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Artigo

# Vitamin D - Physiological, Nutritional, Immunological, Genetic aspects. Actions in autoimmune, tumor, and infectious diseases. Musculoskeletal and cognitive functions

## *Vitamina D - Aspectos Fisiológicos, Nutricionais, Imunológicos, Genéticos. Ações em doenças autoimunes, tumorais, infecciosas. Funções musculoesqueléticas e cognitivas*

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**ABSTRACT:** Vitamin D represents, in fact, a fat-soluble steroid hormone with endocrine, paracrine and autocrine functions. This article aimed to review physiological, environmental, nutritional and genetic aspects related to this vitamin, classification the serum levels of the circulating form representative of the status, as well as its storage sites in tissues. Suggestions are promoted, according to the literature consulted, regarding eating habits, adequate sun exposure, oral supplementation and/or need for maintenance doses, risks of toxicity. Immunological, immunomodulatory functions, participation at the cellular and tissue levels in autoimmune, tumor, infectious and contagious diseases, with emphasis on SARS-CoV-2, were also discussed. There was a highlight, among the numerous actions of this vitamin, on its participation in musculoskeletal metabolism, occurrence of falls, particularly among the elderly, central nervous system, mainly on cognition, dementia, Alzheimer's disease. Consensual or controversial aspects were also commented, as well as suggestions for new studies worldwide to clarify questionable results.

**KEYWORDS**: Vitamin D; COVID-19; Nutrition.

**RESUMO:** Vitamina D representa de fato, um hormônio esteroide lipossolúvel com funções endócrinas, parácrinas e autócrinas. Este artigo buscou realizar revisão de aspectos fisiológicos, ambientais, nutricionais e genéticos relacionados a esta vitamina, classificação dos níveis séricos da forma circulante representativa do status, bem locais de armazenamento em tecidos. Sugestões são apresentadas, de acordo com literatura consultada, quanto a hábitos alimentares, exposição solar adequada, suplementação oral e/ou necessidade de doses de manutenção, riscos de toxicidade. Funções imunológicas, imunomoduladoras, participação a nível celular e tecidual em doenças autoimunes, tumorais, infecto-contagiosas, com ênfase ao SARS-CoV-2 também foram abordadas. Entre as inúmeras ações da vitamina D, houve destaque à participação no metabolismo musculoesquelético, ocorrência de quedas, particularmente entre os idosos, sistema nervoso central, com ênfase à cognição, demência, doença de Alzheimer. Aspectos consensuais ou controversos também foram abordados, bem como sugestões de novos estudos a nível mundial para esclarecimento de resultados questionáveis.

**PALAVRAS-CHAVE**: Vitamina D; COVID-19; Nutrição.

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## 1. Endocrine, paracrine and autocrine functions

From a technical point of view, according to Fraser, cited by Demer, Hsu and Titut [1], the term "vitamin D" is inappropriate. It does not represent the exact concept of a vitamin because the human body has the ability to synthesize cholecalciferol ($D_3$), except in rare cases of absence of skin exposure to solar ultraviolet (UV) radiation. Thus, it would be more appropriate to consider it a steroid hormone. The International Union of Pure and Applied Chemistry Commission on the Nomenclature of Biological Chemistry defines vitamin $D_3$ as a steroid or secosteroid. Different steroid hormones are considered as "vitamin D", with varying levels of activity: the endogenous precursor, cholecalciferol ($D_3$), also present in various foods of animal origin; calcidiol [25(OH)D3]; calcitriol [1,25(OH)2D3]; the ergocalciferol ($D_2$), present in fungi, which has two metabolites, monohydroxy and dihydroxy $D_2$.

Therefore, vitamin D constitutes a fat-soluble steroid hormone with endocrine, paracrine, and autocrine functions[2]. The physiologically active form of vitamin D, calcitriol or 1,25 $(OH)_2D$, has well-established functions in the maintenance of normal bone structure[2,3].

Thus, the endocrine actions of calcitriol are manifested mainly in serum calcium homeostasis. The primary one consists in controlling calcemia, by means of intestinal absorption of this ion and of phosphorus, mobilization of bone calcium in the presence of parathormone (PTH), and increasing renal calcium absorption, thus regulating bone metabolism[3,4,5].

The paracrine and autocrine effects of vitamin D depend on genetic transcription, unique to the cell type expressing the nuclear receptors for vitamin D. These potential effects include inhibition of cell proliferation, promotion of cell differentiation, and apoptosis, which in turn may represent relevant actions in cancer, immunity, and several systems and organs[6].

## 2. Physiological, Environmental, Nutritional and Genetic Aspects

There are two precursor forms of vitamin D: ergocalciferol or vitamin $D_2$ and cholecalciferol or vitamin $D_3$. Vitamin $D_2$ is synthesized by fungi, such as mushrooms exposed to UV radiation. The second comes from two sources: a) ingestion of foods of animal origin, such as fish with high lipid content, including salmon, mackerel and tuna, as well as egg yolk, milk and fish oil and b) cutaneous synthesis in humans, from the precursor 7-dehydrocholesterol (7-DHC or provitamin D), under the action of solar UV radiation. These precursors, vitamins $D_2$ and $D_3$, are transported via systemic circulation to the liver, where 25-hydroxylation occurs, originating 25(OH) D or calcidiol[7] and later to the kidneys, responsible for 1-hydroxylation, resulting in 1,25(OH)2D or calcitriol. This represents the active form of vitamin D, involved in calcium homeostasis. However, the main metabolite determined in the blood and the best indicator of clinical status is 25(OH) D, because it represents the circulating form in larger quantities and with a half-life of approximately two weeks[5].

There are therefore two main sources of vitamin D, the exogenous from the diet and the endogenous from skin synthesis. In the 1930s, researchers found that exposure of the skin to sunlight and artificial UV rays stimulated the production of vitamin $D_3$ from the conversion of a precursor, 7-DHC[5]. During sun exposure, UVB (ultraviolet B, 290-315 nm) photons penetrate the epidermis and produce photochemical fragmentation that results in precolecalciferol. Subsequently, temperature-dependent isomerization converts this intermediate into vitamin $D_3$ or cholecalciferol[8].

About 80% of the vitamin D needed by the body is produced in the skin after exposure to UVB radiation. However, if there is prolonged exposure to radiation, there is an intrinsic mechanism to regulate this synthesis, which prevents overproduction and consequent intoxication due to endogenous vitamin D[5]. Considering that the largest percentage of the daily vitamin D needs can be obtained by exposure to sunlight, it is important to provide consistent medical advice to individuals regarding the timing and length of sun exposure, according to age, skin type, exposed body areas, latitude, and season. Contraindications to sun exposure, related to diseases, should also follow medical guidelines[5].

The distribution of these two sources of vitamin D varies widely among individuals and geographic regions. It is known that part of solar UV radiation is absorbed by clouds, ozone, and air pollution, and 60% of the effective UV radiation occurs between 11:00 am and 3:00 pm. In countries of the northern hemisphere there is no UVB radiation of appropriate wavelengths (280 to 310 mm) between November and March, as well as in the other months of the year. Also, food sources containing vitamin D are scarce, including enriched cereals, fish, and eggs[5]. Seasonal factors also interfere in serum vitamin D levels, as mentioned by Maeda et al.[9] in young adults living in São Paulo, Brazil, besides occupational activity, sun exposure habits, among others. Unger et al.[10] found significant increases in serum levels after summer, on average 10 ng/mL, inversely related to age. Female gender and body mass index were also inversely and linearly associated with serum vitamin D levels. Although it is well documented that synthesis of cutaneous vitamin D from solar UV radiation is shown to be affected by the aging process, there is marked unawareness of nutrition-related public health services. Thus, in the UK, National Dietary and Nutrition Surveys revealed that 97% of non-institutionalized elderly women and 99% of institutionalized women had vitamin D intakes below the recommended nutritional values. Furthermore, they found vitamin D deficiency in more than one third

of institutionalized women, with the highest prevalence of insufficiency in this group. Therefore, lack of exposure to sunlight, diets low in milk or exclusively vegetarian, non-white ethnicity, urban residence, and less favorable economic conditions are factors cited as contributors to reduced serum levels of vitamin D[7,9,10,11].

Thus, inadequate vitamin D intake constitutes a global health problem related to serious diseases, mainly involving individuals with dark skin pigmentation, patients affected by malnutrition, those with malabsorption syndromes, obesity, and the elderly. Some vitamin D fortified foods have been used in vivo, but fortification strategies with global reach are still lacking[12]. Thus, in order to evaluate various presentations, Lavelli et al.[12] in a review article collected information on formulation strategies, stability during processing and storage, and in vitro bioaccessibility of vitamin D fortified foods. These authors concluded that the effective administration of this vitamin through fortified foods, with careful formulation in nano and microstructures to be dispersed in the food matrix, represents a promising strategy.

Similarly, Adebayo et al.[13] analyzed the possible safety issues arising from vitamin D intake and/or supplementation. The study included data from 20 randomized controlled trials (RCTs), 20 national health surveys, as well as prospective cohort studies (PCSs) included in the European Union ODIN project ("Food-based solutions for optimal vitamin D nutrition and health across the life cycle"). Adverse consequences evaluated included elevated serum levels of 25(OH)D (>125 nmol/L) and calcium, as well as vitamin D intakes above age-tolerable upper limits. There were no reports of adverse effects among RCTs (n = 3353), with vitamin D intakes ranging from 5-175 g/day. The prevalence of elevated 25(OH)D levels was <10% when vitamin D supplements were given and <0.1% for fortified foods. Elevated serum calcium was observed among <0.5% in both types of administration. No participants in the ODIN project RCTs studies exceeded the age-specific upper limits. In observational studies (n=61,082), the prevalence of elevated 25(OH)D levels among children/adolescents, adults, and the elderly was <0.3%, with no evidence of adverse effects. Thus, the authors concluded that high 25(OH)D concentrations (>125 nmol/L) were rare in RCTs and PCSs in European populations and associated adverse effects were not observed. However, the risk of elevated serum 25(OH)D levels may increase with high doses of vitamin D supplementation (above 70 µg/day (2,800 IU)). In addition, high-dose vitamin D supplement use also increases the risk of exceeding the upper limit set by the European Food Safety Agency for vitamin D, the touchstone of the public health safety index.

The effect of genetic variations in enzymes participating in metabolic pathways involved in vitamin D synthesis and catabolism on serum 25 (OH) D concentrations is less well known[14].

Thus, vitamin $D_3$, resulting from cutaneous synthesis from UVB radiation on precursors, as well as dietary or supplemental $D_2$ and $D_3$ absorbed in the intestinal tract, represent the substrates required for the next steps. These are converted to 25(OH)D by 25-hydroxylases (cytochrome P450 (CYP) 2R1, 27A1 and 3A4) in the liver. Further hydroxylation of 25(OH)D via α1-hydroxylase (CYP27B1) in the kidney or at the tissue level results in $1,25(OH)_2D$. This represents the active form of vitamin D, involved in calcium homeostasis, acts in intestinal absorption, maintenance of blood levels of this element, as well as phosphorus, both relevant in bone metabolism. The catabolism of vitamin D metabolites occurs via 24-hydroxylase (CYP24A1)[15]. The vitamin D binding protein, also called Group-Specific Component (GSC), represents the transport protein of vitamin D metabolites in circulation. Also, there are vitamin D receptors called VDR (Vitamin D Receptor), present on the surface of cells, among them monocytes, lymphocytes, and by binding to them $1,25(OH)_2D$ triggers a series of events affecting cell differentiation and proliferation, inflammation, immune[5], endocrine systems, including renin angiotensin system, insulin resistance, and lipid metabolism[11,16].

Genetic variations in any of these steps have the potential to alter blood 25(OH)D concentrations. Currently, the total serum level of 25(OH)D, the main circulating metabolite, is considered the best indicator of clinical vitamin D supply status, including cutaneous synthesis and nutritional intake or in the form of oral supplementation[7,14,17,18].

As for the 25-hydroxylases, CYP2R1 is considered to be primarily responsible for the synthesis of 25(OH) D from vitamins $D_3$ and $D_2$. CYP27A1 represents an essential enzyme in the biosynthesis of bile acids and with lesser participation in the 25-hydroxylation of $D_3$. CYP3A4 is the most abundant CYP expressed in the liver and intestine, contributes to the metabolism of about 50% of the drugs used, is active on D2 and undetectable on D3. However, there are drugs that affect the expression of the gene related to this enzyme and can modulate the activation of $D_3$[19]. Several drugs act as inducers and others as inhibitors of CYP3A4 activity, which can cause possible drug interactions and interference in the activation of $D_3$[20].

### 2.1 Classification of serum 25(OH)D levels

The Institute of Medicine (IOM/USA) has recently proposed ≥50 nmol/L (20 ng/mL) as the definition of adequate serum 25(OH)D level based only on requirements for optimizing bone metabolism, due to lack of data to support recommendations for prevention of other disease outcomes. However, the Society of Endocrinology (SE/US) recommends serum 25(OH)D concentrations ≥ 75 nmol / L (30 ng / mL) as adequate for greater individual

assurance of bone mineralization, lower fracture risk21 as well as achieving broader health benefits[14].

A cohort study of the northern European population with a high prevalence of vitamin D deficiency, which contributed to this recommendation[21], was developed by Primel et al.[22]. These authors performed histomorphometric analysis of iliac crest biopsies as the most direct approach to assessing bone mineralization, in addition to serum parathormone (PTH) determination. They examined 675 iliac crest biopsies from subjects of both sexes and excluded all who showed signs of secondary bone disease at autopsy. Structural histomorphometric parameters including osteoid index were quantified using the Osteomeasure System (Partiff et al, cited in [22]) according to ASBMR (American Society for Bone and Mineral Research) standards and serum 25(OH)D levels were determined in all participants. Histological results showed that altered bone mineralization, i.e., a pathological increase in osteoid, occurred in subjects with serum 25(OH)D levels less than 75 nmol/L. The authors argued that these results, coupled with adequate calcium intake and doses of vitamin D supplementation, should ensure circulating levels of 25(OH)D above this minimum threshold (75 nmol/L or 30 ng/mL) for maintenance of bone integrity[22]. However, there is no consensus on the cut-off values for classifying serum 25(OH)D levels into adequate and inadequate. According to SE/USA, values ≤ 50 nmol /L (≤ 20 ng/mL) are considered deficient, between > 50 and < 75 nmol /L (>20 and < 30 ng/mL) insufficient and ≥75 nmol/L (≥30 ng /mL) as sufficient[2]. However, IOM/USA proposes as adequate serum level ≥50 nmol /L (20 ng/mL) for general population and ≥75 nmol /L (30 ng/mL) for high-risk populations, due to greater benefits in osteometabolic diseases, prevention of secondary hyperparathyroidism, decreased risk of falls, and improved bone mineral density. These recommendations have been adopted by the Brazilian Society of Endocrinology and Metabology (SBEM)[8].

### 2.2 Supplementation, maintenance, and toxicity risks

Vitamin D is a fat-soluble substance, absorbed along with fats, circulates through the enterohepatic cycle, is present in bile secretion, and is reabsorbed in the small intestine. 25(OH)$D_3$ has a half-life of two weeks to three months, is deposited mainly in the adipose tissue and to a lesser extent in the liver. This hepatic storage source is probably available for release back into plasma, as indicated by a long-term study in Norwegians (references 10-15, mentioned in[1]).

In general, when 25(OH)D levels are below recommended levels, a top-up scheme will be needed to replenish body stores. The most widely used supplementation currently consists of vitamin D doses of 50,000 IU weekly or 7,000 IU daily for 6 to 8 weeks. If adequate 25(OH)D levels are not obtained, a new cycle will be proposed[2,8].

Supplementation doses for maintenance of frequently recommended levels should be instituted depending on age group and associated conditions. Among adults, daily maintenance doses range from 400 to 2,000 IU, according to the degree of sun exposure and skin coloration. Among the elderly, recommended doses range from 1,000 to 2,000 IU daily or 7,000 to 14,000 IU weekly. Obese individuals, those taking medications that accelerate 25(OH)D catabolism (anticonvulsants, glucocorticoids, prescribed for the treatment of acquired immune deficiency syndrome), or those with malabsorption syndrome[8] may require doses two to three times higher than usual (references 3, 42-43, cited by[2]).

As for obesity, there is evidence that adults with a body mass index (BMI) >30 kg/m$^2$ are at high risk of vitamin D deficiency because body fat sequesters the fat-soluble vitamin. Obese and non-obese adults exposed to simulated sunlight or given oral replacement of 50,000 IU of vitamin D2 had increased blood levels of 25(OH)D by no more than 50% compared to non-obese adults[2].

Similarly, the VITAL (Vitamin D and Omega-3 Trial)[23] reported no benefit in primary outcomes for cancer or relevant cardiovascular disease events. However, when Tobias et al.[24] analyzed the subset consisting of 2,742 participants before randomization, total serum levels of 25-OHD were shown to be gradually lower in those with higher BMI: underweight (BMI<18.5)-32.3±0.7 ng/mL; normal weight (BMI 18.5-24.9)-32.3±0.1ng/mL; overweight (BMI 25.0-29.9)-30.5±0.1 ng/mL; class I obesity (BMI-30.0-34.9)-29.0±0.2 ng/mL and class II obesity (BMI≥35.0)-28.0±0.2 ng/mL; $p < 0.001$, linear trend). Similarly, basal levels of biomarkers of 25-OH$D_3$, FVD (Free Vitamin D), BioD (Bioavailable 25(OH)D), VDBP (Vitamin D-Binding Protein), albumin and calcium were inversely proportional to BMI and PTH level was directly proportional ($p < 0.001$, linear trend).

Likewise, these authors[24] observed that randomization to vitamin D supplementation was associated with an increase in total levels of vitamin D biomarkers: 25(OH)D, 25(OH)$D_3$, FVD, and BioD compared with placebo over two consecutive years. There were significant increases in serum 25(OH)D levels (11.9 ng/mL) among those randomized, compared to slight modification in the placebo group (-0.7 ng/mL). When stratified by BMI level, however, the magnitude of increase was smaller among those with higher baseline BMI ($p < 0.001$). Thus, the mean increments in total 25(OH)D level in the group with supplementation versus placebo reached 13.5 ng/mL among participants with BMI < 25.0 kg/m$^2$ versus 10.0 ng/mL among those with BMI ≥ 35.0 kg/m$^2$. They also found that individuals with higher BMI values and inadequate vitamin D levels at baseline were not able to achieve sufficient levels as those with normal BMI did.

Among the main theories about why higher BMI would be associated with reduced serum vitamin D levels

and less response to supplementation is that because it is a fat-soluble vitamin. Thus, increased adiposity and lipid storage capacity in individuals with high BMI result in greater removal of circulating vitamin. Other theories suggest that obesity-induced liver dysfunction may contribute to impaired vitamin D metabolism[24]. There is evidence that CYP2R1 dysfunction occurs in animal models of obesity and diabetes mellitus. Among them, Elkhwanky et al. (cited by Tobias et al.[24]), demonstrated in humans that surgically induced weight loss led to increased CYP2R1 activity in adipose tissue.

Thus, Tobias et al.[24] concluded that when there is more clarity about what mechanism is responsible for these results, it would make sense to consider what doses of supplementation would be necessary to achieve targeted serum vitamin D levels among obese individuals.

Likewise, Bachmann[25], in an editorial about vitamin D supplementation in overweight or obese individuals, commented on the relevant results of Tobias et al[24]. He even added the need for further studies to determine the optimal dose or adequate circulating level of vitamin D in obese individuals for results unrelated to bone metabolism.

Both initial and subsequent supplementation for maintenance of adequate vitamin D levels can be performed with vitamin $D_3$ (cholecalciferol) or $D_2$ (ergocalciferol). The former has some advantages over the latter, because it is part of most formulations and clinical studies, allows more versatile dosages, promotes more effective elevations, and can be determined by all available laboratory methods[8].

Excessive use of vitamin D hormone supplements causes significant risks that have been described for decades, traditionally resulting from hypercalcemia and generally occurring with plasma 25(OH)$D_3$ concentrations > 150 ng/ml (> 375 nmol/L). Thus, the traditional clinical manifestations associated with vitamin D toxicity arising from hypercalcemia include general (fatigue, weakness), neurological (altered mental status, irritability, coma), gastrointestinal (nausea, vomiting, constipation), endocrine (polyuria, polydipsia) symptoms. In addition, kidney damage and kidney stone formation may be present. Thus, studies evaluating the safety of various dosing regimens usually include serum and urinary calcium determinations to monitor the assurance of administered doses (Hollis et al.; Hollis and Wagner cited by [1]).

According to the available literature, vitamin D toxicity is a rare event resulting from inadvertent ingestion, among them, inaccurate handling[26], or intentional ingestion of excessively high amounts of vitamin D. Although the safe upper limit (UL) serum 25(OH)D to avoid hypercalcemia is not known, most studies in children and adults suggest that these need to be above 150 ng/ml to motivate any concern. Therefore, UL of 100 ng/ml allows margin of safety in reducing the risk of hypercalcemia. Although no long-term studies have examined the consequences of these high doses of vitamin D on serum calcium levels, there are no reported cases of vitamin D intoxication in the literature to suggest that daily intake of up to 4,000 IU vitamin D causes hypercalcemia. In healthy adults, five months of daily intake of 10,000 IU vitamin D did not trigger hypercalcemia or increased urinary calcium excretion, which is a more sensitive indicator for potential vitamin D intoxication. Therefore, UL of 10,000 IU vitamin D per day for adults is considered reasonable (reference 127 cited by[2]). Patients with chronic granuloma-forming disorders, including sarcoidosis or tuberculosis, chronic fungal infections, and some types of lymphoma, have activated macrophages that produce 1,25$(OH)_2$D dysregulately. These patients develop increased efficiency of intestinal absorption and mobilization of bone calcium that can trigger hypercalciuria and hypercalcemia. Thus, 25(OH)D, serum and urinary calcium levels should be carefully monitored in these patients[1,2,8].

### 3. Immunological and immunomodulatory functions

Vitamin D regulates innate and adaptive immune responses. It also exerts actions on the control of autoimmunity induced mainly by T cells, in particular those called Th1. Vitamin D receptor agonists preferentially inhibit the differentiation of dendritic cells, inflammatory and pro-pathogenic T cells, such as Th1 and Th17 cells, favoring a shift to the Th2 pathway and thus providing a profile of greater immune tolerance (Mattner et al. mentioned by [27]).

Besides the immunomodulatory function, vitamin D seems to suppress the production of inflammatory cytokines, especially interleukin (IL) 6 (IL-6) by monocytes, which trigger the systemic inflammatory response syndrome (Almerighi et al. cited by [27]).

In addition to its endocrine functions, vitamin D can act in a paracrine or autocrine manner. Some of the more recently recognized non-classical actions of vitamin D include effects on cell proliferation and differentiation, as well as immunological effects, resulting in the ability to maintain tolerance and promote protective immunity. Because antigen-presenting cells (macrophages and dendritic cells), T cells, and B cells have the necessary machinery to synthesize and respond to 1,25$(OH)_2$D, it can act in a paracrine or autocrine manner in an immune environment. In addition, local levels of 1,25$(OH)_2$D may differ from systemic circulating levels because local regulation of its synthesizing and inactivating enzymes differs from controls present in the kidneys. The extrarenal 1-α-hydroxylase enzyme in macrophages differs from renal hydroxylase in that it is not regulated by parathormone (PTH), rather by circulating levels of 25(OH)D or by cytokines such as interferon gamma (IFNγ), IL-1, tumor necrosis factor alpha (TNFα) (Wu et al., van Etten et al., cited by [27]). Furthermore, the macrophage 24-hydroxylase enzyme represents a non-functional "splicing" variant,

so there is no negative feedback of local $1,25(OH)_2D$ production by itself[27]. The English term "splicing", which occurs in the cell nucleus, consists of the precise removal of introns and correct bolding of exons immediately after RNA transcription.

Vitamin D appears to interact with the immune system through its action on the regulation and differentiation of cells such as lymphocytes, macrophages, and natural killer cells, as well as interfering with cytokine production in vivo and in vitro. Among the demonstrated immunomodulatory effects are: decreased production of IL-2, IL-6, IL-8, IL-12, IFNγ, FNTα, inhibition of IL-6 expression, and inhibition of secretion and production of autoantibodies by B lymphocytes (Almerighi et al., mentioned by [27]).

**4. Actions in autoimmune, tumor, and infectious diseases**

Because of the numerous sites where vitamin D receptors can be found, their deficiency is also associated with autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, and rheumatoid arthritis, as well as association with cancers and systemic arterial hypertension[5].

The cohort study VITAL[23] represents one of the clinical trials that sought to clarify, among other aspects, the association between vitamin D and the occurrence of autoimmune diseases. The authors showed that individuals with BMI <25.0 kg/m$^2$ had significant benefits from cholecalciferol supplementation (2,000 IU/day) compared to the control group regarding the occurrence of autoimmune disease (22%). However no protection was found among participants with obesity (BMI-25.0-29.9) or overweight (BMI≥35.0) (Hahn et al., cited by [24]).

Non-endocrine vitamin D functions are only affected in states of extreme vitamin D deficiency. Changes in gene expression of the VDR, vitamin D 25-hydroxylase, and calcitriol have been shown to be associated with inhibition of carcinogenesis[5]. Similarly, $1,25(OH)_2D$ has hormonal and paracrine actions described in several tumors: breast carcinoma, melanoma, some types of leukemia, prostate carcinoma, and bowel carcinoma[5,28]. Numerous clinical trials have sought to clarify the association between vitamin D and cancer incidence and mortality. Among them, one can mention the VITAL cohort study, which evaluated the daily supplementation of cholecalciferol (2,000 IU) and/or omega-3 fatty acids (1 g) versus placebo for primary prevention of cancer and cardiovascular disease[23]. This US-based trial included 25,871 participants, aged over 50 years (male) and 55 years (female), follow-up time 5.2 years. The authors analyzed primary outcomes (invasive cancer of any type) and relevant cardiovascular events (associated heart attack, stroke, or death from cardiovascular causes). Secondary endpoints included specific cancers, cancer death, and additional cardiovascular events. The authors concluded that vitamin D supplementation did not result in lower incidence of invasive cancer or cardiovascular events compared to the placebo group.

However, pre-specified secondary analyses demonstrated that individuals with a BMI < 25.0 kg/m$^2$ showed significant benefits from supplementation compared to the control group in terms of lower cancer incidences (24%)[23] and cancer mortality (42%) (Chandler et al., cited by [24]). However, no corresponding benefit was observed among overweight or obese individuals[23,24].

Trials have also demonstrated the presence of hypermethylation and underexpression of the vitamin $D_3$ receptor promoter (VDR) in adrenocortical carcinomas of adult patients (Latronico et al., cited by[29]). Likewise, pediatric adrenocortical tumors (pACT) exhibit complex genomic origins, lack relevant prognostic markers and specific therapeutic options. Thus, Bueno et al.[29] evaluated VDR expression and methylation status in pACT carriers. They studied clinical and prognostic significance in a retrospective cross-sectional study model that included pediatric patients with ACT from two tertiary referral institutions. They evaluated clinicopathological features, VDR (mRNA, quantitative polymerase chain reaction), protein expression (immunohistochemistry) and broad VDR methylation of ACT samples from 108 pediatric patients. Normal adrenal tissues from fourteen pediatric, 32 fetal and postnatal participants were used as controls. In contrast to pre- and postnatal normal adrenals, most pACT carriers showed no nuclear expression of VDR and had reduced mRNA levels, especially the carcinomas. Analysis of VDR methylation data revealed that tumors with high methylation had lower mRNA levels and the respective patients had advanced disease as well as reduced disease-free and overall survival.

The authors[29] concluded that VDR had a relevant function in normal adrenocortical development and homeostasis, which became impaired during tumorigenesis. Thus, hypermethylation and underexpression of the VDR may represent predictive and prognostic biomarkers of pACT.

Bueno et al.[30] demonstrated, in another trial, that DNA hypermethylation in patients with pACT represented a reserved prognostic factor. Two methylation patterns were found, pACT-1 and pACT-2. The first was observed in children older at diagnosis, more likely to be carriers of carcinomas and non-localized, advanced, recurrent or metastatic disease. Also, this pattern was associated with a higher risk rate of disease progression and death compared to the prognostic factors currently considered. The authors concluded that the tumor methylation profile represents a relevant and independent prognostic biomarker for pACT.

As for the therapeutic applications of calcitriol, the trial conducted by Bueno et al.[31] stands out. These authors conducted in vitro and in vivo studies regarding the participation of calcitriol and its synthetic analog seocalcitol

in the development of adrenocortical carcinomas (ACC). These tumors occur most frequently in children in the first and in adults in the fourth decade of life. In the USA, the estimated annual incidence approaches 0.2 to 0.3 cases per million (Bernstein and Gurney, cited in[31]). However, it is particularly high in southeastern and southern Brazil, about 10 to 15 times higher than in the United States. Although the cause of this higher rate has not been identified, predisposing genetic factors have been implicated in most cases, such as germline TP53 mutations in patients from Brazil or the USA[32].

Surgical resection represents the only curative treatment for localized disease. However, when the disease is advanced or metastatic, the available adjuvant systemic therapies result in limited improvement in survival. Thus, there is an effort to develop new specific therapeutic options to be made available to these patients[31].

Bueno et al.[29] identified a cellular mechanism associated with the formation of pACT. They subsequently performed studies[31] in culture of H295R ACC cells and in mice that received H295R xenografts. In the in vitro study the cells were treated with calcitriol, seocalcitol, or vehicle (controls), then subjected to analyses of cell proliferation, expression, methylation, VDR activation, and its effects on the Wnt/B-catenin (Wingless-related integration site) signaling pathway. In the in vivo study, mice were treated with seocalcitol five times a week for five weeks or vehicle. The authors demonstrated in vitro that calcitriol and seocalcitol damaged Wnt/B-catenin signaling, restored activation of the gene encoding the VDR, resulting in antiproliferative effects in this type of carcinoma. This response was possible due to the restoration of this pathway existing in healthy cells, but inactive in tumor cells. On the other hand, in vivo, seocalcitol restricted the growth of H295R xenografts and reduced the autonomic secretion of tumor steroids and did not cause side effects associated with hypercalcemia.

Bueno et al.[31] concluded in this study that H295R cells showed VDR hypermethylation, which could be responsible for the underexpression and inactivation of signaling under basal conditions. VDR signaling promoted antiproliferative effects in vitro and in vivo, suggesting that it may represent a potential therapeutic target and valuable tool for the clinical treatment of ACC patients.

There is evidence that vitamin D acts in inducing more adequate defense against bacterial and viral agents by stimulating antimicrobial peptides, such as β2-defensin, which acts against Mycobacterium tuberculosis, promoting the production of cathelicidin, which decreases viral replication (Hewison cited by[8]),[33,34]. Besides these actions, it increases the secretion of antimicrobial substances such as $H_2O_2$ and of the lysosomal enzyme called acid phosphatase[33].

Numerous clinical trials have aimed to analyze the associations between serum vitamin D levels and clinical evolution of patients admitted to the intensive care unit (ICU) and among them some are reported below:

Hu et al.[35] demonstrated that reduced serum vitamin D concentrations in patients on ICU admission were associated with greater intensity of organ dysfunction.

Also, individuals in severe sepsis and septic shock had lower vitamin D concentrations when compared to septic patients without organ dysfunction[36].

McKinney et al.[37] conducted a study in critically ill patients and found that the risk of death was 1.81 times higher in the population with vitamin D concentrations <20ng/mL.

Higgins et al.[38] found that vitamin D deficiency was also associated with longer hospitalization and a tendency to contract infections in the ICU.

Thus, vitamin D may also represent a marker of severity in patients with critical medical conditions. However, the literature reports several physiological mechanisms dependent on vitamin D, suggesting that this deficiency is involved in the pathogenesis of organ dysfunction and in critically ill patients, maybe mediated by effects on immunity and the cardiovascular system[39].

**5. Vitamin D and coronaviruses**

The new coronavirus, SARS-CoV-2 (Severe Acute Respiratory Syndrome-Corona Virus 2), was identified in December 2019, when the first affected patients were publicly released, in Wuhan, Hubei Province, China.

The corresponding disease is called COVID-19 (English Corona Virus Disease) according to the World Health Organization (WHO), which declared SARS-CoV-2 a global pandemic on February 11, 2020[40].

It is characterized by triggering respiratory syndrome that can evolve into severe interstitial pneumonia and acute respiratory distress syndrome. The causative agent SARS-CoV-2 is transmitted mainly between individuals by contact, respiratory droplets, aerosols, and spreads rapidly[40].

The mechanism of SARS-CoV-2 infection involves binding of the SARS-CoV-2 spike protein to the angiotensin-converting enzyme 2 (ACE2) in the host lung epithelial cells to enter the cell and trigger infection. However, ACE2 expression levels are elevated in numerous organs, such as the intestine, heart, and kidneys, which propitiate the systemic involvement of this disease[40].

However, in SARS-CoV-2 infection, negative regulation of ACE2 has been demonstrated, which causes subsequent storm of pro-inflammatory cytokines and thus severe COVID-19. Calcitriol, however, causes increased expression of ACE2[33], acts as an essential regulator of the ACE2/Angiotensin axis by suppressing renin activity. Vitamin D also exerts actions on the immune system, including modulation of innate and adaptive immune responses of the body to aggressive agents, such as bacteria

and viruses. In COVID-19 there are manifestations in several tissues and organs, either from viral aggressiveness or from the release of pro-inflammatory cytokines. There is evidence that vitamin D modulates the macrophage response by inhibiting the release of inflammatory cytokines and chemokines[33].

Thus, in SARS-CoV-2 infection and in the presence of adequate levels of vitamin D, there is a predominance of anti-inflammatory cytokine release, suppression of renin activity, among other modulating functions of the immune response. These actions of calcitriol contribute, therefore, to the reduction of cytokine storm and evolution to less severe clinical forms of COVID-19[40].

Researchers in numerous countries, from the beginning of the pandemic, have sought to analyze the risk factors, such as nutritional status, serum vitamin D levels according to age, latitude, ethnicity, gender, comorbidities, among others, associated with Covid-19 mobimortality,[41,42,43,44].

Thus, Ilie et al.[33] hypothesized a possible association between mean vitamin D levels in 20 European countries and morbidity and mortality caused by Covid-19. The study included 27868 affected individuals and 1608 deaths. These authors found negative correlations between mean vitamin D levels (56 nmol/L) in each country, the number of cases affected by COVID-19/per million population (mean 295.95), and mortality/per million population (mean 5.96). Vitamin D levels were very low in the aging population, especially in Spain, Italy, and Switzerland. This also represented the most vulnerable group with respect to COVID-19.

As for the probable mechanisms, the authors commented that calcitriol may play modulating actions in the body's reaction to SARS-CoV-2 infection. Among them, the release of inflammatory cytokines and chemokines by macrophages, responsible for the cytokine storm, would be attenuated[33,34].

The authors[33] concluded by suggesting specific studies on vitamin D levels in patients with COVID-19 and different levels of disease severity.

Maghbooli et al.[41] conducted a cross-sectional study with the database of Sina hospital in Tehran, Iran, with 235 patients infected with COVID-19, age above 18 years. Among them, 74% had severe COVID-19 infection and 32.8% had sufficient serum vitamin D levels. After adjusting for 25(OH)D levels, there was a significant association between vitamin D sufficiency, reductions in clinical severity, serum C-reactive protein (CRP) levels, and an increase in the percentage of lymphocytes. Only 9.7% of patients over the age of 40 who had sufficient vitamin D concentrations succumbed to infection, compared with 20% of those with a circulating 25(OH)D level <30 ng/ml. The significant reduction in serum CRP, an inflammatory marker, associated with the increased percentage of lymphocytes suggests that vitamin D sufficiency collaborates in modulating the immune response, possibly reducing the risk of the cytokine storm in response to SARS-CoV-2 infection.

Kaufman et al.[42] conducted a retrospective, observational study of unidentified tests performed in a USA national clinical laboratory to determine whether circulating levels of 25(OH)D would be associated with positivity for SARS-CoV-2. Over 190,000 patients residing in 50 states were included, with SARS-CoV-2 results performed between March and June 2020 and serum 25(OH)D levels performed within the previous 12 months. A total of 191,779 patients were evaluated, (median age-54 years, 68% female). The SARS-CoV-2 positivity rate was shown to be 9.3% and the mean seasonally adjusted 25(OH) D was 31.7 ng/mL. The SARS-CoV-2 positivity rate was higher in 39,190 patients with deficient 25(OH)D levels (<20 ng/mL) (12.5%, 95% C.I. 12.2-12.8%) compared to 27,870 with adequate levels2 (30-34 ng/mL) (8.1%, 95% C.I. 7.8-8.4%) and 12,321 with values of 55 ng/mL (5.9%, 95% C.I. 5.5-6.4%).

The results of these authors42 demonstrated an inverse relationship between circulating levels of 25(OH) D and positivity for SARS-CoV-2. All participants with a circulating 25(OH)D level <20 ng / mL had a 54% higher positivity rate compared to those with blood levels between 30 and 34 ng/mL. The risk of positivity for SARS-CoV-2 remained downward until serum levels reached 55 ng/mL.

Patients with lower circulating levels of 25(OH) D had approximately 5-7% higher absolute positivity for SARS-CoV-2 at northern, central, and southern latitudes. Therefore, positivity for SARS-CoV-2 was shown to be strongly and inversely associated with serum 25(OH)D levels, and persisted regardless of latitude, ethnicity, sex, and age group. The authors suggested studies addressing whether vitamin D supplementation would reduce the risk of infection and disease attributed to SARS-CoV- 2.

In the retrospective cohort study by Charoenngam et al.[43], 1478 patients hospitalized for COVID-19 were evaluated; however, they only included, 287 in the study. Among these, 35% had adequate vitamin D levels (>30 ng/mL), 32% insufficiency (20-30 ng/mL) and 33%, deficiency (< 20 ng/mL). During hospitalization, 14% of patients died. Most of the vitamin D sufficient patients were older (66.2 ± 15.7) than the others (55.9 ± 15.8 among deficient and 63.7 ±4.3 among insufficient) and had a higher frequency of hypertension, dyslipidemia, heart failure and neurovascular disease. They also had significantly higher levels of serum albumin (p=0.007) and oxygen saturation (p=0.005), and lower levels of plasma ferritin, which has pro-inflammatory activity (p=0.09). Multivariate analysis among patients aged ≥65 years evidenced that sufficient vitamin D levels were associated with lower odds ratios (OR) of septic shock (OR 0.26, 95% CI, 0.08-0.88), acute respiratory distress syndrome (ARDS) (OR 0.22, 95% CI, 0.05- 0.96) and death (OR 0.33, 95% CI, 0.12-0.94). The

study did not obtain conclusive results for patients younger than 65 years of age and with a BMI over 30. The authors concluded that the observed results suggested potential benefit of increasing serum 25(OH)D level around 30 ng/mL for reducing the risk of morbidity and mortality from COVID-19. However, they suggested that further clinical trials are needed to determine the benefit of vitamin D supplementation for this purpose.

Various research demonstrates that serum calcidiol levels correlate strongly with severity of SARS-CoV-2 infection. However, there is open discussion as to whether reduced serum vitamin $D_3$ levels stem from the infection or whether prior deficiency would negatively affect immune defense. Thus, Borsche et al.[44] conducted a systematic search in order to collect more evidence on these associations. These authors conducted a meta-analysis study that included two independent data sets. The first was a population-based study based on mean pre-infection serum vitamin $D_3$ levels documented in 19 European countries, and the second was represented by seven hospital studies that included 1,601 hospitalized patients, 784 of whom had vitamin D levels determined one day after admission. Mortality rates from the clinical trials were corrected for age, sex, and diabetes mellitus. Data were analyzed by Pearson correlation and linear regression. Results from the two independent data sets revealed negative Pearson correlation of 25(OH)D levels and mortality risk (r(17) = -0.4154, p = 0.0770/r(13) =-0.4886, p=0.0646). For the combined data, mean vitamin D3 levels were 23.2 ng/mL (17.4-26.8), and a negative and significant Pearson correlation was found (r(32) =-0.3989, p=0.0194). Linear regression suggested a theoretical point of zero mortality at serum vitamin D3 level around 50 ng/mL.

The authors concluded that both sets provided relevant evidence that reduced 25(OH)D level would represent a predictor, rather than just a side effect of infection.

They also commented that the study they conducted, to the best of their knowledge, would be the first with the goal of determining an optimal 25(OH)D level that would reduce mortality from COVID-19, given that other studies have been limited to identifying PR for cohorts of two to three patients with vitamin D3 levels of 30 ng/mL or lower.

Although vaccinations were ongoing throughout the pandemic, Borsche et al.[44] recommended elevating serum 25(OH)D levels above 50 ng/mL. The purpose of this suggestion would be to prevent or mitigate further outbreaks of SARS-CoV-2 due to escape mutations or reduced immune activity related to antibody production.

A cohort study by Kaufman et al.[45] including about 200,000 participants, confirmed that the number of SARS-CoV-2 infections correlated significantly with respective serum 25(OH)D concentrations. The authors found a reduction in the occurrence of infections at levels around 55 ng/mL.

Pereira et al.[46], in a systematic review and meta-analysis study, analyzed the association between vitamin D deficiency (<50 nmol/L) and severity of COVID-19 by analyzing the prevalence of vitamin D deficiency and insufficiency (<25 nmol/L) in individuals with COVID-19. Five online databases were queried - Embase, PubMed, Scopus, Web of Science, ScienceDirect, and Medrevix preprint. Inclusion criteria were observational studies that determined serum vitamin D levels in adults and the elderly with COVID-19. The main outcome consisted of the prevalence of vitamin D deficiency in severely affected individuals with COVID-19. They performed meta-analysis with random effect measures, identified 1,542 articles and selected 27 of them. The results revealed that vitamin D deficiency was not associated with higher PR of COVID-19 infection (PR = 1.35; 95% CI = 0.80-1.88). However, they identified 64 % (OR = 1.64; 95% CI = 1.30-2.09) vitamin D deficiency among patients with severe COVID-19 compared to mild forms. Insufficient vitamin D concentrations increased hospitalization (OR= 1.81, 95% CI = 1.41-2.21) and mortality from COVID-19 (OR = 1.82, 95% CI = 1.06-2.58). The authors observed a positive association between vitamin D deficiency and disease severity. They commented, however, on the limitations of the respective study, such as stratification by sex, body composition, age, comorbidities among the articles selected for the meta-analysis. These, however, were minimized because they chose to select articles from independent authors and analyzed the risks of bias.

They recommended conducting prospective studies, especially clinical trials, including different age groups and climatic conditions, in order to assess causality between vitamin D and COVID-19. They suggested that diagnostic criteria for COVID-19 and vitamin D dosage be equally adopted for all study participants.

Thus, there is scientific evidence that vitamin D exerts functions related to immune response, which could be associated with lower rates of both infection and disease or severe evolution related to SARS-CoV- 2. However, there is need for larger, multicenter, international studies to confirm or not the results worldwide[33,34,41,42,43,44,45,46].

## 6. Cognitive Functions

Several authors have observed that reduced serum levels of 25(OH)$D_3$, a stable marker of vitamin D, have been related to increased risk of cognitive dysfunction, Alzheimer's disease, and all causes of dementia, suggesting that it is involved in the etiology of these clinical conditions[47,48,49].

Among the functions of vitamin D associated with these neurological changes, one can mention the production of neurotrophic factors, related to survival and neuronal functions[50], vasoprotection, phagocytosis, and amyloid clearance. However, the clinical relevance of

these mechanisms in humans is not yet fully understood[51].

There is also evidence that genetic factors related to vitamin D receptors are associated with cognitive function and depressive symptoms in the elderly[52].

Several prospective studies suggest causal and temporal relationships between vitamin D and cognitive decline (CD). Among them, Llewellyn et al.[53] observed, in a community of 858 elderly Italians, that the relative risk of CD was shown to be 60% higher among those with marked vitamin D deficiency ($25(OH)D_3 < 25$ nmol/L) compared to those with sufficient levels2 (≥75 nmol/L). Analogously, CD occurred at a frequency 41% higher among 1136 elderly US men in the lower quartile (≤ 49.7 nmol / L) compared with those in the upper quartile (≥ 74.4 nmol / L) of serum $25(OH)D_3$ levels[54].

The capacity for cutaneous synthesis of vitamin D decreases significantly with age, which may represent one of the causes responsible for hypovitaminosis D among the elderly. This is reduced by more than 50% at age 70 compared to age 20, while other functions, such as intestinal absorption, are not affected (MacLaughlin J, Holick MF, cited by[55]).

On the other hand, vitamin D deficiency has been shown to be an accelerating factor in the progression of the aging process. Gómez-Oliva et al.[55], in a review article, addressed the effect vitamin D has on the senescent brain, highlighting the neurogenic process. Neurogenesis occurs in the adult brain in regions such as the dentate gyrus of the hippocampus (DG) and generates new neurons that participate in cognitive functions. The neurogenic rate in the DG is shown to be reduced in the brain of the elderly because there is a decrease in the number of neural stem cells (NSC). Homeostatic mechanisms, controlled by the Wnt[56] signaling pathway, protect the depletion of the NSC pool. These pathways are also involved in various types of neuropathic pain (NP), related to acquired immunodeficiency virus, cancer pain, diabetic neuralgia, multiple sclerosis, endometriosis, as well as cell proliferation in ACC, as studied by Bueno et al.[29].

Furthermore, Wnt signaling is related to pain resulting from sciatic nerve compression and selective spinal nerve ligation. Thus, this pathway may represent a potential future therapeutic target for NP treatment[56].

Gómez-Oliva et al.[55] also discussed the "crosstalk activation" between Wnt and vitamin D and hypothesized that hypovitaminosis D may trigger imbalance in the control of cerebral neurogenic homeostatic mechanisms in aging, resulting in cognitive impairment.

In conclusion, these authors[55] commented that vitamin D has been shown to exert a relevant effect on neurogenesis and neuronal survival. Vitamin D could therefore potentially act in hippocampal progenitor cells as a co-activator of Wnt/β-catenin, a signaling pathway for preserving brain neurogenesis in aging. Thus, the reduction in serum vitamin D levels during senescence would play a role in the positive regulation of Wnt antagonistic signals responsible for decreased neurogenesis, even preceding cognitive decline. However, further studies are needed for a better understanding of the relationships between vitamin D, neurogenesis, and cognitive performance in the elderly.

Arosio et al.[57] in a cohort study of 509 community-dwelling elderly subjects aged 64 to 92 years assessed the association between vitamin D levels, cognitive decline, dementia from various causes, and contribution to frailty. This was estimated using an index, which included laboratory parameters, clinical symptoms, and comorbidities. The assessment of cognitive status included a modified version of the MMSE (Mini Mental State Examination) and a series of neuropsychological tests.

These authors[57] found a significant association between vitamin D levels and MMSE, regardless of cognitive impairment, age, gender and frailty. Patients with dementia (Alzheimer's disease (AD) and mixed dementia (MD)) had lower vitamin D levels, while those with mild cognitive disorder, higher levels than the other groups. Marked 25(OH)D deficiency was observed in patients with DM, advanced age, as well as those with cognitive and functional impairment. In conclusion, in this community with elderly people analyzed for cognitive status, the authors observed an association between vitamin D levels and cognitive decline, regardless of the frailty index.

However, there is controversy regarding the role of vitamin D in cognitive decline in several clinical studies. Thus, CSHA (Canadian Study of Health and Aging)[58] consisted of a 10-year cohort study that included 661 non-demented individuals aged 65 years or older. Frozen blood samples were analyzed for 25 OHD and follow-up data on cognitive function, criteria for dementia, including AD, among others. The authors found over a 5.4-year follow-up period that 141 individuals developed dementia, 100 of them with a diagnosis of AD. They observed no significant association between 25(OH)D and cognitive decline, dementia, or AD. However, higher concentrations of 25(OH)D were associated with an increased risk of dementia and AD in women, but not in men. They also commented on some limitations of the study attributed to vitamin D, such as a single serum dosage, which may not have represented status throughout follow-up, failure to classify serum levels non-differentially, which may have underestimated their true effect on cognition. So also, the significant association with dementia and AD found among women, and apparently more pronounced among older women, should be analyzed with caution because of the possibility of a survival bias in the cohort analyzed.

Duchaine et al.[58] concluded that the CSHA cohort study did not demonstrate a protective effect of vitamin D status on cognitive function and suggested further research, particularly to clarify the relationship between 25OHD and gender. Likewise, Kang et al.[59] evaluated CD among participants in the VITAL trial over a period of

two to three years. They concluded that cholecalciferol supplementation (2000IU/day) was not associated with this decline in community-dwelling elderly participants. However it did provide discrete cognitive benefits in black elderly people, and they suggested that these results would need future confirmation.

Although results from clinical trials are not homogeneous, the role of vitamin D in maintaining cognitive function and preventing dementia remains grounded in plausible biological mechanisms[60]. There is evidence from animal models that vitamin D may influence the occurrence of neurodegenerative disorders. Epidemiological studies also reveal associations between lower serum 25(OH)D concentrations and impaired cognitive performance in community-dwelling elderly populations, although an optimal 25(OH)D level for cognitive health cannot be determined. The effect of increasing 25(OH)D concentrations on cognitive function remains unclear, as there is a paucity of interventional evidence. At the very least, it seems prudent to prevent vitamin D deficiency in older adults, coupled with other protective factors arising from lifestyle, as a viable component of brain health strategies[60].

Among the few interventional studies regarding the benefits of vitamin D supplementation in animal models and particularly among older adults with AD, there are those performed by Lai et al.[61,62]. These authors demonstrated in a study with mice affected by AD61 that the genomic vitamin D receptor (GVDR) originates a complex with p53[63] in the brain with AD. It is noteworthy that the tumor suppressor protein p53 induces cell cycle arrest or apoptosis. Several studies have reported increased immunoreactivity of this in AD (Kitamura et al., Ohyagi et al. mentioned by Hooper et al.[63]).

Lai et al.[62] subsequently observed that mice fed a diet sufficient in vitamin D had significantly lower serum 25(OH)D levels, suggesting that deficiency may be a consequence rather than a cause of AD. Furthermore, vitamin D supplementation triggered increment of beta amyloid (βA) deposition and exacerbation of AD. Mechanistically, vitamin D supplementation increased the GVDR/p53 complex in brains of AD mice. The authors[62] also analyzed, elderly people not with dementia (n = 14,648) in a population-based longitudinal study. They found that participants who underwent vitamin D3 supplementation for more than 146 days a year had a 1.8-fold increased risk of developing dementia than those who did not receive supplements. Among individuals with pre-existing dementia (n = 980), those who took vitamin $D_3$ supplements for more than 146 days a year had a 2.17 times greater risk of mortality than those who did not receive supplements.

Among individuals with pre-existing dementia (n = 980), those who took vitamin $D_3$ supplements for more than 146 days per year had a 2.17 times greater risk of mortality than those who did not receive supplementation, particularly among older adults with pre-existing AD and reduced serum vitamin D levels. The authors concluded that only in the face of evidence to the contrary should the use of vitamin D supplementation to prevent dementia be reconsidered.

So too, there are studies that have evaluated which nutritional factors have been significantly related to cognition. In the systematic review[64] of articles published between 2011 and 2021 the authors looked at the effectiveness of using vitamin supplements in the diet as a solution to nutritional deficiencies and prevention of dementia and mild cognitive impairment. They found that individuals receiving folic acid supplementation performed better on cognitive tests than those in the control group. Combined supplementation of folic acid and vitamin B12 revealed discrepancies between the studies. Thiamine as supplementation showed positive impact on cognitive performance, either administered alone or in combination with folic acid. In this review, the studies of vitamin D supplementation were inconclusive in assessing the potential benefits vitamin D may have on cognition. However, the authors did mention the results found by Anweiler et al.[65] who compared vitamin $D_3$ supplementation with no intervention. Participants in the group with vitamin $D_3$ supplementation scored significantly higher on cognitive assessment scales and executive functioning compared to the control group.

Therefore, a thorough understanding of the relationships between vitamin D, neurogenesis, and cognitive performance in the senescent brain becomes critical both for conducts to prevent cognitive decline and to stimulate future studies on new therapeutic perspectives.

## 7. Musculoskeletal Function and Falls

Vitamin D deficiency is mainly associated with mild hypocalcemia, secondary hyperparathyroidism, osteopenia, osteoporosis, osteomalacia (in adults), and rickets (in children)[2,5]. There is an increased risk of fractures from minor trauma and bone deformities as a consequence of increased bone remodeling, loss of trabecular bone, and narrowing of the cortical bone5. Proximal muscle weakness represents a clinical sign of hypovitaminosis D, related to changes in muscle relaxation and contraction and consequent increased risk of falls and fractures, especially in the elderly[5,66].

Although the occurrence of falls varies according to age, housing conditions, among others, it is estimated that the annual rate of occurrence is approximately 30% among elderly people 65 years of age or older, and 50% among those 85 years of age or older[67].

The reduction in muscle strength with age is related to poor nutritional quality, the occurrence of chronic diseases, physical inactivity, among others[68].

Moreover, falls in senescence are also associated with increased mortality and degree of dependence, as well as with the need for hospital admissions, follow-up by health professionals, including in the home environment[69,70].

Therefore, studies that identify the risk factors, as well as their better control, elimination or even minimization, can result in behaviors that reduce the occurrence and frequency of falls, especially in the elderly population. Among them, the results of the meta-analysis Bischoff-Ferrari et al.[71] suggested that vitamin D supplementation decreased the risk of falls[71].

Likewise, Bischoff-Ferrari et al.[72] demonstrated that 25(OH)$D_3$ administration reduced the risk of fractures among institutionalized and non-institutionalized elderly. Concentrations between 40 and 94 nmol/L were associated with improved musculoskeletal function in the lower limbs compared with concentrations below 40 nmol/L.

The results of a randomized trial also suggested that vitamin D supplementation for two years for institutionalized elderly people reduced the occurrence of falls, even among those initially not deficient in vitamin D[73].

Vitamin D and calcium supplementation may also result in reduction of falls through improvements in gait, mobility, body balance and normalization of blood pressure[66,72].

Although recent studies comparing various dosages and intervals of vitamin D supplementation have been published, it is still unclear whether there is an appropriate dose or interval that provides benefits with respect to fracture risk. Thus, Kong et al.[74] in a meta-analysis study including 35 randomized controlled trials evaluated the associations between vitamin D supplementation and risks of fractures and falls. These authors found that vitamin D supplementation with daily doses of 800 to 1,000 IU was associated with lower risks of osteoporotic fracture and falls. However, doses less than 800 or greater than 1,000 mg per day did not reduce these risks. In addition, daily vitamin D administration was associated with reduced risk of falls, while intermittent dosing was not. Likewise, patients with vitamin D deficiency had a significantly reduced risk of falls after vitamin D supplementation. The authors concluded that the daily vitamin D dose of 800 to 1,000 IU represented the most appropriate formulation in reducing the risk of fracture and falls. However, they suggested that studies designed with various concentrations and forms of vitamin D administration would be needed to elucidate the benefits of vitamin D supplements.

Mary Waterhouse et al.[75] conducted a randomized, double-blind, placebo-controlled D Health Trial conducted in Australia. The purpose of this study was to determine whether monthly supplementation of high doses of vitamin D reduced the risk and incidence of falls. A total of 21,315 participants aged 60-84 years were included and randomized (1:1) to monthly doses of 60,000 IU cholecalciferol or placebo for a maximum of 5 years. Each year, the authors collected blood samples from about 450 randomly selected participants for 25(OH)D determination. Falls were checked in annual surveys and, for a subset of participants, 3-month fall diaries. Mean serum 25(OH)D concentrations during the study were 114.8±30.3 nmol/L and 77.5±25.2 nmol/L in the groups receiving vitamin D supplementation and placebo, respectively.

Monthly 25(OH)D supplementation had no effect on falling in the last month. However, there was a significant interaction with BMI: 25(OH)D increased the risk in participants with BMI < 25 kg/$m^2$, but not among those with BMI ≥ 25 kg/$m^2$. The authors concluded that monthly high-dose vitamin D supplementation did not reduce the risk of falling, and possible increase in this risk in individuals with normal BMI would warrant further investigation. They also suggested not to extrapolate results obtained for populations with high prevalence of vitamin D deficiency.

LeBoff et al.[76] evaluated the effects of daily vitamin $D_3$ supplementation (2,000 IU) on fall prevention in a cohort of the VITAL (Vitamin D and Omega-3 Trial) study that included 25,871 adults, 49% male, age ≥50 years, mean age 67.1 years. Participants were recruited by mail, enrolled in 50 US states, and followed for 5.3 years. These authors found that baseline serum 25(OH)D levels of 77 nmol/L were considered sufficient for maintenance of musculoskeletal health. However they observed no evidence that vitamin D supplementation altered the risk of falls among baseline 25(OH)D levels less than 30 nmol/L or greater than 125 nmol/L in the general US population. However there was a potential increase in falls resulting in hospitalization among those with free vitamin D ($25(OH)_2D$) levels above the median. They also commented that the study had limitations, including the underestimation of incident falls because they were assessed annually by questionnaires, as well as the administration of a single dose of vitamin D. So also the lack of a standard program for dosing $25(OH)_2D$ levels may have represented a bias due to trial variation. They considered that the results cannot be generalized to women and men domiciled in nursing homes or residential communities because the study included community-dwelling population. They concluded that daily supplementation of 2,000 IU of vitamin D3 over 5.3 years did not reduce the risk of falls among generally healthy elderly people not selected for vitamin D insufficiency.

**Conclusions**

This article presented as objectives related to vitamin D: approach about physiological, environmental, nutritional, immunological, and genetic aspects; classification of serum levels, indications for oral supplementation and/or maintenance doses, and toxicity risks; immunological and immunomodulatory actions in autoimmune, tumor, and infectious diseases, with emphasis on Covid-19; consequences and controversies associated with vitamin D deficiency, among them dementia, Alzheimer's disease, cognitive functions, musculoskeletal disorders, and falls.

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