Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Vitamin D: role in chronic and acute diseases

Ana I. Álvarez-Mercado[a,b], **María Dolores Mesa**[a,b], **and Ángel Gil**[a,b,c], [a] Department of Biochemistry and Molecular Biology II, Institute of Nutrition and Food Technology "José Mataix", Center of Biomedical Research, University of Granada, Granada, Spain; [b] Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain; and [c] CIBEROBN (Physiopathology of Obesity and Nutrition Network CB12/03/30038), Institute of Health Carlos III (ISCIII), Madrid, Spain

Key points

- To know the role of vitamin D in the prevention and treatment of non-communicable chronic diseases.
- To understand how vitamin D deficiency is related to obesity, insulin resistance and metabolic syndrome, type 2 diabetes, cancer, rheumatoid arthritis, osteoporosis, chronic pulmonary obstructive disease, and inflammatory bowel disease.
- To know the function of vitamin D in the prevention and treatment of acute infectious diseases of bacterial and viral origins, namely respiratory infections.
- To understand the role of vitamin D in the prevention of HIV and SARS-Cov2 infections
- To know how vitamin D status affects the course of critical illness diseases

Introduction

Vitamin D is involved in bone health by promoting calcium absorption in the gut and maintaining serum calcium and phosphate concentrations, and by its action on bone growth and reorganization through osteoblasts and osteoclasts cells. Moreover, during the last three decades, novel actions of vitamin D have been discovered. Indeed, active vitamin D also regulates cell proliferation and differentiation and has a key role in the responses of the immune and nervous systems. Current effects of vitamin D include xenobiotic detoxification, oxidative stress reduction, neuroprotective functions, antimicrobial defense, immunoregulation, *anti*-inflammatory/anticancer actions, and cardiovascular benefits (Gil et al., 2018).

Several systematic reviews and meta-analyses have shown links between serum vitamin D levels and non-communicable diseases. In line with these findings, a wide number of studies have suggested associations of vitamin D deficiency (VDD) with respiratory tract infections, osteoporosis, and other chronic and metabolic diseases such as obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), cancer, rheumatoid arthritis (RA), and inflammatory bowel disease (IBD). **Fig. 1** shows a summary of the benefits of vitamin D supplementation on main non-communicable chronic diseases.

Hence, clinical trials addressed to evaluate the efficacy of administration of vitamin D and its metabolites for the treatment of both chronic and acute diseases are of great interest, although variable outcomes are being reported. In this concern, evidence shows

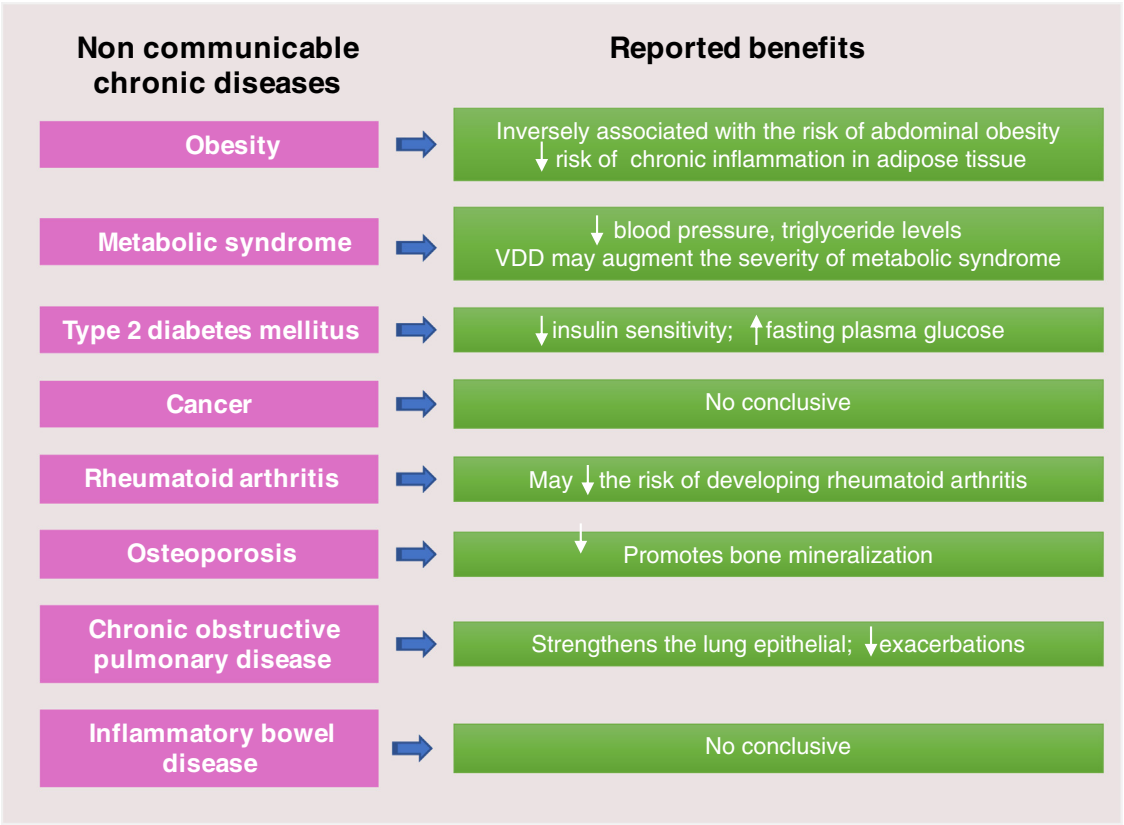

Fig. 1 Summary of reported benefits of vitamin D in non-communicable chronic diseases.

a notorious inter-individual difference in gene expression in human peripheral blood mononuclear cells in response to vitamin D supplementation, which suggests that some individuals might present a higher grade of benefits from vitamin D supplementation than others (Charoenngam, 2021) (**Table 1**).

Vitamin D also exerts important actions in the clinical course of infectious and other acute diseases, particularly respiratory bacterial infections, tuberculosis, and virus infections, e.g., those generated by human immunodeficiency and SARS-CoV-2 (COVID-19) viruses.

In humans, the recommended daily dietary allowance of vitamin D is 400–800 IU depending on age and sex. The circulating 25-hydroxy-vitamin D [25(OH)D] is the most used biomarker of VDD recommended by clinical guidelines and 1,25 dihydroxy-vitamin D [1,25 $(OH)_2D$], named calcitriol, the active form-of vitamin D. Other biomarkers and immune assay methods are also being evaluated and compared, such as bioavailable and free 25(OH)D, 24,25 dihydroxy-vitamin D [24,25$(OH)_2D$], other vitamin D metabolites, vitamin D binding protein or parathyroid hormone (Ganmaa et al., 2021).

According to the guidelines of the American Endocrine Society, serum levels of 25(OH)D below 20 ng/mL (50 nmol/L) are considered as VDD, while 25(OH)D serum levels between 21 and 29 ng/mL (52.5–72.5 nmol/L) are defined as vitamin D insufficiency (Holick et al., 2011). To maintain adequate levels in the preferred range of 40–60 ng/mL (100–150 nmol/L) (Ganmaa et al., 2021; Charoenngam, 2021) and thus avoid the risk of VDD, it is advisable to increase the intake of vitamin D and have adequate exposure to sunlight. However, it remains controversial what is the optimal serum level of 25(OH)D. For this, some professional societies recommend higher vitamin D intakes, and, in consequence, physicians sometimes prescribe more than 4000 IU to compensate for VDD. This can be biologically explained by: (1) the fact that the vitamin D receptor is expressed in the majority of human tissues; (2) vitamin D levels in northern latitudes are far lower than the hominids evolved in the equatorial Africa area and (3) the stimulation of vitamin D receptor by calcitriol alter the expression of over two hundred genes to support a large range of physiological responses with the potential to protect against the development of several pathologies (Ganmaa et al., 2021).

Vitamin D and chronic diseases

Obesity

Evidence shows that obesity negatively regulates circulating vitamin D levels. In fact, obesity decreases the detectable serum levels of 25(OH)D through the sequestration of vitamin D in body fat tissue (since vitamin D is a fat-soluble vitamin) or reduce skin synthesis of vitamin D because of limited outdoor activity and sun exposure (Al Anouti et al., 2020).

Table 1 Doses of vitamin D recommended or administered in interventions studies with reported benefits in chronic diseases.

Disease	*Dose*
Obesity/MetS	Obese adults and the elderly obese adults and the elderly (BMI 30+ kg/m^2): (BMI 30+ kg/m^2):
T2DM	1250–1500 μg/week (prevention)
Cancer	400 IUs or 2000 IU/day (reduced cancer mortality but not cancer incidence)
Rheumatoid arthritis	25–75,000 IU (decrease in fatigue severity and in pain)
Osteoporosis	2000 IU/day
COPD	Keeping the <25 nmol/L but not higher levels reduced the rate of moderate/severe exacerbations
IBD	5000–10,000 IU/day

BMI, body mass index; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; IU, international units; MetS, metabolic syndrome; T2DM, type 2 diabetes *mellitus*.

Moreover, alternations in vitamin D metabolism in obese subjects manifesting low serum levels of 25(OH)D is well-recognized, while weight reduction with loss of adipose tissue is associated with improvement in circulating 25(OH)D. Additionally, patients with obesity and intestinal malabsorption require a two to three times higher intake of vitamin D to maintain the same serum 25(OH)D concentrations (Charoenngam, 2021). It has been also demonstrated that abdominal obesity is more prevalent in those individuals with lower serum vitamin D levels. By contrast, results from observational studies aimed to investigate the relationship between VDD and the risk of central obesity are inconsistent. However, a meta-analysis of epidemiologic studies revealed that serum vitamin D level was inversely associated, in a dose-response manner, with the risk of abdominal obesity, particularly in adults. Furthermore, vitamin D reduced the risk of chronic disease and chronic inflammation in adipose tissue. In addition, dose-response analysis showed that every 25 nmol/L increments in serum vitamin D were related to an 8% reduced risk of abdominal obesity, 10% decreased central adiposity risk in representative populations, and 13% lower risk of metabolic syndrome.

The entire mechanisms throughout vitamin D affect the lipid profile is still undeciphered, even though observational and interventional studies report conflicting evidence. Moreover, it has been suggested that the association between vitamin D and metabolic disorders may be confounded by obesity rather than being a causal relationship. Accordingly, usual chronic inflammatory processes in obese patients might decrease 25(OH)D levels and, at the same time, affect several metabolic parameters (Al Anouti et al., 2020).

Metabolic syndrome

Metabolic syndrome is known as one of the most important risk factors of T2DM and cardiovascular disease and can increase the risk of myocardial infarction and stroke two-fold. According to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria of metabolic syndrome has six main components, namely obesity, dyslipidemia, high blood pressure, insulin resistance or glucose intolerance, pro-inflammatory state, and prothrombotic state (Ganmaa et al., 2021). Although this disease is a well-known and serious public health burden, the metabolic syndrome does not have any direct and ultimate treatment due to its multifactorial nature. In consequence, clinical management to reduce the risk factors is the most common intervention.

Results from randomized control trials (RCTs) suggest that vitamin D supplementation positively impacts blood pressure and abdominal obesity. However, most trials have revealed that vitamin D supplementation has no effect in reducing myocardial cardiovascular events, heart attack, death from cardiovascular disease, or in the treatment of chronic heart failure. In this concern, 1-year supplementation with 4000 IU/day vitamin D3 did not affect cardiovascular disease, lipid profiles, or C-reactive protein levels in T2DM patients, but reduced triglyceride levels. Another trial reported that supplementation with 150,000 IU bolus of vitamin D every 3 months was unable to alter inflammatory markers and lipids in adults with metabolic syndrome. In addition, a Cochrane review including 159 RCTs suggested that vitamin D supplementation may reduce all-cause mortality compared with placebo or no intervention; by contrast, vitamin D supplementation had no significant effect on mortality related to cardiovascular events (Ganmaa et al., 2021).

Despite the populations recruited for the study of the role of vitamin D in metabolic syndrome vary by sex, age, and country, data from observational studies highlight specific associations between vitamin D and individual components of this disease such as obesity, dyslipidemia and blood pressure, as well as with metabolic syndrome as a complete entity.

VDD or low levels of 25(OH)D is related to a higher risk of this disease. Additionally, suboptimal levels of vitamin D may augment the severity of the metabolic syndrome. Concentrations of 25(OH)D are lower in patients with metabolic syndrome than in those without it. The prevalence of metabolic syndrome is reduced by half if individuals have high 25(OH)D concentrations. Specifically, vitamin D might modulate the atherogenic components of metabolic syndrome (Al Anouti et al., 2020).

Considering that inflammation plays a key role in the development of the metabolic syndrome, and under the premise that the *anti*-inflammatory effect of vitamin D would decrease the risk of this disease, a dose-response analysis reported that an increase of 25 nmol/L in plasma 25(OH)D was associated with a 13% lower risk of metabolic syndrome.

Type 2 diabetes mellitus

T2DM is a worldwide disease that grows in parallel with other diseases affecting multi-body systems. Thus, it is mandatory to develop strategies to treat T2DM effectively, maintaining glucose homeostasis to avoid complications such as diabetic nephropathy, peripheral neuropathy, and retinopathy.

Vitamin D has *anti*-inflammatory action, inhibiting cytokine production, which has an important role in suppressing the chronic low-grade inflammation present in T2DM. Vitamin D regulates insulin secretion by binding to vitamin D receptors present on pancreatic beta cells. Vitamin D increases insulin sensitivity by upregulating the expression of insulin receptors and binding to the vitamin D response element present in the human insulin receptor gene promoter. It also affects fatty acid metabolism in insulin-responsive tissues through the activation of its transcription factor. Hence, the role of vitamin D in glucose metabolism and fuel homeostasis is supported by several observational studies revealing an inverse relationship seen between vitamin D and T2DM.

Although not many studies address the relationship between insulin sensitivity and vitamin D, one study reported that serum 25(OH)D concentration is responsible for 21.2% of the variation of the insulin sensitivity index. In addition, serum 25(OH)D concentration accounted for 8.2% of the variation of beta-cell function.

Data from meta-analyses of RCTs showed favorable effects of vitamin D intervention in T2DM non-obese individuals [BMI < 30] but not in those with BMI ≥ 30. Furthermore, supplementation with vitamin D in pre-diabetic subjects prevented progression to T2DM, improved insulin sensitivity, decreased insulin resistance and systemic inflammation, and lowered fasting plasma glucose (Ganmaa et al., 2021).

Since vitamin D affects different organs and tissues in patients with T2DM a systematic review was conducted to evaluate the effect of vitamin D supplementation in glycemic homeostasis and its impact on the T2DM patients. This study was focused on how this vitamin influences effectively, maintaining glucose homeostasis to avoid its complications. The authors found an inverse relationship between vitamin D levels and neuropathy and diabetic retinopathy.

Cancer

Biological functions of vitamin D include modulation of the immune system and *anti*-carcinogenic effects. The association of VDD with cancer (along with other effects), has been described because of its potential effect on cell differentiation and the suppression of cell proliferation. Consequently, recent studies have assessed the association between serum vitamin D and the risk of some types of cancer.

In a meta-analysis of RCTs, the authors reported that vitamin D supplementation significantly reduced total cancer mortality but did not reduce total cancer incidence (Ganmaa et al., 2021). On the other hand, a dose-response meta-analysis demonstrated that each five nmol/L increase in blood vitamin D levels was associated with a 6% decrease in the risk of breast cancer, while a 400 IU/day increase in vitamin D intake was not significantly correlated to this type of cancer. By contrast, other dose-response meta-analyses found that both serum vitamin D and vitamin D intake were inversely related to colorectal cancer. Further, another meta-analysis of RCTs showed a protective effect of vitamin D supplementation on cancer incidence and mortality. Additionally, a significant reduction in metastatic or fatal cancers has been reported in men $\leq$50 years and women $\leq$55 years (Ganmaa et al., 2021).

Given these controversial results, to date, neither 1,25(OH)2D nor its analogs have ever been successfully developed as a strategy to treat or prevent any type of cancer.

Rheumatoid arthritis

RA is a chronic autoimmune condition resulting in synovial inflammation around joints, progressively leading to cartilage and bone destruction. Results from multiple observational studies have evidenced a link between a low level of serum 25(OH)D and the presence and/or severity of several rheumatic diseases (Charoenngam, 2021). Indeed, vitamin D is believed to play a role in modulating RA's pathogenesis and disease activity, based on the actions of 1,25(OH)2D on the adaptive immune response that suppresses the proliferation and activity of T helper 1 cells (Th1) and Th17, and enhances the T regulatory cells (Treg) activity. Furthermore, genomic studies have shown that certain polymorphisms of the gene encoding vitamin D receptor and vitamin D binding protein are associated with susceptibility to RA (Charoenngam, 2021). An inverse correlation between circulating vitamin D levels and RA incidence and disease activity is also known.

Despite these promising results, unfortunately, evidence from clinical trials demonstrating the impact of any form of vitamin D supplementation on most rheumatic diseases has not been established yet. Moreover, it is still unclear whether the association between vitamin D and these conditions are causal or more likely explained by confounders and reverse causation, such as limited physical activity or corticosteroid administration (Charoenngam, 2021).

Concerning studies about dose-response, it is recommendable that patients with rheumatic diseases should maintain a serum 25(OH)D level of at least 30 ng/mL (75 nmol/L) to prevent osteomalacia, secondary osteoporosis and fracture, and possibly 40–60 ng/mL (100–150 nmol/L) to reach the higher benefit of vitamin D (Charoenngam, 2021). In treatment-naive RA patients, a significant negative association was observed between vitamin D levels and disease activity parameters. Notably, the association of vitamin D with the incidence and severity of RA is very well supported by evidence. However, due to heterogeneity in dosages and durations of supplementation, robust evidence supporting vitamin D supplementation in ameliorating clinical outcomes is still needed. In sum, observational studies suggest that increasing vitamin D intake to raise serum 25(OH)D may reduce the risk of

developing RA. However, there is no demonstration from a reliable clinical trial that vitamin D supplementation can reduce the risk of RA. In addition, there is moderate evidence that vitamin D supplements or the oral administration of 1,25(OH)2D can mitigate RA severity (Charoenngam, 2021).

Osteoporosis

Vitamin D regulates the absorption of calcium and phosphorus and, thus, is universally accepted as an essential vitamin for bone strength and as a promotor of the immune system function; it has been reported to have an *anti*-inflammatory role and established benefits in osteoporosis and osteomalacia.

Accordingly, VDD is a well-recognized health problem and contributes to bone loss and calcium dysregulation, which causes or aggravates osteoporosis. 1,25(OH)2D regulates calcium and phosphate homeostasis by acting on the small intestine, kidneys, and bones. It passively promotes bone mineralization by inducing intestinal absorption of calcium and phosphate and renal tubular calcium reabsorption, which helps maintain adequate calcium-phosphate crystallizing in the collagen matrix.

However, multiple studies failed to demonstrate any benefit from vitamin D supplementation in patients with osteoporosis, and a systematic review and meta-analysis also were unable to confirm any beneficial effect on bone density or fracture prevention. Additionally, placebo-control RTCs revealed a threshold effect of vitamin D with no benefit observed on the subjects with baseline 25(OH)D level $\geq$75 nmol/L (30 ng/mL). Furthermore, possible detrimental effects on bone mineral density were observed in subjects who received a higher dose of vitamin D (250 μg or 10,000 IU daily) with a mean 25(OH)D of 200 nmol/L or 80 ng/mL.

On the other hand, a maternal vitamin D osteoporosis study reported that daily vitamin D supplementation in pregnant women did not increase offspring whole-body bone mineral content above that of the placebo group (Ganmaa et al., 2021).

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is related to high mortality and morbidity worldwide, and its exacerbations cause significant morbidity, mortality, impaired quality of life, and costs (Lokesh et al., 2021). The main pathogenesis associated with COPD development is inflammation, oxidative stress, protease–antiprotease imbalance, and lung rebuilding (Ganmaa et al., 2021).

Having this into account, supplementation with vitamin D is particularly interesting due to its various effects on lungs, tissue remodeling, reduction of pro-inflammatory cytokines, and beneficial modulation of both innate and adaptive immune systems (Lokesh et al., 2021). In fact, lower vitamin D levels have been related to the regulation of typical characters associated with COPD (i.e., higher expression of proteases, modulation of inflammation and extracellular matrix turnover, and increased oxidative stress), their pathogenesis and severity. Some evidence suggests that vitamin D strengthens the lung epithelial. Accordingly, a recent meta-analysis of RCTs suggested that vitamin D supplementation may safely and substantially reduce the rate of moderate/severe COPD exacerbations in patients with baseline 25(OH)D levels $<$25 nmol/L, improve lung function and acute exacerbation. However, barrier studies focused on investigating a potential causal effect remain limited, and randomized trials report conflicting results for vitamin D supplementation and prevention (Ganmaa et al., 2021) Moreover, most of the studies focused on studying the relationship of vitamin D with COPD, its severity and exacerbations were performed in areas with sub-optimal sunlight and lack of sunlight throughout the year, or in cities where most residents spend time indoors (i.e., homes or offices). In consequence, reported data aimed to relate the association of vitamin D with the severity of COPD and its exacerbation in populations that are both adequately exposed to sunlight or keep higher levels of physical activity through the life course are quite limited (Lokesh et al., 2021).

On the other hand, it is deeply needed to perform longitudinal studies to evaluate whether young healthy subjects exposed to risk factors such as smoking or biomass fuel with low levels of vitamin D would present a higher risk of developing COPD, as well as whether vitamin D supplementation in these subjects would have the ability to prevent or delay the development of this disease (Lokesh et al., 2021).

Inflammatory bowel disease

IBD is a chronic inflammatory condition of the gastrointestinal tract that includes ulcerative colitis and Crohn's disease (Myint et al., 2020). It has been observed that samples from colonic biopsies of patients with IBD present a decreased concentration of vitamin D receptors and have a higher level of pro-inflammatory cytokines such as TNF-α and IL-1β. The most important IBD pharmacological strategy is to reduce inflammation. Due to the immunomodulatory properties that possess vitamin D, it is considered a very appropriate candidate for modifying risk factors and preventing the development of IBD, as well as ameliorating its severity. In fact, vitamin D protects the intestinal mucosa by increasing the expression of the proteins responsible for tight junction creation and affects epithelial integrity by the inhibition of the intestine epithelial apoptosis, which contributes to intestinal inflammation and the healing process.

However, although epidemiological and clinical observational studies have demonstrated an association between vitamin D and IBD, it is necessary to identify whether VDD is a consequence or a cause of IBD (Myint et al., 2020). Despite being limited by issues with trial design such as small sample size, uncertain use of control groups, inconsistent definitions of VDD, and/or absence of clinical outcomes, vitamin D supplementation trials suggest a variable association between VDD and IBD activity (Myint et al., 2020). However, the mentioned inconsistencies indicate that data from trials to evaluate dosing strategies for treatment are not sufficiently reliable.

Vitamin D and acute diseases

As mentioned previously, calcitriol is involved in the regulation of cell proliferation and differentiation and has a key role in the inflammatory and immune system response. This regulation confers an important role in the defense against bacterial and virus infections, which is mediated by its capacity to activate the innate defense response and to exert an *anti*-inflammatory action on the adaptive response, resulting in an overall immunotolerance effect (Gil et al., 2018).

The European Food Safety Authority (EFSA) considers vitamin D, within other vitamins and minerals, to be essential for the normal growth and functioning of the immune system. Impaired nutritional status or deficiencies of this vitamin is associated with increased risk and severity of many different types of infections. However, the immunomodulatory role of vitamin D against infections is complex and varies according to the nature of the pathogen. Moreover, the effectiveness of vitamin D is uncertain and appears to be highly dependent on the genetic polymorphisms of its receptor and epigenetic modifications. Fig. 2 shows a summary of the association of vitamin D with the main acute diseases.

Vitamin D and the immune system

Innate immunity is the first defense against invading microorganisms, including bacteria, viruses, fungi and protozoa. These mechanisms recognize microorganisms or their products and trigger a cascade of events that will eliminate and/or destruct the invading agents through the release of cytokines and antimicrobial peptides. Adaptive immunity is the second defense mechanism that mediates an antigen-specific immune response through antigen presentation cells (APC), namely dendritic cells (DCs), and the antigen recognition cells, T and B lymphocytes. Their activation causes the production of various cytokines and antibodies and induces cell killing.

The roles of vitamin D in the regulation of immunity are particularly well known. Immune system cells express the vitamin D receptors (VDR) when activated by external stimuli, indicating that vitamin D is especially involved in regulating their defense mechanisms. The binding of vitamin D to its cellular VDR activates immunity surveillance signaling pathways that modulate gene expression of proteins, such as cathelicidins (LL37) and defensins, involved in inflammation, oxidation, cell proliferation and differentiation, in apoptosis, and the processes of autophagy and bacterial destruction of infected macrophages (Gil et al., 2018).

On the other hand, related to the antimicrobial defense, vitamin D can inhibit the Th1, Th2 and Th17 adaptive response directly on lymphocytes via VDR signaling, or indirectly through paracrine signaling on APC. Vitamin D decreases the maturation of DCs and their ability to present antigens and alters the profile of Th and Treg. Specifically, vitamin D inhibits Th1, Th17, and Th9 cells development and leads to immune tolerance, and suppresses T-cell-mediated inappropriate proinflammatory mediators production. On the other hand, vitamin D enhances differentiation and proliferation of Th2 and Treg cells, which stimulate the release of *anti*-inflammatory cytokines (IL-4, IL-5, and IL-10) to be a significant mechanism by which vitamin D could be advantageous in autoimmune diseases by promoting an *anti*-inflammatory vs. inflammatory response.

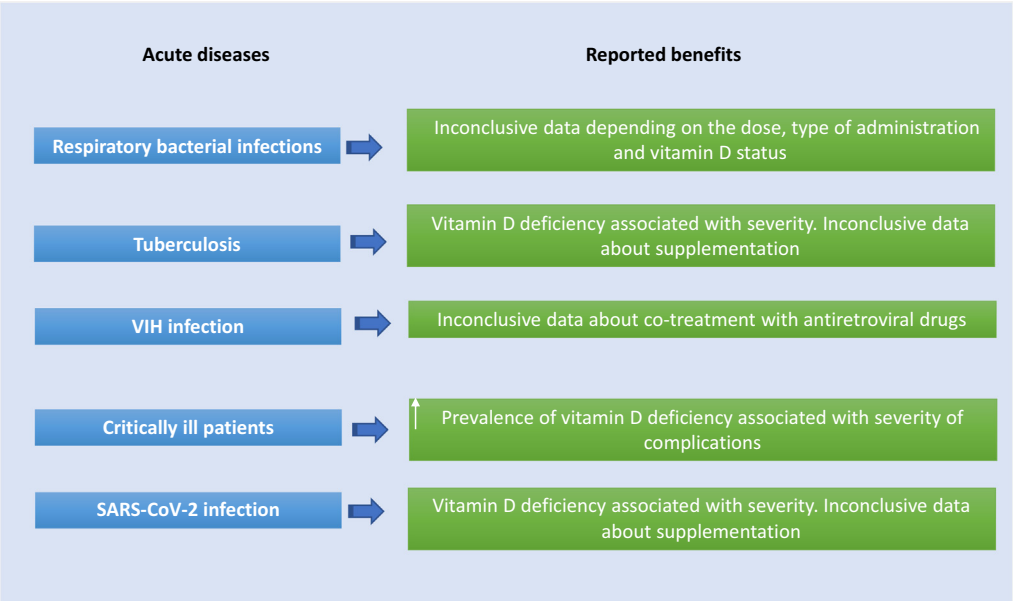

Fig. 2 Summary of reported benefits of vitamin D in acute diseases.

Vitamin D and respiratory bacterial infections

A large number of studies have associated a deficit of vitamin D blood levels and increased risk and severity of acute respiratory infections in children, adolescents and adults. Randomized controlled trials exploring the potential of vitamin D to prevent acute respiratory infections have yielded mixed results. Meta-analysis has the potential to identify factors that may explain this heterogeneity. Vitamin D supplementation is safe, and it protects against acute respiratory infections overall. Very deficient individuals and those receiving continuous supplements and not bolus doses are the ones who experienced the benefits. Incorporation of additional individual participant data from ongoing trials will be useful to increase the knowledge in these fields.

Tuberculosis is one of the most common and devastating infectious diseases worldwide. Several systematic reviews have found low vitamin D blood levels in patients with tuberculosis compared to healthy controls. These works have concluded that VDD may be a risk factor for tuberculosis disease progression. Current studies have shown that vitamin D plays a significant role in the host immune defense against *Mycobacterium tuberculosis*, but clinical trials reported inconsistent results. In 2021, a systematic review and meta-analysis have concluded an association between low levels of vitamin D and tuberculosis infections in adults and children. However, this analysis showed considerable heterogeneity of included studies, and therefore, the findings should be applied with caution (Kafle et al., 2021).

VDD can predict the risk of tuberculosis in a dose-dependent manner and is more likely a risk factor for tuberculosis than its consequence. But unfortunately, the beneficial effect of vitamin D supplementation for treating *M. tuberculosis* infection in vitamin D-deficient patients is not still clear, and it seems that several factors such as genetic and the mode of administration, among others, may influence clinical outcomes. Intervention clinical trials have reported that vitamin D supplementation has no clinical benefits on tuberculosis therapy. However, it reduced the time to sputum culture conversion in patients with tt genotype of the TaqI vitamin D receptor gene polymorphism and improved the multidrug-resistant tuberculosis sputum culture conversion. Another meta-analysis has concluded that vitamin D administration together with *anti*-tuberculosis treatment may be well tolerated and effective, improving sputum smear conversion rate and chest radiological appearance, while exhibiting an inflammation resolution effect. In addition, meta-analyses of vitamin D supplementation in the prevention of tuberculosis and other acute respiratory conditions support the efficacy of daily low dose supplementation but not after intermittent bolus dosing. Indeed, the optimal dose to achieve benefits remains unclear; anyhow, it is suggested to continue studies since vitamin D has shown a synergistic benefit on the immune system. Therefore, long-term prospective cohort studies in tuberculosis endemic countries should be conducted to understand better the causal relationship between VDD and this disease as well as its possible therapeutical application.

1,25D3 upregulates human cathelicidin from monocytes/macrophages infected with *M. tuberculosis*, resulting in autophagy, and upregulates nitric oxide synthase, suppressing mycobacterial growth. A meta-analysis has revealed a significant difference in vitamin D and cathelicidin LL-37 blood levels among tuberculosis and healthy subjects. It seems that active pulmonary tuberculosis infection is associated with hypovitaminosis D and elevated blood cathelicidin concentrations. In contrast, in local tissue lesions, cathelicidin LL-37 expression was lower in tuberculosis than in healthy subjects. Therefore, the mechanism involved in vitamin D-mediated immune regulation against *M. tuberculosis* needs to be further investigated.

Vitamin D and virus infections

Virus infections have also been associated with VDD. Children with hand-foot-and-mouth disease have very low vitamin D levels, associated with a poor prognosis. Patients with atopic dermatitis are susceptible to microbial infection due to the decreased production of cathelicidin and other antimicrobial peptides, and they can be improved by vitamin D supplementation. In these cases, the participation of vitamin D in the regulation of the secretion of antimicrobial peptides is also altered. This occurs in cathelicidins (LL37) and defensins, molecules that through different mechanisms prevent the entry of viruses and their activity, by interacting with the viral coatings and limiting its replication directly or indirectly by modulating the immune cells, migration, activation, proliferation and differentiation, specifically neutrophils, monocytes-macrophages, and T lymphocytes. These antimicrobial peptides are also able to regulate autophagy and apoptosis of infected cells, thus contributing to the reduction of viral load. Indeed, vitamin D supplementation in healthy subjects appears to confer some protection against virus respiratory tract infection in healthy adults from the USA and Canada but not in other world regions. However, these conclusions cannot be generalized for all types of virus infections, and their potential effect must be demonstrated. For example, associations between vitamin D and herpesviruses remain inconclusive and further studies are needed in the general population.

Indeed, vitamin D-modulated immune response against viral infection is mediated by its VDR, which acts as a transcription factor modulating the expression of genes triggering the response against viruses. To date, six major VDR polymorphisms (*Cdx, A1012G, FokI, BsmI, ApaI,* and *TaqI*) have been studied in the context of viral infection susceptibility. Reported studies show controversial results, probably due to statistical lack of power and population genetic differences. In this sense, *FokI* polymorphism is a relevant variant capturing the association of VDR polymorphisms with viral infections.

Vitamin D and the human immunodeficiency virus infection

Human immunodeficiency virus (HIV) infection is a heavy burden worldwide. Observational studies have reported a high prevalence of VDD among people living with HIV compared with the general population. Low 25(OH)D is common in diverse HIV-infected populations and is an independent risk factor for clinical and virologic failure. It has been associated with increased HIV mortality, although it may also be influenced by other factors such as older age, lower body mass index, lower latitude, male sex and antiretroviral treatments.

The disagreement regarding the effect of antiretroviral therapy drugs on vitamin D metabolism is still unresolved. The Prospective Evaluation of Antiretrovirals in Resource Limited Settings (PEARLS) study (ACTG5175) is a large-scale, randomized controlled trial in diverse populations in many different settings from four continents. This study investigated whether simplified antiretroviral regimens (once daily) were as effective as standard twice-daily regimens, which may make it more suitable for low-income settings, and decrease adverse effects. It was observed that baseline VDD was associated with diminished CD4 recovery after combined antiretroviral therapy initiation, and that impaired CD4 recovery may contribute to the poor clinical outcomes observed in individuals with VDD (Ewald et al., 2019). Prospective studies assessing the potential benefit of vitamin D supplementation among HIV patients that initiate a combined antiretroviral therapy are lacking and therefore warranted, to demonstrate if vitamin D recommendation policies should be part of routine clinical practice.

Vitamin D and critically ill patients

It has been suggested that vitamin D insufficiency is a risk factor in intensive care and plays an essential role in infectious, immunologic, neurologic, cardiovascular, and respiratory complications. VDD has been hypothesized not only to be common but also to represent a potentially modifiable risk factor for greater illness severity and outcomes during critical illness. Observational studies have demonstrated an association between VDD and increased risk of morbidity and mortality in critically ill patients. Cohort studies and pilot trials have suggested promising beneficial effects of vitamin D replacement in critical illness, at least in patients with severe VDD. However, the results are inconclusive.

Vitamin D insufficiency is reported in up to 77% of critically ill patients. It is associated with increased mortality, length of stay in an intensive care unit (ICU) and hospital, as well as with respiratory disorders in prolonged ventilated patients (Langlois et al., 2018). In critically ill children, the status and the effect of VDD on the outcome are still unclear. In 2017, a systematic review and meta-analysis stated that approximately 50% of critically ill children have VDD (blood total 25(OH)D concentration under 50 nmol/L) at the time of pediatric ICU (PICU) admission. VDD was also associated with greater illness severity, multiple organ dysfunction, and mortality in the PICU setting. Another meta-analysis has confirmed that 25(OH)D deficiency is prevalent in critically ill children at PICU admission and seems to be associated with higher cardiovascular sequential organ failure assessment and pediatric risk of mortality III scores, sepsis, length of hospital stays, and duration of mechanical ventilation.

However, clinical trials are not consistent in confirming the beneficial effects of improving vitamin D status on patient outcomes. Studies are needed to determine if improving low 25OHD levels (to a level of about 30 ng/mL) is associated with reduced mortality and can improve the functional discharge status of ICU patients. Some studies have stated that vitamin D administration might be associated with reducing mortality without significant adverse events in critically ill patients. However, other studies concluded that vitamin D administration did not improve clinical outcomes and was not significantly associated with reduced mortality or with the length of ICU stay, although statistical imprecision could be explained by the sparse number of trials (Langlois et al., 2018). Therefore, the causal association between VDD and worse outcomes of the critically ill needs further investigations, and large multicenter randomized trials are necessary to conclusively establish the potential beneficial effect of vitamin D supplementation. Indeed, vitamin D supplementation does not provide additional advantages over placebo for critically ill patients and is not associated with reduced all-cause mortality in critically ill patients. Therefore, large-scale prospective studies are needed to validate these findings.

VDD has been related to the risk of sepsis. Different meta-analyses have evaluated the relationship between serum 25(OH)D at admission and mortality risk and concluded that severe VDD might be independently associated with increased mortality in septic adult patients and in septic children compared to those without sepsis. Even though a high prevalence of VDD was found in sepsis, it was not associated with greater severity of illness or other clinical outcomes.

A burn is a severe form of injury associated with severe altered pathophysiological immune-inflammatory responses. In addition, burn patients are a group of critically ill patients in which vitamin D skin synthesis is compromised. Therefore, burn patients suffer common complications that overlap with those reported by patients with VDD. Burn patients with low vitamin D are more susceptible to higher complication rates, including sepsis, pneumonia, cardiovascular complications, and graft loss. However, the literature regarding vitamin D status and its influence on clinical outcomes remains insufficient in this type of patient.

Sufficient vitamin D concentrations and vitamin D supplementation may be of benefit in burn-injured patients since this supplementation is the only means to avoid vitamin D insufficiency in burn victims. However, as in other critically ill situations, the adequate dose, formulation, and route of administration remain unknown, and there is limited data on the impact of vitamin D status on clinical outcomes. Indeed, the high incidence of low serum D25 levels 1 year after major burn injury indicates prolonged compromise of vitamin D metabolism. Therefore, continued treatment with vitamin D3 beyond the acute phase postburn is recommended to improve the abnormal blood levels and associated co-morbidities in adults and children.

Another critical situation that a vitamin D deficient state may impair is patients with traumatic injuries, in which inflammation is a consequence of the trauma. For example, traumatic brain injury is the most frequent trauma and a leading cause of injury-related death and disability, in which inflammation processes influence severity and mortality incidences. VDD may induce impaired immune responses and increase the risk of infections in these patients, and therefore, vitamin D intervention has been proposed as a good tool for preventing these complications. To date, there is no actual data on the effectiveness of vitamin D for the improvement of immune function in traumatic brain injury patients. 25(OH)D level measured within 24 h after admission to the trauma

ICU was unrelated to clinical outcomes. However, patients with increased 25(OH)D levels after 7 days of hospitalization had better clinical outcomes than those with decreased levels.

Since vitamin D supplements are inexpensive and safe, their use could potentially improve clinical outcomes in all critical ill situations by reducing inflammation and infection-associated morbidity and mortality rates. However, more clinical interventional trials are mandatory to ascertain its effectiveness and the appropriateness of its prescription.

Vitamin D and SARS-CoV-2 infection

Special mention should be made of the effects of vitamin D against SARS-CoV2 infection. Vitamin D inadequacy may be involved in the mechanisms of SARS-CoV-2 infection and in potential risk factors for disease propagation or control of coronavirus disease 2019 (COVID-19). Several studies have been performed, but the inconsistency of results, due to heterogeneity of studies design and patients, do not allow to establish final conclusions. A Cochrane systematic review has concluded that at this moment, we cannot know whether vitamin D helps prevent death from COVID-19. However, it may reduce the need for assisted ventilation, although the evidence is still uncertain. This effect is most notable in vitamin D-deficient COVID-19 subjects (Stroehlein et al., 2021).

The discussion is open regarding the relationship between blood levels of calcitriol and SARS-CoV-2 infection severity. Most of the COVID-19 patients suffered from VDD or insufficiency. In addition, there is about a three times higher chance of getting infected with SARS-CoV-2 among vitamin D-deficient subjects, and about five times higher probability of developing the severe disease associated with VDD. Another meta-analysis has found strong evidence of low blood D3 as a predictor rather than just a side effect of this infection. Other meta-analysis has associated VDD with the risk of SARS-CoV-2 infection and with the severity of the disease but did not find any association with mortality rates.

Lower vitamin D levels have been related to key altered clinical and biochemical parameters during SARS-CoV-2 infection. In this type of critical patients, a vitamin D deficit has been recognized at admission and further deterioration after three days of stay. Given the different responses of the 25OHD3 and 25OHD2 forms, it would be useful to monitor them on the evolution of these critically ill patients. A meta-analysis has stated that relations between VDD and ICU admission, pulmonary complications, hospitalization, and inflammation were inconsistent and insufficient since although studies were heterogeneous in methodological and statistical approach, most of them showed a significant relation between 25(OH)D and SARS-CoV-2 infection, COVID-19 composite severity, and mortality. Regarding infection, caution should be taken for the interpretation of the results, due to intrinsic study limitations. Although the current findings indicate a potential role of vitamin D in improving COVID-19 severity in hospitalized patients, no significant difference with vitamin D supplementation on major health-related outcomes in COVID-19 patients has been found, and more robust data from randomized controlled trials are needed to verify its effects on mortality.

As it occurs with tuberculosis and other conditions, it is hypothesized that the administration mode may influence the outcomes, i.e., low daily doses may be more useful than intermittent bolus, and there is an urgent need for well-designed and sufficiently powered randomized controlled trials to address this matter.

Conclusions

Vitamin D plays a key role in the regulation and maintenance of innate immunity. A poor vitamin D status is related to noncommunicable chronic diseases, namely obesity, metabolic syndrome, T2DM, cancer, RA, COPD, and IBD. Also, a low vitamin D status is associated with an increased incidence of acute respiratory illnesses of both bacterial and viral origin. Likewise, low 25(OH)D levels are associated with a worse prognosis of patients with acute illness. Well-designed randomized intervention clinical trials addressed to evaluate the efficacy of administration of vitamin D and its metabolites for the treatment of both chronic and acute diseases are needed.

References

Al Anouti, F., et al., 2020. Effects of vitamin D supplementation on lipid profile in adults with the metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. Nutrients 12 (11), 3352.

Charoenngam, N., 2021. Vitamin D and rheumatic diseases: a review of clinical evidence. Int. J. Mol. Sci. 22 (19), 10659.

Ewald, E.R., et al., 2019. Effect of baseline micronutrient and inflammation status on CD4 recovery post-cART initiation in the multinational PEARLS trial. Clin. Nutr. 38 (3), 1303–1309.

Ganmaa, D., et al., 2021. Vitamin D, respiratory infections, and chronic disease: review of meta-analyses and randomized clinical trials. J. Intern. Med. 291 (2).

Gil, Á., Plaza-Diaz, J., Mesa, M.D., 2018. Vitamin D: classic and novel actions. Ann. Nutr. Metab. 72 (2), 87–95.

Holick, M.F., et al., 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J. Clin. Endocrinol. Metab. 96 (7), 1911–1930.

Kafle, S., et al., 2021. Association of vitamin D deficiency with pulmonary tuberculosis: a systematic review and meta-analysis. Cureus 13 (9), E17883.

Langlois, P.L., et al., 2018. Vitamin D supplementation in the critically ill: a systematic review and meta-analysis. Clin. Nutr. 37 (4), 1238–1246.

Lokesh, K.S., et al., 2021. Vitamin D deficiency is associated with chronic obstructive pulmonary disease and exacerbation of COPD. Clin. Respir. J. 15 (4), 389–399.

Myint, A., Sauk, J.S., Limketkai, B.N., 2020. The role of vitamin D in inflammatory bowel disease: a guide for clinical practice. Expet Rev. Gastroenterol. Hepatol. 14 (7), 539–552.

Stroehlein, J.K., et al., 2021. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst. Rev. 5 (5), CD015043.

Further reading

Acen, E.L., et al., 2021. Impact of vitamin D status and cathelicidin antimicrobial peptide on adults with active pulmonary TB globally: a systematic review and meta-analysis. PLoS One 16 (16), E0252762.

Chang Villacreses, M.M., et al., 2021. Conundrum of vitamin D on glucose and fuel homeostasis. World J. Diabetes 12 (9), 1363–1385.

Griffin, G., et al., 2021. "Perspective: vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19". Clin. Med. 21 (2), E144–E149.

He, M., et al., 2021. Vitamin D deficiency relation to sepsis, paediatric risk of mortality III score, need for ventilation support, length of hospital stay, and duration of mechanical ventilation in critically ill children: a meta-analysis. Int. J. Clin. Pract. 75 (4), E13908.

Kazemi, A., et al., 2021. Association of vitamin D status with SARS-CoV-2 infection or COVID-19 severity: a systematic review and meta-analysis. Adv. Nutr. 12 (5), 1636–1658.

Kikut, J., et al., 2021. Diet supporting therapy for inflammatory bowel diseases. Eur. J. Nutr. 60 (5), 2275–2291.

Martineau, A.R., et al., 2019. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. Health Technol. Assess. 23 (2), 1–44.

Peng, L., et al., 2020. Association between Vitamin D supplementation and mortality in critically ill patients: a systematic review and meta-analysis of randomized clinical trials. PLoS One 15 (12), E0243768.

Verma, S., et al., 2021. Vitamin D deficiency: concern for rheumatoid arthritis and COVID-19? Mol. Cell. Biochem. 476 (12), 4351–4362.

Wang, Y., et al., 2021. Increased risk of vitamin D deficiency among HIV-infected individuals: a systematic review and meta-analysis. Front. Nutr. 8, 722032.

Zakhary, C.M., et al., 2021. Protective role of vitamin D therapy in diabetes mellitus type II. Cureus 13 (8), E17317.