the only mitochondrial hydroxylase with a 25-hydroxlase-like function. Nevertheless, it cannot form 25-hydroxylate Vit D2. Another one with 25-hydroxlase-like activity is CYP2R1, founded in mouse livers [15]. 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

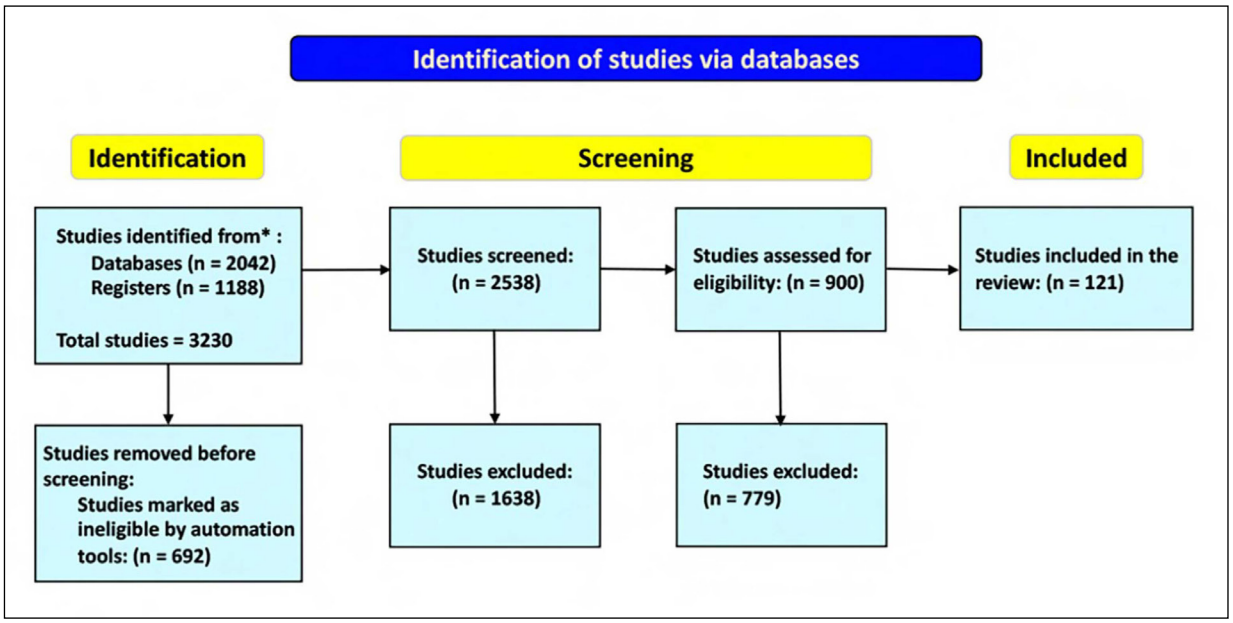

Figure 3. PRISMA diagram. The databases were last accessed on September 2023.

and 3-epi-25(OH)D3 to 1α,25(OH)2D3 in the kidneys (Figure 4). The epimeric forms 3-Epi-25(OH)D3 and 3-Epi-1α,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 CYP11A1 [18-21].

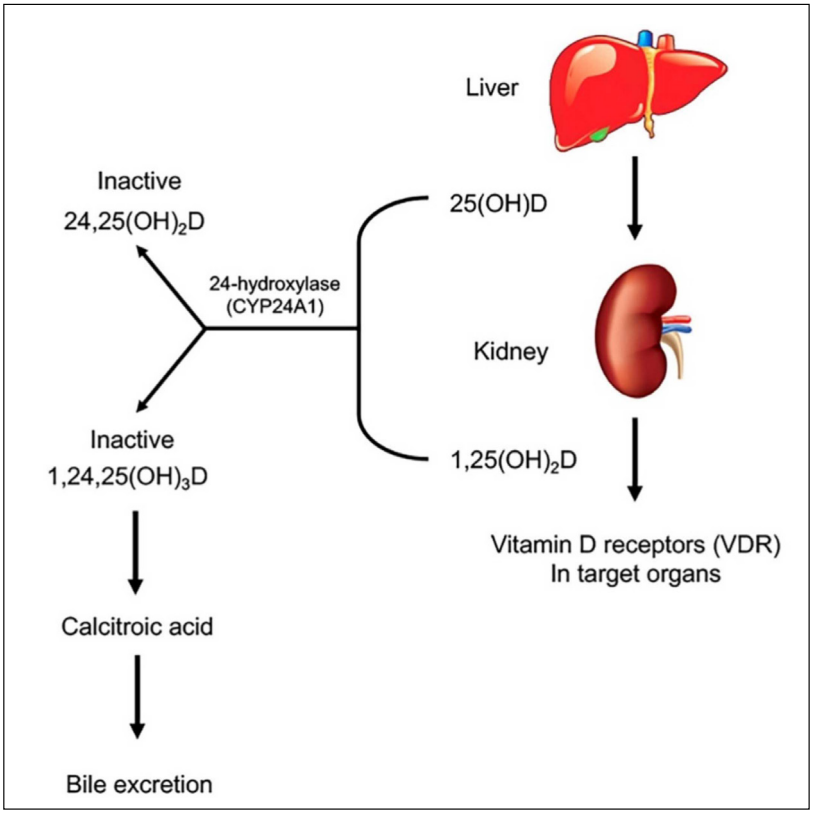

Figure 4. Vitamin D catabolism. Vitamin D is metabolized first to 25 hydroxyvitamin D (25(OH)D), then to 1,25-dihydroxyvitamin D (1,25(OH)2D). CYP27B1 is the key 1-hydroxylase. Both 25(OH)D and 1,25(OH)2D are catabolized by CYP24A1. Once inactive, 1,24,25(OH)3D is then converted in calcitroic acid and 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 al [22] and Haussler et al [23]. 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-hydroxinonenal, 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 examinate 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/ Substance	Action	Clinical Action	Interaction
Erdafitinib	Pharmacodynamic effects of (FGFR/aKlontho) inhibition by erdafitinib can cause hyperphosphatemia	It is recommended to reduce phosphate intake to 600-800 mg per day	Major
Ergocalciferol and Vit D3 derivates	Additional toxicity, manifesting hypercalcemia, hypercalciuria and hyperphosphatemia	In case of hypercalcemia, vitamin D and any Calcium supplements should be immediately avoided	Major
Oxcarbazepine	It Induces CYP450 inducers. It may decrease the pharmacologic effects of vitamin D analogues, inducing the hepatic conversion of Vitamin D to inactive metabolites.	Patients who metabolize CYP450 poorly must be supplemented with double doses of Vi D when receiving oxcarbazepine	Moderate
Magnesium salts	Possible increases in plasma hypermagnesemia, particularly in chronic renal dialysis patients, due to potentially additive pharmacologic effects. Chronic hypermagnesemia may be one of the causes of adynamic bone disease in dialysis patients	Patients on chronic dialysis treatment with a vitamin D analogue should avoid magnesium-containing products	Moderate
Indapamide and others thiazide diuretics	Thiazide diuretics inhibit the renal excretion of calcium and may also enhance the responsiveness 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.	Serum calcium should be monitored if patients experience sign of hypercalcemia.	Moderate

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 bulk [56]. 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 variant	Functional consequence	MAF	Medical conditions
rs2228570	FokI T>C (Met1Pro)	T>C eliminates translation start site	0.35 T	Calcium absorption and calcium accretion to skeleton Vitamin D and parathyroid hormone levels[60] Invasive ovarian carcinoma and breast cancer risk[61]
rs1544410	BsmIIntron 8	A>G nucleotide substitution	0.26 A	Cutaneous malignant melanoma[60] and colorectal carcinoma risk[62]
rs731236	TaqIExon 9 nucleotide 352T>C	T>C methylation	0.26 C	Breast Cancer Prognosis Psoriasis[60]
r7975232	ApaI T>g	T>G nucleotide substitution	0.50 T	Renal Cancer Carcinoma risk[63]
rs11568820	CDx2	A >G eliminates Cdx binding site	0.46 T	Prostate cancer risk[60] Calcipotriol response Growth defect and urinary calcium/ keratinise[60] levels
rs4516035	GATA	T>C eliminates GATA binding site	0.18 C	Growth defect and urinary calcium/ 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-1α- 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 orosteomalacia, 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

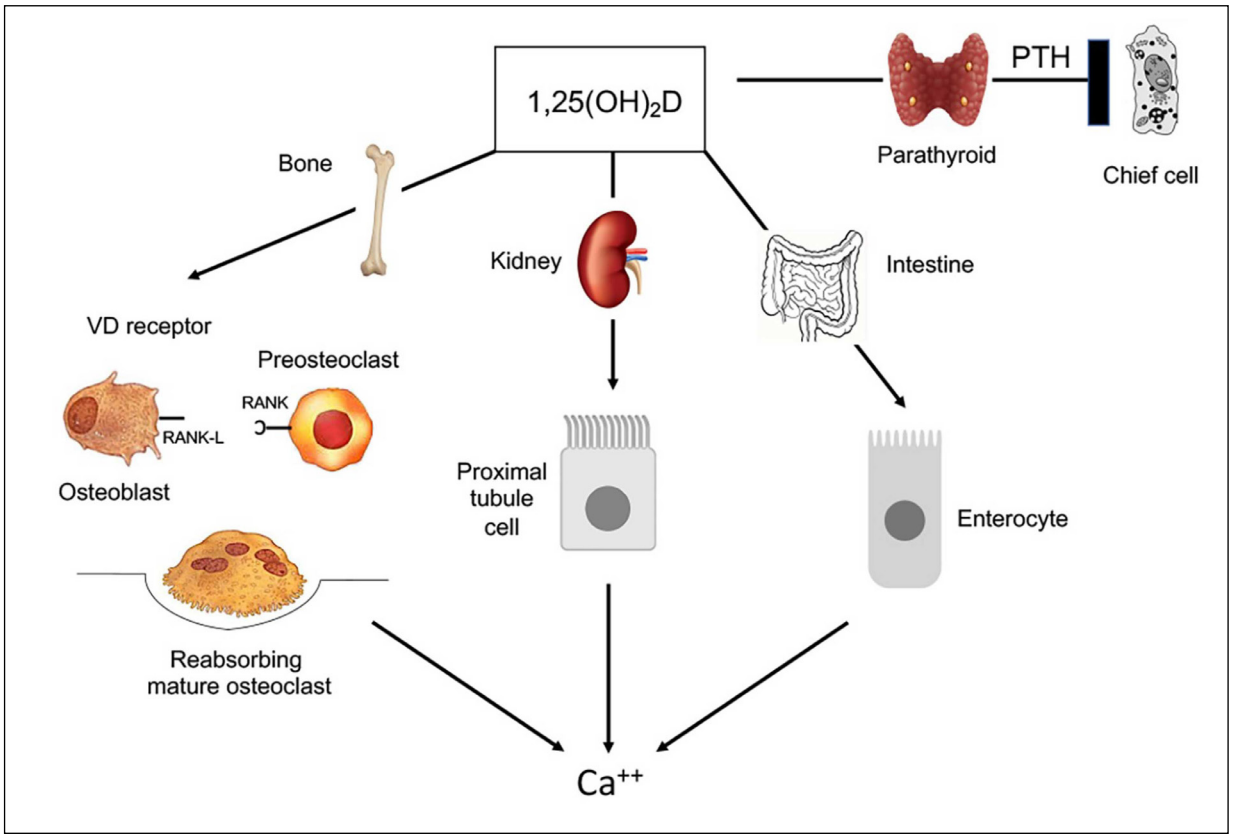

Figure 5. Calcium homeostasis regulation by vitamin D in bone, kidney, intestine and parathyroid glands.

action of macrophage colony-stimulating factor (m-CSF), stimulates the precursor cells to differentiate into osteoclasts, also increasing their activity [76]. 1,25(OH)2D mediates this process by binding to the VDR expressed on osteoblasts surface so as to induce RANKL's production [77].

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 neck [78]. 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 deficiency [79]. 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 treatments [79]. 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 age [80].

Moreover, the muscle weakness observed in hypovitaminosis D enhances the risk of falling, and indirectly also the risk of pathological fractures [81]. 250HD serum levels represent a valuable indicator of Vit D status. According to most experts, Vit D deficiency occurs when serum levels are<50 nmol/L (<20 ng/mL), while other societies, such as the Endocrine Society, advocate larger ranges. 25(OH)D serum levels >75 nmol/L (>30 ng/mL) are considered normal overall, while levels between 50–75 nmol/L (20–30 ng/mL) are considered as Vit D insufficiency [82].

VITAMIN D AND MUSCLE HOMEOSTASIS

Persistent Vitamin D deficiency could lead to proximal myopathy and unsteady gait [84]. Moreover, typical characteristics of rickets and osteomalacia are muscular aches and hypotonia. Muscle protein production is stimulated by 1,25(OH)2D, which is responsible of calcium transport in the sarcoplasmic reticulum, contributing to muscle contraction [85]. 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 diameter [86]. Another study suggests the possibility of a Vit D modulation on myostatin, that negatively regulate muscle mass [87]. 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 low [88]. 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/mL [89]. Obese people or people with malabsorption probably require higher doses [90]. 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 D [91]. 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 been [92]. Some interventional studies, aimed to improve the levels of 25(OH)D in patients suffering from immune-related disorders, have produced contrasting results [93].

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 sunlight [93]. 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 cathelicidin [94], 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 infection [95]. 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 II [96] (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 activity [96]. 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-17 [97]. 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 inhibitors [98].

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' comorbidities [99]. 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 both [100-102]. Oncological patients develop one or more comorbidities, such as cardiopathy, hypertension, diabetes, osteoporosis, apparently not related to the concomitant neoplasia [103]. 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 al [12], 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 intake [104]. 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 symptoms [105].

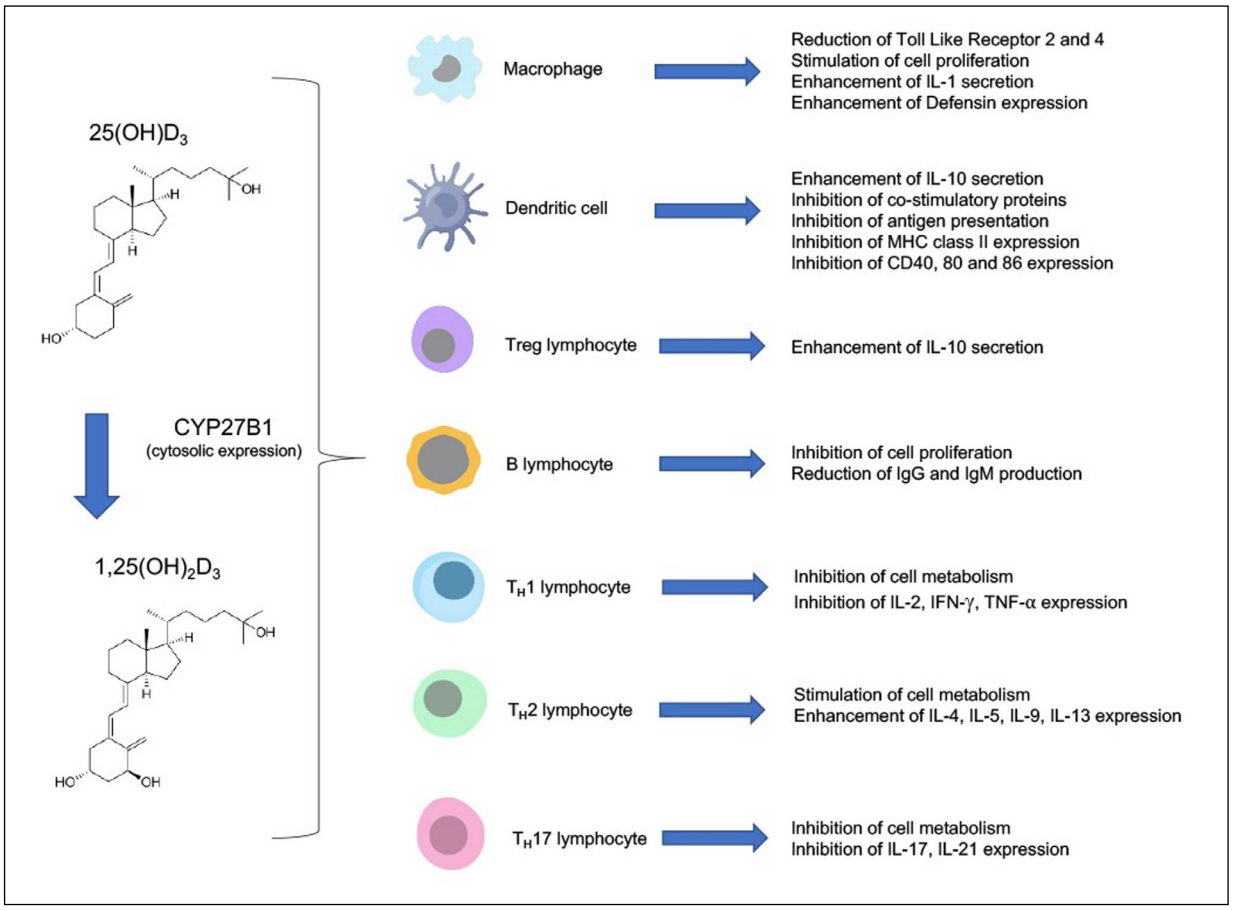

Figure 6. Schematic representation of Vitamin D functions on cells of the innate and adaptive immune system.

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 uncertain [106]. Manson et al [107] 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 ≥55y.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 inclusion [107]. 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 cancer [108]. 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)D enough to suppress cell proliferation [111]. It was suggested that, in breast cells, Vit D core receptor and metabolic complexes may exert their action in an autocrine or paracrine way [111]. 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 cancer [112]. 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 cancer [113]. 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 signaling [114].

Prostate Cancer and Vitamin D

There are numerous studies about how Vit D could influence the clinical history of prostate cancer. Chen et al [115] evaluated calcitriol, 1alpha-hydroxiVit D2 (doxercalciferol), and 19-nor-1alpha-25-dihydroxyVit D2 (paricalcitriol) 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 studies [116]. 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 activity [117]. 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. Paricalcitriol 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/m^2 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 carcinogenesis [121]. 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 D3 [122]. 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 production [140]. 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 mortality [141]. 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 patients [142]. 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 deficiency [145]. 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 diabetes [146]. Another, similar trial, showed that the everyday administration of 2000 IU and 800 IU of Vit D for two years sensibly lowered systolic blood pressure [147].

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 protists [148]. 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 pathophysiology [149]. The gut microbiota is being considered as an organ given its importance [150]. 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 Firmicutes [161-163]: 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 function [164]. Furthermore, the modulation of bacteria like Firmicutes engages genes that control mucus and butyrate enhances gut healing processes [155]. An observational study of 567 elderly men showed an association between high serum Vit D levels and an increment in butyrate-producing bacteria [161]. 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 Lactobacilli [167]. A GWAS evaluation of the microbiota showed changes in VDR according to diet and non-genetic factors from 1812 subjects [168]. 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 dysbiosis [154], 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 health [169]. 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 composition [170]. 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 conditions [86]. 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/L [171]. 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 quality [172-174]. 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)2, 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 disease [10]. 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 T2DM [175]. 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 deficiency [183-185]. 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 ferroptosis [182-184].

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REFERENCES

1. Berretta M, Quagliariello V, Bignucolo A, Facchini S, Maurea N, Di Francia R, Fiorica F, Sharifi S, Bressan S, Richter SN. The Multiple Effects of Vitamin D against Chronic Diseases: From Reduction of Lipid Peroxidation to Updated Evidence from Clinical Studies. Antioxidants 2022; 11: 1090.
2. Lamberg-Allardt C. Vitamin D in Foods and as Supplements. Prog Biophys Mol Biol 2006; 92: 33-38.
3. Dominguez LJ, Farruggia M, Veronese N, Barbagallo M. Vitamin D Sources, Metabolism, and Deficiency: Available Compounds and Guidelines for Its Treatment. Metabolites 2021; 11: 255.
4. Klein GL, Chen TC, Holick MF, Langman CB, Price H, Celism MM, Herndon DN. Synthesis of Vitamin D in Skin after Burns. Lancet 2004; 363: 291-292.
5. Carlberg C. The Physiology of Vitamin D-Far More than Calcium and Bone. Front Physiol 2014; 5: 335.
6. Boccuzzi L, Infante M, Ricordi C. The potential therapeutic role of vitamin D in inflammatory bowel disease Eur Rev Med Pharmacol Sci 2023; 47: 4678-4687.
7. Holick MF, Uskokovic M, Henley JW, MacLaughlin J, Holick SA, Potts JT. The Photoproduction of 1 Alpha,25- Dihydroxyvitamin D3 in Skin: An Approach to the Therapy of Vitamin-D-Resistant Syndromes. N Engl J Med 1980; 303: 349-354.
8. Medrano M, Carrillo-Cruz E, Montero I, Perez-Simon, JA. Vitamin D: Effect on Haematopoiesis and Immune System and Clinical Applications. Int J Mol Sci 2018; 19: E2663.
9. Uchiyama Y, Higuchi Y, Takeda S, Masaki T, Shira-Ishi A, Sato K, Kubodera N, Ikeda K, Ogata, E. ED-71, a Vitamin D Analog, Is a More Potent Inhibitor of Bone Resorption than Alfacalcidol in an Estrogen-Deficient Rat Model of Osteoporosis. Bone 2002; 30: 582-588.
10. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes, B, Lips P, Munns CF, Lazaretti-Castro M, Giustina A, Bilezikian J. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev 2019; 40: 1109-1151.
11. Çetin Daglı S, Tunalı Çokluk S, Ozkan Z, Pancar Z. Comparison of individuals doing sports in indoor and outdoor areas and sedentary individuals in terms of vitamin D, body fat content, and obesity values. Eur RevMedPharmacol Sci 2023; 27: 7401-7408.

12. Rusińska A, Płudowski P, Walczak M, Borszewska-Kornacka MK, Bossowski A, Chlebna-Sokól D, Czech-Kowalska J, Dobrzańska A, Franek E, Helwich E, Jackowska T, Kalina MA, Konstantynowicz J, Książyk J, Lewiński A, Łukaszkiewicz J, Marcinowska-Suchowierska E, Mazur A, Michałus I, Peregud-Pogorzelski J, Romanowska H, Ruchała M, Socha P, Szalecki M, Wielgoś M, Zwolińska D, Zygmunt A. Vitamin D Supplementation Guidelines for General Population and Groups at Risk of Vitamin D Deficiency in Poland-Recommendations of the Polish Society of Pediatric Endocrinology and Diabetes and the Expert Panel With Participation of National Specialist Consultants and Representatives of Scientific Societies-2018 Update. Front Endocrinol 2018; 9: 246.
13. Gandini S, Francesco F, Johanson H, Bonanni B, Testori A. Why Vitamin D for Cancer Patients? Ecancermedicalscience 2009; 3: 160.
14. Guryev O, Carvalho RA, Usanov S, Gilep A, Estabrook RW. A Pathway for the Metabolism of Vitamin D3: Unique Hydroxylated Metabolites Formed during Catalysis with Cytochrome P450scc (CYP11A1). Proc Natl Acad Sci U S A 2003; 100: 14754-14759.
15. Zhu JG, Ochalek JT, Kaufmann M, Jones G, Deluca HF. CYP2R1 Is a Major, but Not Exclusive, Contributor to 25- Hydroxyvitamin D Production in Vivo. Proc Natl Acad Sci USA 2013; 110: 15650-15655.
16. Bischof MG, Siu-Caldera ML, Weiskopf A, Vouros P, Cross HS, Peterlik M, Reddy GS. Differentiation-Related Pathways of 1 Alpha,25-Dihydroxycholecalciferol Metabolism in Human Colon Adenocarcinoma-Derived Caco-2 Cells: Production of 1 Alpha,25-Dihydroxy-3epi-Cholecalciferol. Exp Cell Res 1998; 241: 194-201.
17. Kamao M, Tatematsu S, Hatakeyama S, Sakaki T, Sawada N, Inouye K, Ozono K, Kubodera N, Reddy GS, Okano T. C-3 Epimerization of Vitamin D3 Metabolites and Further Metabolism of C-3 Epimers: 25-Hydroxyvitamin D3 Is Metabolized to 3-Epi-25-Hydroxyvitamin D3 and Subsequently Metabolized through C-1alpha or C-24 Hydroxylation. J Biol Chem 2004; 279: 15897-15907.
18. Slominski AT, Kim TK, Li W, Yi AK, Postlethwaite A, Tuckey RC. The Role of CYP11A1 in the Production of Vitamin D Metabolites and Their Role in the Regulation of Epidermal Functions. J Steroid Biochem Mol Biol 2014; 144: 28-39.
19. Slominski AT, Kim TK, Shehabi HZ, Semak I, Tang EKY, Nguyen MN, Benson HAE, Korik E, Janjetovic Z, Chen J,Yates CR, Postlethwaite A, Li W, Tuckey RC. In Vivo Evidence for a Novel Pathway of Vitamin D_3 Metabolism Initiated by P450scc and Modified by CYP27B1. FASEB J 2012; 26: 3901-3915.
20. Slominski AT, Kim TK, Li W, Postlethwaite A, Tieu EW, Tang EKY, Tuckey RC. Detection of Novel CYP11A1- Derived Secosteroids in the Human Epidermis and Serum and Pig Adrenal Gland. Sci Rep 2015; 5: 14875.
21. Slominski AT, Li W, Kim TK, Semak I, Wang J, Zjawiony JK, Tuckey RC. Novel Activities of CYP11A1 and Their Potential Physiological Significance. J Steroid Biochem Mol Biol 2015; 151: 25-37.
22. Pike JW, Meyer MB. The Vitamin D Receptor: New Paradigms for the Regulation of Gene Expression by 1,25- DihydroxyvitaminD(3). Endocrinol Metab Clin N Am 2010; 39: 255-269.
23. Haussler MR, Jurutka PW, Mizwicki M, Norman, AW. Vitamin D Receptor(VDR)-Mediated Actions of $1\alpha,25(OH)_2$vitamin D_3: Genomic and Non-Genomic Mechanisms. Best Pract Res Clin Endocrinol Metab 2011; 25: 543-559.
24. Rochel N, Wurtz JM, Mitschler A, Klaholz B, Moras D. The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. Mol Cell 2000; 5: 173-179.
25. Mangelsdorf DJ, Evans RM. The RXR heterodimers and orphan receptors. Cell 1995; 83: 841-850.
26. Norman AW, Okamura WH, Hammond MW, Bishop JE, Dormanen MC, Bouillon R, van Baelen H, Ridall AL, Daane E, Khoury R, Farach-Carson MC. Comparison of 6-s-Cis- and 6-s-Trans-Locked Analogs of 1alpha,25-Dihydroxyvitamin D3 Indicates That the 6-s-Cis Conformation Is Preferred for Rapid Nongenomic Biological Responses and That Neither 6-s-Cis- nor 6-s-Trans-Locked Analogs Are Preferred for Genomic Biological Responses. Mol Endocrinol 1997; 11: 1518-1531.
27. Dede S, Taşpinar M, Yüksek V, Çetin S, Usta A. The Effects of Vitamin D Application on NaF-Induced Cytotoxicity in Osteoblast Cells (hFOB 1.19). Biol Trace Elem Res 2023; 201: 698-705.
28. Lin S, Wang W, Shi L, Yang X, Chen Y, Liu X, Li J, Ye F, An X, Zhang X. Severe Vitamin D Deficiency Is Strongly Associated with Liver Dysfunction and Disease Severity in Hepatitis B Virus Related Cirrhosis and Liver Failure Patients. J Nutr Sci Vitaminol 2022; 68: 16-22.
29. Russo C, Valle MS, Casabona A, Spicuzza L, Sambataro G, Malaguarnera L. Vitamin D Impacts on Skeletal Muscle Dysfunction in Patients with COPD Promoting Mitochondrial Health. Biomedicines 2022; 10: 898.
30. Śledzińska K, Landowski P, Żmijewski MA, Kamińska B, Kowalski K, Liberek A. Diet, Sun, Physical Activity and Vitamin D Status in Children with Inflammatory Bowel Disease. Nutrients 2022; 14: 1029.
31. Trasciatti S, Piras F, Bonaretti S, Marini S, Nencioni S, Biasci E, Egan CG, Nannipieri F. Effect of Oral Cholecalciferol in a Murine Model of Celiac Disease: A Dose Ranging Study. J Steroid Biochem Mol Biol 2022; 220: 106083.
32. Balion C, Griffith LE, Strifler L, Henderson M, Patterson C, Heckman G, Llewellyn DJ, Raina P. Vitamin D, Cognition, and Dementia: A Systematic Review and Meta-Analysis. Neurology 2012; 79: 1397-1405.
33. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture Prevention with Vitamin D Supplementation: A Meta-Analysis of Randomized Controlled Trials. JAMA 2005; 293: 2257-2264.
34. Peterson AL, Murchison C, Zabetian C, Leverenz JB, Watson GS, Montine T, Carney N, Bowman GL, Edwards K, Quinn JF. Memory, Mood, and Vitamin D in Persons with Parkinson's Disease. J Parkinsons Dis 2013; 3: 547-555.
35. Koduah P, Paul F, Dörr JM. Vitamin D in the Prevention, Prediction and Treatment of Neurodegenerative and Neuroinflammatory Diseases. EPMA J 2017; 8: 313-325.
36. Lee SS, Ling KH, Tusimin M, Subramaniam R, Rahim KF, Loh SP. Interplay between Maternal and Neonatal Vitamin D Deficiency and Vitamin-D-Related Gene Polymorphism with Neonatal Birth Anthropometry. Nutrients 2022; 14: 564.
37. Manousaki D, Mitchell R, Dudding T, Haworth S, Harroud A, Forgetta V, Shah RL, Luan J, Langenberg C, Timpson NJ,Richards JB . Genome-Wide Association Study for Vitamin D Levels Reveals 69 Independent Loci. Am J Hum Genet 2020; 106: 327-337.
38. Wang Z, Lin YS, Zheng XE, Senn T, Hashizume T, Scian M, Dickmann LJ, Nelson SD, Baillie TA, Hebert MF,Blough D, Davis CL, Thummel KE . An Inducible Cytochrome P450 3A4-Dependent Vitamin D Catabolic Pathway. Mol Pharmacol 2012; 81: 498-509.
39. Nicolaido P, Georgouli H, Kotsalis H, Matsinos Y, Papadopoulou A, Fretzayas A, Syriopoulou V, Krikos X, Karantana A, Karpathios T. Effects of Anticonvulsant Therapy on Vitamin D Status in Children: Prospective Monitoring Study. J Child Neurol 2006; 21: 205-209.

40. Christiansen C, Rodbro P, Lund M. Incidence of Anticonvulsant Osteomalacia and Effect of Vitamin D: Controlled Therapeutic Trial. Br Med J 1973; 4: 695-701.
41. Carlberg C, Haq A. The Concept of the Personal Vitamin D Response Index. J Steroid Biochem Mol Biol 2018; 175: 12-17.
42. Smith LM, Gallagher JC, Suiter C. Medium Doses of Daily Vitamin D Decrease Falls and Higher Doses of Daily Vitamin D3 Increase Falls: A Randomized Clinical Trial. J Steroid Biochem Mol Biol 2017; 173: 317-322.
43. Seuter S, Virtanen JK, Nurmi T, Pihlajamäki J, Mursu J, Voutilainen S, Tuomainen TP, Neme A, Carlberg C. Molecular Evaluation of Vitamin D Responsiveness of Healthy Young Adults. J Steroid Biochem Mol Biol 2017; 174: 314-321.
44. Kim YA, Yoon JW, Lee Y, Choi HJ, Yun JW, Bae E, Kwon SH, Ahn SE, Do AR, Jin H, Won S, Park DJ, Shin CS, Seo JH. Unveiling Genetic Variants Underlying Vitamin D Deficiency in Multiple Korean Cohorts by a Genome-Wide Association Study. Endocrinol Metab 2021; 36: 1189-1200.
45. Thacher TD, Fischer PR, Singh RJ, Roizen J, Levine MA. CYP2R1 Mutations Impair Generation of 25-Hydroxyvitamin D and Cause an Atypical Form of Vitamin D Deficiency. J Clin Endocrinol Metab 2015; 100: 1005-1013.
46. Cheng JB, Levine MA, Bell NH, Mangelsdorf DJ, Russell DW. Genetic Evidence That the Human CYP2R1 Enzyme Is a Key Vitamin D 25-Hydroxylase. Proc Natl Acad Sci U S A 2004; 101: 7711-7715.
47. Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, Gallicchio L, Jacobs EJ, Ascherio A, Helzlsouer K, Jacobs KB, Li Q, Weinstein SJ, Purdue M, Virtamo J, Horst R, Wheeler W, Chanock S, Hunter DJ, Hayes RB, Kraft P, Albanes D. Genome-Wide Association Study of Circulating Vitamin D Levels. Hum Mol Genet 2010; 19: 2739-2745.
48. Bu FX, Armas L, Lappe J, Zhou Y, Gao G, Wang HW, Recker R, Zhao LJ. Comprehensive Association Analysis of Nine Candidate Genes with Serum 25-Hydroxy Vitamin D Levels among Healthy Caucasian Subjects. Hum Genet 2010; 128; 549-556.
49. Simon KC, Munger KL, Kraft P, Hunter DJ, De Jager PL, Ascherio A, Genetic Predictors of 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis. J Neurol 2011; 258: 1676-1682.
50. Cooper JD, Smyth DJ, Walker NM, Stevens H, Burren OS, Wallace C, Greissl C, Ramos-Lopez E, Hyppönen E, Dunger DB, Spector TD, Ouwehand WH, Wang TJ, Badenhoop K, Todd JA. Inherited Variation in Vitamin D Genes Is Associated with Predisposition to Autoimmune Disease Type 1 Diabetes. Diabetes 2011; 60: 1624-1631.
51. Dorjgochoo T, Shi J, Gao YT, Long J, Delahanty R, Xiang YB, Cai Q, Shu XO. Genetic Variants in Vitamin D Metabolism-Related Genes and Body Mass Index: Analysis of Genome-Wide Scan Data of Approximately 7000 Chinese Women. Int J Obes 2012; 36: 252-1255.
52. Di Spigna G, Del Puente A, Covelli B, Abete E, Varriale E, Salzano S, Postiglione L. Vitamin D Receptor Polymorphisms as Tool for Early Screening of Severe Bone Loss in Women Patients with Rheumatoid Arthritis. Eur Rev Med Pharmacol Sci 2016; 20: 4664-4669.
53. Divanoglou N, Komninou D, Stea EA, Argiriou A, Papatzikas G, Tsakalof A, Pazaitou-Panayiotou K, Georgakis MK, Petridou E. Association of Vitamin D Receptor Gene Polymorphisms with Serum Vitamin D Levels in a Greek Rural Population (Velestino Study). Lifestyle Genom 2021; 14: 81-90.
54. Usategui-Martín R, De Luis-Román DA, Fernández-Gómez JM, Ruiz-Mambrilla M, Pérez-Castrillón JL. Vitamin D Receptor (VDR) Gene Polymorphisms Modify the Response to Vitamin D Supplementation: A Systematic Review and Meta- Analysis. Nutrients 2022; 14: 360.
55. Zhao XQ, Chen K, Wan HY, He SY, Qin HJ, Yu B, Jiang N. Vitamin D Receptor Genetic Variations May Associate with the Risk of Developing Late Fracture-Related Infection in the Chinese Han Population. J Immunol Res 2022; 2022: 9025354.
56. Jurutka PW, Remus LS, Whitfield GK, Thompson PD, Hsieh JC, Zitzer H, Tavakkoli P, Galligan MA, Dang HT, Haussler CA, Haussler MR. The Polymorphic N Terminus in Human Vitamin D Receptor Isoforms Influences Transcriptional Activity by Modulating Interaction with Transcription Factor IIB. Mol Endocrinol 2000; 14; 401-420.
57. D'Alésio A, Garabédian M, Sabatier J.P, Guaydier-Souquières G, Marcelli C, Lemaçon A, Walrant-Debray O, Jehan F. Two Single-Nucleotide Polymorphisms in the Human Vitamin D Receptor Promoter Change Protein-DNA Complex Formation and Are Associated with Height and Vitamin D Status in Adolescent Girls. Hum Mol Genet 2005; 14: 3539-3548.
58. Arai H, Miyamoto K.I, Yoshida M, Yamamoto H, Taketani Y, Morita K, Kubota M, Yoshida S, Ikeda M, Watabe F, Kanemasa Y, Takeda E. The Polymorphism in the Caudal-Related Homeodomain Protein Cdx-2 Binding Element in the Human Vitamin D Receptor Gene. J Bone Miner Res 2001; 16: 1256-1264.
59. Rowland GW, Schwartz GG, John EM, Ingles SA, Calcium Intake and Prostate Cancer among African Americans: Effect Modification by Vitamin D Receptor Calcium Absorption Genotype. J Bone Miner Res 2012; 27; 187-194.
60. Poon AH, Gong L, Brasch-Andersen C, Litonjua AA, Raby BA, Hamid Q, Laprise C, Weiss ST, Altman RB, Klein TE. Very important pharmacogene summary for VDR. Pharmacogenet Genomics 2012; 22: 758-63.
61. Lurie G, Wilkens LR, Thompson PJ, Carney ME, Palmieri RT, Pharoah PD, Song H, Hogdall E, Kjaer SK, Di Cioccio RA, McGuire V, Whittemore AS, Gayther SA, Gentry-Maharaj A, Menon U, Ramus SJ, Goodman MT. Ovarian Cancer Association Consortium. Vitamin D receptor rs2228570 polymorphism and invasive ovarian carcinoma risk: pooled analysis in five studies within the Ovarian Cancer Association Consortium. Int J Cancer 2011; 128: 936-43.
62. Alkhayal KA, Awadalia ZH, Vaali-Mohammed MA, Al Obeed OA, Al Wesaimer A, Halwani R, Zubaidi AM, Khan Z, Abdulla MH. Association of Vitamin D Receptor Gene Polymorphisms with Colorectal Cancer in a Saudi Arabian Population. PLoS One 2016; 11: e0155236
63. Jianhai T, Jian L, Long Z, Wei W, Shumao Z, Yiming W, Xiaojuan L. Vitamin D receptor gene polymorphisms and its interactions with environmental factors on renal cell carcinoma risk. Genes Environ 2021; 43: 19.
64. Goltzman D. Functions of Vitamin D in Bone. Histochem Cell Biol 2018; 149: 305-312.
65. Khundmiri SJ, Murray RD, Lederer E. PTH and Vitamin D. Compr Physiol 2016; 6: 561-601.
66. Goltzman D, Mannstadt M, Marcocci C. Physiology of the Calcium-Parathyroid Hormone-Vitamin D Axis. Front Horm Res 2018; 50: 1-13.
67. Marks K.H, Kilav R, Naveh-Many T, Silver J. Calcium, Phosphate, Vitamin D, and the Parathyroid. Pediatr Nephrol 1996; 10: 364-367.
68. De Luca HF, The Metabolism and Functions of Vitamin D. Adv Exp Med Biol 1986; 196; 361-375.
69. Kostecka D, Schneider-Matyka D, Barczak K, Starczewska M, Szkup M, Ustianowski P, Brodowski J, Grochans E. The effect of vitamin D levels on lipid, glucose profiles and depression in perimenopausal women. Eur Rev Med Pharmacol Sci 2022; 26: 3493-3505.

70. Ubesie AC, Heubi JE, Kocoshis SA, Henderson CJ, Mezoff AG, Rao MB, Cole CR. Vitamin D Deficiency and Low Bone Mineral Density in Pediatric and Young Adult Intestinal Failure. J Pediatr Gastroenterol Nutr 2013; 57: 372-376.
71. Salovaara K, Tuppurainen M, Kärkkäinen M, Rikkonen T, Sandini L, Sirola J, Honkanen R, Alhava E, Kröger H. Effect of Vitamin D(3) and Calcium on Fracture Risk in 65- to 71-Year-Old Women: A Population-Based 3-Year Randomized, Controlled Trial--the OSTPRE-FPS. J Bone Miner Res 2010; 25: 1487-1495.
72. Seeman E, Bone Modeling and Remodeling. Crit Rev Eukaryot Gene Expr 2009; 19: 219-233.
73. Langdahl B, Ferrari S, Dempster DW, Bone Modeling and Remodeling: Potential as Therapeutic Targets for the Treatment of Osteoporosis. Ther Adv Musculoskelet Dis 2016; 8: 225-235.
74. Boyce BF, Yao Z, Xing L, Osteoclasts Have Multiple Roles in Bone in Addition to Bone Resorption. Crit Rev Eukaryot Gene Expr 2009; 19: 171-180.
75. Raggatt LJ, Partridge NC, Cellular and Molecular Mechanisms of Bone Remodeling. J Biol Chem 2010; 285: 25103-25108.
76. Natsag J, Kendall MA, Sellmeyer DE, McComsey GA, Brown TT, Vitamin D, Osteoprotegerin/Receptor Activator of Nuclear Factor-Kappa B Ligand (OPG/RANKL) and Inflammation with Alendronate Treatment in HIV-Infected Patients with Reduced Bone Mineral Density. HIV Med 2016; 17: 196-205.
77. Anderson PH, Sawyer RK, Moore AJ, May BK, O'Loughlin PD, Morris HA. Vitamin D Depletion Induces RANKL- Mediated Osteoclastogenesis and Bone Loss in a Rodent Model. J Bone Miner Res 2008; 23: 1789-1797.
78. Chu YR, Xu SQ, Wang JX, Zong HX, Chen KM, Wang C, Tong WQ, Wang XL. Synergy of sarcopenia and vitamin D deficiency in vertebral osteoporotic fractures in rheumatoid arthritis. Clin Rheumatol 2022; 41: 1979-1987.
79. Kulenović I, Rasić S, Kulenović E, Osteoporosis: Current Trends in Diagnosis and Management. Bosn J Basic Med Sci 2006; 6: 24-28.
80. Sadat-Ali M, Al Elq AH, Al-Turki HA, Al-Mulhim FA, Al-Ali AK, Influence of Vitamin D Levels on Bone Mineral Density and Osteoporosis. Ann Saudi Med 2011; 31: 602-608.
81. Mokta J, Balraj null, Mokta K, Ranjan A, Joshi I, Garg M, High Prevalence of Hypovitaminosis D in Patients Presenting with Proximal Muscle Weakness: A Sub-Himalayan Study. J Assoc Phys India 2017; 65: 55-58.
82. Vieth R, Why the Minimum Desirable Serum 25-Hydroxyvitamin D Level Should Be 75 Nmol/L (30 Ng/Ml). Best Pract Res Clin Endocrinol Metab 2011; 25: 681-691.
83. Bischoff-Ferrari HA, Optimal Serum 25-Hydroxyvitamin D Levels for Multiple Health Outcomes. Adv Exp Med Biol 2014; 810: 500-525.
84. Chiang CM, Ismaeel A, Griffis RB, Weems S, Effects of Vitamin D Supplementation on Muscle Strength in Athletes: A Systematic Review. J Strength Cond Res 2017; 31: 566-574.
85. Bislev LS, Grove-Laugesen D, Rejnmark L, Vitamin D and Muscle Health: A Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials. J Bone Miner Res 2021; 36: 1651-1660.
86. Girgis CM, Mokbel N, Cha KM, Houweling PJ, Abboud M, Fraser DR, Mason RS, Clifton-Bligh RJ, Gunton JE, The Vitamin D Receptor (VDR) Is Expressed in Skeletal Muscle of Male Mice and Modulates 25-Hydroxyvitamin D (25OHD) Uptake in Myofibers. Endocrinology 2014; 155: 3227-3237.
87. Garcia LA, King KK, Ferrini MG, Norris KC, Artaza JN. 1,25(OH)2vitamin D3 Stimulates Myogenic Differentiation by Inhibiting Cell Proliferation and Modulating the Expression of Promyogenic Growth Factors and Myostatin in C2C12 Skeletal Muscle Cells. Endocrinology 2011; 152: 2976-2986.
88. Lee YM, Kim SA, Lee DH, Can Current Recommendations on Sun Exposure Sufficiently Increase Serum Vitamin D Level? One-Month Randomized Clinical Trial. J Korean Med Sci 2020; 35: 50
89. Tepper S, Shahar DR, Geva D, Ish-Shalom S, Predictors of Serum 25(Oh)D Increase Following Bimonthly Supplementation with 100,000IU Vitamin D in Healthy, Men Aged 25-65 Years. J Steroid Biochem Mol Biol 2014; 144: 163-166.
90. Bassatne A, Chakhtoura M, Saad R, Fuleihan GEH. Vitamin D Supplementation in Obesity and during Weight Loss: A Review of Randomized Controlled Trials. Metabolism 2019; 92: 193-205.
91. Arora J, Wang J, Weaver V, Zhang Y, Cantorna MT, Novel Insight into the Role of the Vitamin D Receptor in the Development and Function of the Immune System. J Steroid Biochem Mol Biol 2022; 219: 1060.
92. Charoenngam N, Holick MF, Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients 2020; 12: E2097.
93. Wu Y, Lin X, Song F, Xue D, Wang Y. Vitamin D3 Promotes Autophagy in THP-1 Cells Infected with Mycobacterium Tuberculosis. Exp Ther Med 2022; 23: 240.
94. Matos C, Renner K, Peuker A, Schoenhammer G, Schreiber L, Bruss C, Eder R, Bruns H, Flamann C, Hoffmann P. Physiological Levels of 25-Hydroxyvitamin D3 Induce a Suppressive CD4+ T Cell Phenotype Not Reflected in the Epigenetic Landscape. J Immunol 2022; 95 e13146.
95. Schlingmann KP. Vitamin D-Dependent Hypercalcemia. Endocrinol Metab Clin N Am 2021; 50: 729-742.
96. Pérez-Ferro M, Romero-Bueno FI, Serrano Del Castillo C, Mahillo I, Alvear A, Largo R, Herrero-Beaumont G, Sánchez- Pernaute O. A Subgroup of Lupus Patients with Nephritis, Innate T Cell Activation and Low Vitamin D Is Identified by the Enhancement of Circulating MHC Class I-Related Chain A. Clin Exp Immunol 2019; 196: 336-344.
97. Komisarenko YI, Bobryk MI. Vitamin D Deficiency and Immune Disorders in Combined Endocrine Pathology. Front Endocrinol 2018; 9: 600.
98. Oh S, Chun S, Hwang S, Kim J, Cho Y, Lee J, Kwack K, Choi SW. Vitamin D and Exercise Are Major Determinants of Natural Killer Cell Activity, Which Is Age- and Gender-Specific. Front Immunol 2021; 12: 594356.
99. Abrahamsson H, Porojnicu AC, Lindstrøm JC, Dueland S, Flatmark K, Hole KH, Seierstad T, Moan J, Redalen KR, Meltzer S, Ree AH. High Level of Circulating Vitamin D during Neoadjuvant Therapy May Lower Risk of Metastatic Progression in High-Risk Rectal Cancer. BMC Cancer 2019; 19: 488.
100. Buttigliero C, Monagheddu C, Petroni P, Saini A, Dogliotti L, Ciccone G, Berruti A. Prognostic Role of Vitamin d Status and Efficacy of Vitamin D Supplementation in Cancer Patients: A Systematic Review. Oncologist 2011; 16: 1215-1227.
101. Karata F, Adahan D. Is Low Serum Vitamin D Level Associated with Cancer? Vitamin D and cancer. WCRJ 2020; 7: e1683.
102. Shah SIA. Beneficial Role of Vitamin D in Common Cancers: Is the Evidence Compelling Enough? WCRJ 2020; 7: e1574.
103. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The Role of Vitamin D in Reducing Cancer Risk and Progression. Nat Rev Cancer 2014; 14: 342-357.

104. Dalle Carbonare L, Valenti MT, Del Forno F, Caneva E, Pietrobelli A. Vitamin D: Daily vs. Monthly Use in Children and Elderly-What Is Going On? Nutrients 2017; 9: E652.
105. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, Holick MF. The Role of Vitamin D in Cancer Prevention. Am J Public Health 2006; 96: 252-261.
106. Sluyter JD, Manson JE, Scragg R. Vitamin D and Clinical Cancer Outcomes: A Review of Meta-Analyses. JBMR Plus 2021; 5: e10420.
107. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, Zhang SM, Buring JE. The Vitamin D and OmegA-3 TriaL (VITAL): Rationale and Design of a Large Randomized Controlled Trial of Vitamin D and Marine Omega-3 Fatty Acid Supplements for the Primary Prevention of Cancer and Cardiovascular Disease. Contemp Clin Trials 2012; 33: 159-171.
108. Chandler PD, Chen WY, Ajala ON, Hazra A, Cook N, Bubes V, Lee IM, Giovannucci EL, Willett W, Buring JE, Manson JE. Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial. JAMA Netw Open 2020; 3: e2025850.
109. Shao T, Klein P, Grossbard ML. Vitamin D and Breast Cancer. Oncologist 2012; 17: 36-45.
110. Hossain S, Beydoun MA, Beydoun HA, Chen X, Zonderman AB, Wood R.J. Vitamin D and Breast Cancer: A Systematic Review and Meta-Analysis of Observational Studies. Clin Nutr Espen 2019; 30: 170-184.
111. Townsend K, Banwell CM, Guy M, Colston KW, Mansi JL, Stewart PM, Campbell MJ, Hewison M. Autocrine Metabolism of Vitamin D in Normal and Malignant Breast Tissue. Clin Cancer Res 2005; 11: 3579-3586.
112. Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL. Plasma Vitamin D Levels, Menopause, and Risk of Breast Cancer: Dose-Response Meta-Analysis of Prospective Studies. Medicine 2013; 92: 123-131.
113. Krishnan AV, Swami S, Feldman D. The Potential Therapeutic Benefits of Vitamin D in the Treatment of Estrogen Receptor Positive Breast Cancer. Steroids 2012; 77: 1107-1112.
114. Swami S, Krishnan AV, Peng L, Lundqvist J, Feldman D. Transrepression of the Estrogen Receptor Promoter by Calcitriol in Human Breast Cancer Cells via Two Negative Vitamin D Response Elements. Endocr Relat Cancer 2013; 20: 565-577.
115. Chen TC, Holick MF. Vitamin D and Prostate Cancer Prevention and Treatment. Trends Endocrinol Metab 2003; 14: 423-430.
116. Petrou S, Mamais I, Lavranos G, Tzanetakou IP, Chrysostomou S. Effect of Vitamin D Supplementation in Prostate Cancer: A Systematic Review of Randomized Control Trials. Int J Vitam Nutr Res 2018; 88: 100-112.
117. Flaig TW, Barqawi A, Miller G, Kane M, Zeng C, Crawford ED, Glodé LM. A Phase II Trial of Dexamethasone, Vitamin D, and Carboplatin in Patients with Hormone-Refractory Prostate Cancer. Cancer 2006; 107: 266-274.
118. Trump DL, Potter DM, Muindi J, Brufsky A, Johnson CS. Phase II Trial of High-Dose, Intermittent Calcitriol (1,25 Dihydroxyvitamin D3) and Dexamethasone in Androgen-Independent Prostate Cancer. Cancer 2006; 106: 2136-2142.
119. Beer TM. ASCENT: The Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere. BJU Int 2005; 96: 508-513.
120. Fink M. Febrile Neutropenia and Infection in the ASCENT Studies. J Clin Oncol 2011; 29: 4337.
121. Podgorska E, Kim TK, Janjetovic Z, Urbanska K, Tuckey RC, Bae S, Slominski AT. Knocking out the Vitamin D Receptor Enhances Malignancy and Decreases Responsiveness to Vitamin D3 Hydroxyderivatives in Human Melanoma Cells. Cancers 2021; 13: 3111.
122. Skobowiat C, Oak ASW, Kim TK, Yang CH, Pfeffer LM, Tuckey RC, Slominski AT. Noncalcemic 20- Hydroxyvitamin D3 Inhibits Human Melanoma Growth in in Vitro and in Vivo Models. Oncotarget 2017; 8: 9823-9834.
123. Newton-Bishop JA, Chang YM, Elliott F, Chan M, Leake S, Karpavicius B, Haynes S, Fitzgibbon E, Kukalizch K, Randerson-Moor J,Elder DE, Bishop DT, Barrett JH. Relationship between Sun Exposure and Melanoma Risk for Tumours in Different Body Sites in a Large Case-Control Study in a Temperate Climate. Eur J Cancer 2011; 47: 732-741.
124. Johansson H, Spadola G, Tosti G, Mandalà M, Minisini AM, Queirolo P, Aristarco V, Baldini F, Cocorocchio E, Albertazzi E,Zichichi L, Cinieri S, Jemos C, Mazzarol G, Gnagnarella P, Macis D, Tedeschi I, Salè EO, Stucci LS, Bonanni B, Testori A, Pennacchioli E, Ferrucci PF, Gandini S. Vitamin D Supplementation and Disease-Free Survival in Stage II Melanoma: A Randomized Placebo Controlled Trial. Nutrients 2021; 13: 1931.
125. Lopez-Caleya JF, Ortega-Valín L, Fernández-Villa T, Delgado-Rodríguez M, Martín-Sánchez V, Molina AJ. The Role of Calcium and Vitamin D Dietary Intake on Risk of Colorectal Cancer: Systematic Review and Meta-Analysis of Case-Control Studies. Cancer Causes Control 2022; 33: 167-182.
126. Lee JE, Li H, Chan AT, Hollis BW, Lee IM, Stampfer MJ, Wu K, Giovannucci E, Ma J. Circulating Levels of Vitamin D and Colon and Rectal Cancer: The Physicians' Health Study and a Meta-Analysis of Prospective Studies. Cancer Prev Res 2011; 4: 735-743.
127. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B, Sneyd MJ, Mullie P, Autier P. Meta-Analysis of Observational Studies of Serum 25-Hydroxyvitamin D Levels and Colorectal, Breast and Prostate Cancer and Colorectal Adenoma. Int J Cancer 2011; 128: 1414-1424.
128. Touvier M, Chan DSM, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, Riboli E, Hercberg S, Norat T. Meta- Analyses of Vitamin D Intake, 25-Hydroxyvitamin D Status, Vitamin D Receptor Polymorphisms, and Colorectal Cancer Risk. Cancer Epidemiol Biomark Prev 2011; 20: 1003-1016.
129. Maalmi H, Walter V, Jansen L, Boakye D, Schöttker B, Hoffmeister M, Brenner H. Association between Blood 25- Hydroxyvitamin D Levels and Survival in Colorectal Cancer Patients: An Updated Systematic Review and Meta-Analysis. Nutrients 2018; 10: E896.
130. Ng K, Nimeiri HS, McCleary NJ, Abrams TA, Yurgelun MB, Cleary JM, Rubinson DA, Schrag D, Miksad R, Bullock AJ, et al. Effect of High-Dose vs Standard-Dose Vitamin D3 Supplementation on Progression-Free Survival Among Patients With Advanced or Metastatic Colorectal Cancer: The SUNSHINE Randomized Clinical Trial. JAMA 2019; 321: 1370-1379.
131. Ottaiano A, Facchini S, Santorsola M, Nasti G, Facchini G, Montella L, Maurea N, Cascella M, Iervolino D, Facchini BA, Montopoli M, Consolo P, Quagliarello V, Rinaldi L, Berretta M. Circulating Vitamin D Level and Its Impact or Mortality and Recurrence in Stage III Colorectal Cancer Patients: A Systematic Review and Meta-Analysis. Cancers 2023; 15: 3012.
132. Bochen F, Balensiefer B, Körner S, Bittenbring JT, Neumann F, Koch A, Bumm K, Marx A, Wemmert S, Papaspyrou G, Zuschlag D, Kühn JP, Al Kadah B, Schick B, Linxweiler M. Vitamin D Deficiency in Head and Neck Cancer Patients—Prevalence, Prognostic Value and Impact on Immune Function. Oncoimmunology 2018; 7: e1476817.

133. Pu Y, Zhu G, Xu Y, Zheng S, Tang B, Huang H, Wu IXY, Hunag D, Liu Y, Zhng X. Association Between Vitamin D Exposure and Head and Neck Cancer: A Systematic Review With Meta-Analysis. Front Immunol 2022; 12: 627226.
134. Baykan O, Akgul M, Uren N, Yaman A, Tinay I, Ergul E, Sazci A, Turkeri L, Haklar G. The Relationship Between Urothelial Type Bladder Cancer, Plasma 25-Hydroxyvitamin D Levels, and Vitamin D Receptor ApaI BsmI FokI, and TaqI Polymorphisms. Clin Lab 2019; 65: 4.
135. Zhang H, Zhang H, Wen X, Zhang Y, Wei X, Liu T. Vitamin D Deficiency and Increased Risk of Bladder Carcinoma: A Meta-Analysis. Cell Physiol Biochem 2015; 37: 1686-1692.
136. Zhao Y, Chen C, Pan W, Gao M, He W, Mao R, Lin T, Huang J. Comparative Efficacy of Vitamin D Status in Reducing the Risk of Bladder Cancer: A Systematic Review and Network Meta-Analysis. Nutrition 2016; 32: 515-523.
137. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of Non-Hodgkin's Lymphoma. Med Sci 2021; 9: 5.
138. Park HY, Hong YC, Lee K, Koh J. Vitamin D Status and Risk of Non-Hodgkin Lymphoma: An Updated Meta-Analysis. PLoS One 2019; 14: e0216284.
139. Drake MT, Maurer MJ, Link BK, Habermann TM, Ansell SM, Micallef IN, Kelly JL, Macon WR, Nowakowski GS, Inwards DJ, Johnston PB, Singh RJ, Allmer C, Slager SL, Weiner GJ, Witzig TE, Cerhan JR. Vitamin D Insufficiency and Prognosis in Non-Hodgkin's Lymphoma. J Clin Oncol 2010; 28: 4191-4198.
140. Gouni-Berthold I, Berthold HK. Vitamin D and Vascular Disease. Curr Vasc Pharmacol 2021; 19: 250-268.
141. Latic N, Erben RG. Vitamin D and Cardiovascular Disease, with Emphasis on Hypertension, Atherosclerosis, and Heart Failure. Int J Mol Sci 2020; 21: E6483.
142. Grandi NC, Breitling LP, Brenner H. Vitamin D and Cardiovascular Disease: Systematic Review and Meta-Analysis of Prospective Studies. Prev Med 2010; 51: 228-233.
143. Zhang W, Yi J, Liu D, Wang Y, Jamilian P, Gaman MA, Prabahar K, Fan J. The Effect of Vitamin D on the Lipid Profile as a Risk Factor for Coronary Heart Disease in Postmenopausal Women: a Meta-Analysis and Systematic Review of Randomized Controlled Trials. Exp Gerontol 2022; 161: 111709.
144. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, Camargo CA Jr. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study: A Randomized Clinical Trial. JAMA Cardiol 2017; 2: 608-616.
145. Amrein K, Parekh D, Westphal S, Preiser JC, Berghold A, Riedl R, Eller P, Schellongowski P, Thickett D, Meybohm P. Effect of High-Dose Vitamin D3 on 28-Day Mortality in Adult Critically Ill Patients with Severe Vitamin D Deficiency: A Study Protocol of a Multicentre, Placebo-Controlled Double-Blind Phase III RCT (the VITDALIZE Study). BMJ Open 2019; 9, e031083.
146. Beveridge LA, Khan F, Struthers AD, Armitage J, Barchetta I, Bressendorff I, Cavallo MG, Clarke R, Dalan R, Dreyer G, Gepner AD, Forouhi NG, Harris RA, Hitman GA, Larsen T, Khadgawat R, Marckmann P, Mose FH, Pilz S, Scholze A, Shargorodsky M, Sokol SI, Stricker H, Zoccali C, Witham MD. Effect of Vitamin D Supplementation on Markers of Vascular Function: A Systematic Review and Individual Participant Meta-Analysis. J Am Heart Assoc 2018; 7: e008273.
147. Abderhalden LA, Meyer S, Dawson-Hughes B, Orav EJ, Meyer U, de Godoi Rezende Costa Molino C, Theiler R, Stähelin HB, Ruschitzka F, Egli A, Forman JP, Willett WC, Bischoff-Ferrari HA. Effect of daily 2000 IU versus 800 IU vitamin D on blood pressure among adults age 60 years and older: a randomized clinical trial. Am J Clin Nutr 2020; 112: 527-537.
148. Rea D, Coppola G, Palma G, Barbieri A, Luciano A, Del Prete P, Rossetti S, Berretta M, Facchini G, Perdonà S, Turco MC, Arra C. Microbiota effects on cancer: from risks to therapies. Oncotarget 2018; 9: 17915-17927.
149. Sorboni SG, Moghaddam HS, Jafarzadeh-Esfehani R, Soleimanpour SA. Comprehensive Review on the Role of the Gut Microbiome in Human Neurological Disorders. Clin Microbiol Rev 2022; 35: e0033820.
150. Baquero F, Nombela C. The Microbiome as a Human Organ. Clin Microbiol Infect 2012; 18: 2-4.
151. Gominak SC. Vitamin D Deficiency Changes the Intestinal Microbiome Reducing B Vitamin Production in the Gut. The Resulting Lack of Pantothenic Acid Adversely Affects the Immune System, Producing a "pro-Inflammatory" State Associated with Atherosclerosis and Autoimmunity. Med Hypotheses 2016; 94: 103-107.
152. Del Chierico F, Vernocchi P, Dallapiccola B, Putignani L. Mediterranean Diet and Health: Food Effects on Gut Microbiota and Disease Control. Int J Mol Sci 2014; 15: 11678-11699.
153. Su D, Nie Y, Zhu A, Chen Z, Wu P, Zhang L, Luo M, Sun Q, Cai L, Lai Y,Xiao Z, Duan Z, Zheng S, Wu G, Hu R, Tsukamoto H, Lugea A, Liu Z, Pandol SJ, Han YP.Vitamin D Signaling through Induction of Paneth Cell Defensins Maintains Gut Microbiota and Improves Metabolic Disorders and Hepatic Steatosis in Animal Models Front Physiol 2016; 7: 498.
154. Jin D Wu S, Zhang YG, Lu R, Xia Y, Dong H, Sun J. Lack of Vitamin D Receptor Causes Dysbiosis and Changes the Functions of the Murine Intestinal Microbiome. Clin Ther 2015; 37: 996-1009.e7.
155. Wu S, Yoon S, Zhang YG, Lu R, Xia Y, Wan J, Petrof EO, Claud EC, Chen D, Sun J. Vitamin D Receptor Pathway Is Required for Probiotic Protection in Colitis. Am J Physiol Gastrointest Liver Physiol 2015; 309: G341-G349.
156. Ooi, JH, Li Y, Rogers CJ, Cantorna MT. Vitamin D Regulates the Gut Microbiome and Protects Mice from Dextran Sodium Sulfate-Induced Colitis. J Nutr 2013; 143: 1679-1686.
157. Jones, ML, Martoni CJ, Prakash S. Oral Supplementation with Probiotic Increases Mean Circulating 25-Hydroxyvitamin D: A Post Hoc Analysis of a Randomized Controlled Trial. J Clin Endocrinol Metab 2013; 98: 2944-2951.
158. Wang TJ, Zhang F, Richards JB, Kestenbaum B, Van Meurs JB, Berry D, Kiel DP, Streeten EA, Ohlsson C, Koller DL, Peltonen L, Cooper JD, O'Reilly PF, Houston DK, Glazer NL, Vandenput L, Peacock M, Shi J, Rivadeneira F, McCarthy MI, Anneli P, de Boer IH, Mangino M, Kato B, Smyth DJ, Booth SL, Jacques PF, Burke GL, Goodarzi M, Cheung CL, Wolf M, Rice K, Goltzman D, Hidiroglou N, Ladouceur M, Wareham NJ, Hocking LJ, Hart D, Arden NK, Cooper C, Malik S, Fraser WD, Hartikainen AL, Zhai G, Macdonald HM, Forouhi NG, Loos RJ, Reid DM, Hakim A, Dennison E, Liu Y, Power C, Stevens HE, Jaana L, Vasan RS, Soranzo N, Bojunga J, Psaty BM, Lorentzon M, Foroud T, Harris TB, Hofman A, Jansson JO, Cauley JA, Uitterlinden AG, Gibson Q, Järvelin MR, Karasik D, Siscovick DS, Econs MJ, Kritchevsky SB, Florez JC, Todd JA, Dupuis J, Hyppönen E, Spector TD. Common Genetic Determinants of Vitamin D Insufficiency: A Genome-Wide Association Study. Lancet 2010; 376: 180-188.
159. Zhang X Shang X, Jin S, Ma Z, Wang H, Ao N, Yang J, Du J, Vitamin D Ameliorates High-Fat-Diet-Induced Hepatic Injury via Inhibiting Pyroptosis and Alters Gut Microbiota in Rats. Arch Biochem Biophys 2021; 705: 108894.

160. Owen JL, Mohamadzadeh M. Microbial Activation of Gut Dendritic Cells and the Control of Mucosal Immunity. J Interferon Cytokine Res 2013; 33: 619-631.
161. Thomas RL, Jiang L, Adams JS, Xu ZZ, Shen J, Janssen S, Ackermann G, Vanderschueren D, Pauwels S, Knight R,Orwoll ES, Kado DM. Vitamin D Metabolites and the Gut Microbiome in Older Men. Nat Commun 2020; 11: 5997.
162. Gaschott T, Werz O, Steinmeyer A, Steinhilber D, Stein J. Butyrate-Induced Differentiation of Caco-2 Cells Is Mediated by Vitamin D Receptor. Biochem Biophys Res Commun 2001; 288: 690-696.
163. Quagliariello V, Masarone M, Armenia E, Giudice A, Barbarisi M, Caraglia M, Barbarisi A, Persico M. Chitosan-Coated Liposomes Loaded with Butyric Acid Demonstrate Anticancer and Anti-Inflammatory Activity in Human Hepatoma HepG2 Cells. Oncol Rep 2019; 41: 1476-1486.
164. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langella P. Faecalibacterium Prausnitzii Is an Anti-Inflammatory Commensal Bacterium Identified by Gut Microbiota Analysis of Crohn Disease Patients. Proc Natl Acad Sci U S A 2008; 105: 16731-16736.
165. Schäffler H, Herlemann DP, Klinitzke P, Berlin P, Kreikemeyer B, Jaster R, Lamprecht G. Vitamin D Administration Leads to a Shift of the Intestinal Bacterial Composition in Crohn's Disease Patients, but Not in Healthy Controls. J Dig Dis 2018; 19: 225-234.
166. Garg M, Hendy P, Ding JN, Shaw S, Hold G, Hart A. The Effect of Vitamin D on Intestinal Inflammation and Faecal Microbiota in Patients with Ulcerative Colitis. J Crohns Colitis 2018; 12: 963-972.
167. Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, Calignano, A, Khan AA, Gilbert JA, Nagler CR. Lactobacillus Rhamnosus GG-Supplemented Formula Expands Butyrate-Producing Bacterial Strains in Food Allergic Infants. ISME J 2016; 10: 742-750.
168. Wang J, Thingholm LB, Skiecevičienė J, Rausch P, Kummen M, Hov JR, Degenhardt F, Heinsen FA, Rühlemann MC, Szymczak S, Holm K, Esko T, Sun J, Pricop-Jeckstadt M, Al-Dury S, Bohov P, Bethune J, Sommer F, Ellinghaus D, Berge RK, Hübenthal M, Koch M, Schwarz K, Rimbach G, Hübbe P, Pan WH, Sheibani-Tezerji R, Häsler R, Rosenstiel P, D'Amato M, Cloppenborg-Schmidt K, Künzel S, Laudes M, Marschall HU, Lieb W, Nöthlings U, Karlsen TH, Baines JF, Franke A. Genome-Wide Association Analysis Identifies Variation in Vitamin D Receptor and Other Host Factors Influencing the Gut Microbiota. Nat Genet 2016; 48: 1396-1406.
169. Kanhere M, He J, Chassaing B, Ziegler TR, Alvarez JA, Ivie EA, Hao L, Hanfelt J Gewirtz AT, Tangpricha V. Bolus Weekly Vitamin D3 Supplementation Impacts Gut and Airway Microbiota in Adults With Cystic Fibrosis: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial. J Clin Endocrinol Metab 2018; 103: 564-574.
170. Bashir M, Prietl B, Tauschmann M, Mautner SI, Kump PK, Treiber G, Wurm P, Gorkiewicz G, Högenauer C, Pieber TR. Effects of High Doses of Vitamin D3 on Mucosa-Associated Gut Microbiome Vary between Regions of the Human Gastrointestinal Tract. Eur J Nutr 2016; 55: 1479-1489.
171. Cashman KD, Ritz C, Kiely M, Odin Collaborators null. Improved Dietary Guidelines for Vitamin D: Application of Individual Participant Data (IPD)-Level Meta-Regression Analyses. Nutrients 2017; 9: E469.
172. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, Clarke R. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-Analysis. JAMA Netw Open 2019; 2: e1917789.
173. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. JAMA 2019; 322: 736-745.
174. Chakhtoura M, Chamoun N, Rahme M, Fuleihan GEH Impact of Vitamin D Supplementation on Falls and Fractures-A Critical Appraisal of the Quality of the Evidence and an Overview of the Available Guidelines. Bone 2020; 131: 115112.
175. Dawson-Hughes B, Nelson J, Pittas AG Intratrial Exposure to Vitamin D and New-Onset Diabetes Among Adults With Prediabetes: A Secondary Analysis From the Vitamin D and Type 2 Diabetes (D2d) Study. Diabetes Care 2021; 44: e106.
176. Barbáchano A, Fernández-Barral A, Ferrer-Mayorga G, Costales-Carrera A, Larriba MJ, Muñoz A. The Endocrine Vitamin D System in the Gut. Mol Cell Endocrinol 2017; 453: 79-87.
177. Martineau AR, Joliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P Dubnov-Raz G, Esposito GS, Ganmaa D, Ginde A, Goodall EC, Grant CC, Janssens W, Jensen ME, Kerley CP, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR, Simpson S, Stelmach I, Trilok Kumar G, Urashima M, Camargo CA, Griffiths CJ, Hooper RL. Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta- Analysis of Individual Participant Data. BMJ 2017; 356: 6583.
178. Radujkovic, A, Hippchen T, Tiwari-Heckler S, Dreher S, Boxberger M, Merle U. Vitamin D Deficiency and Outcome of COVID-19 Patients. Nutrients 2020; 12: E2757.
179. Murai IH, Fernandes AL, Antonangelo L, Gualano B, Pereira RMR. Effect of a Single High-Dose Vitamin D3 on the Length of Hospital Stay of Severely 25-Hydroxyvitamin D-Deficient Patients with COVID-19. Clinics 2021; 76: e3549.
180. Amin HA, Drenos F. No evidence that vitamin D is able to prevent or affect the severity of COVID-19 in individuals with European ancestry: a Mendelian randomisation study of open data. BMJ Nutr Prev Health 2021; 4: 42-48.
181. Manson, JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, Friedenberg G, Ridge C, Bubes V, Giovannucci EL, Willett WC, Buring JE. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med 2019; 380: 33-44.
182. Manson JE, Bassuk SS, Buring JE. VITAL Research Group Principal Results of the VITamin D and OmegA-3 TriaL (VITAL) and Updated Meta-Analyses of Relevant Vitamin D Trials. J SteroidBiochem Mol Biol 2020; 198: 105522.
183. Di Benedetto F, Di Sandro S, De Ruvo N, Berretta M, Masetti M, Montalti R, Ballarin R, Cocchi S, Potenza L, Luppi M, Gerunda GE. Kaposi's Sarcoma after Liver Transplantation. J Cancer Res Clin Oncol 2008; 134: 653-658.
184. Berretta M, Lleshi A, Cappellani A, Bearz A, Spina M, Talamini R, Cacopardo B Nunnari G, Montesarchio V, Izzi I, Lanzafame M, Nasti G, Basile F, Berretta S, Fisichella R, Schiantarelli CC, Garlassi E, Ridolfo A, Guella L, Tirelli U. Oxaliplatin Based Chemotherapy and Concomitant Highly Active Antiretroviral Therapy in the Treatment of 24 Patients with Colorectal Cancer and HIV Infection. Curr HIV Res 2010; 8: 218-222.
185. Zanet E, Berretta M, Martellotta F, Cacopardo B, Fisichella R, Tavio M, Berretta S, Tirelli U. Anal Cancer: Focus on HIV- Positive Patients in the HAART-Era. Curr HIV Res 2011; 9: 70-81.