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REVIEW ARTICLE

Immunomodulatory Effects of Vitamin D and Prevention of Respiratory Tract Infections and COVID-19

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Little is known about potential protective factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as COVID-19. Suboptimal vitamin D status is a risk factor for immune dysfunction, respiratory tract infections (RTIs), and viral infections. Supplementation of vitamin D (2000–4000 IU) has decreased incidence and complications from RTIs, respiratory distress syndrome, and pneumonia and may be beneficial in high-risk populations. Given the possible link between low vitamin D status and RTIs, such as COVID-19, this review examined whether vitamin D supplementation can be supported as a nutritional strategy for reducing risk of infection, complications, and mortality from COVID-19 and found that the relationship between vitamin D and RTIs warrants further exploration. **Key words:** *COVID-19*, *nutrients*, *respiratory tract infection*, *SARS-CoV-2*, *supplementation*, *vitamin D*

THE OUTBREAK of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections started a third major epidemic in 2020. Colloquially known as COVID-19, risk of infection and mortality is significantly higher among those older than 60 years, immunocompromised, and with comorbid conditions,[1-3] with most deaths caused by the resulting pneumonia.[1] Popular media articles about potential preventive, nutritional measures are abundant[4,5] with broad hypotheses about the role nutrition may play in immune function and COVID-19.[6,7] However, these hypotheses lack long-term follow-up and well-designed prospective studies.

In general, COVID-19 is associated with a hyperinflammatory state, involving increased production of pro-inflammatory cytokines[8] and C-reactive protein (CRP).[9,10] Infection typically coincides with increased risk of pneumonia, sepsis, and heart failure.[11,12] Respiratory tract infections (RTIs) have been the most common cause of COVID-19 complications, often resulting in severe respiratory distress syndrome and diffuse alveolar damage.[13,14] Case fatality rates from RTIs following COVID-19 infection are even further

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compounded for those with cardiovascular disease, chronic respiratory tract disease, diabetes, and hypertension.[3,12]

Most promising of nutritional strategies to boost immune function and prevent RTIs or viral infections has been vitamin D supplementation—a topic of high interest in new clinical case research and literature reviews.[6,7,15,16] Measured via serum concentration of 25-hydroxyvitamin D (25(OH)D), vitamin D status appears to not only be proportionately correlated with immune system function in laboratory studies, but may also play a protective role in prevention of acute RTIs.[17] A multitude of factors contribute to suboptimal vitamin D status that place certain populations at higher risk. These may include adults older than 60,[18-21] those with limited sun exposure,[22,23] populations with pigmented skin reducing ability to produce vitamin D from sunlight,[24,25] and/or those who suffer from obesity,[26,27] insulin resistance and/or type 2 diabetes,[28-31] autoimmune disorders,[32] and/or fat malabsorption.[33] Within this context, the aim of the present review is 3-fold: first, to explore the impact of vitamin D on the immune system; second, to identify suboptimal vitamin D status as a risk factor for viral and RTIs, and; third, to assess the potential of vitamin D supplementation as a nutritional strategy to prevent infection, complication, and mortality from COVID-19.

METHODOLOGY

An extensive review of the literature was performed using PubMed, Scopus, OVID MEDLINE, and Google Scholar databases. The following keywords were used: [vitamin D] and [25(OH)D] in combination with, [respiratory tract infections], [covid-19], [influenza], [viral infection], [immunomodulatory], and/or [immunoprotective]. There were no defined exclusion criteria and no exclusions based on publication date. References were exported and duplicates were removed. Relevant articles were identified through screening performed independently by 2 researchers and categorized into the specific aims of the literature review: (1) vitamin D status and its effects on the immune system, (2) vitamin D status as a risk factor for RTIs, including COVID-19, and (3) vitamin D supplementation as a preventive, nutritional strategy.

VITAMIN D STATUS

Metabolism and physiology

Vitamin D, while characterized as a vitamin, functions as a prohormone. Sources of vitamin D are diverse in nature, coming both from sun exposure and dietary sources. Cholecalciferol, or vitamin D_3, can be synthesized from ambient ultraviolet exposure and be obtained from dietary animal sources such as egg yolks and oily fish.[34,35] When the skin is exposed to the sun, 7-dehydrocholesterol provitamin D_3 is converted into pre-vitamin D_3 (pre-calcitriol), which then diffuses from the skin into circulation,[36,37] providing the primary source of vitamin D.[38] In contrast, ergocalciferol, or vitamin D_2, is derived only from plant sources by conversion of a plant sterol.[34,35] Regardless of source, vitamin D must be metabolized to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) to become fully active. The conversion of vitamins D_2 and D_3 is a 2-step process beginning in the liver, where vitamin D is converted to 25-hydroxyvitamin D (25(OH)D).[35,39] When necessary for calcium or phosphate regulation, 25(OH)D is converted to the active form of $1,25(OH)_2D$ (calcitriol) in the kidney.[40]

Current vitamin D recommendations

While definitions of and cutoffs for vitamin D deficiency, inadequacy, and insufficiency are not clear,[41] recommendations for vitamin D status are summarized in Table 1, with sufficient status ranging from 30 to 100 $ng \cdot mL^{-1}$ 25(OH)D and levels of 0 to 30 $ng \cdot mL^{-1}$ considered deficient or inadequate.[42-45] By these definitions and from previous reports, suboptimal vitamin D status is highly

Table 1. Current Recommendations for Vitamin D Status

	Endocrine Society[44]	Food and Nutrition Board[45]	National Institutes of Health[42]	Testing Laboratories[43]
Deficient	0–20 ng · mL^{-1}[a]	0–11 ng · mL^{-1}	0–29 ng · mL^{-1}	0–31 ng · mL^{-1}
Inadequate	21–29 ng · mL^{-1}	12–29 ng · mL^{-1}	30–49 ng · mL^{-1}	. . .
Sufficient	30–100 ng · mL^{-1}	30–100 ng · mL^{-1}	50–124 ng · mL^{-1}	32–100 ng · mL^{-1}
Toxic	. . .	. . .	>125 ng · mL^{-1}	. . .

[a]To convert ng · mL^{-1} to nmol · L^{-1}, multiply the ng · mL^{-1} by 2.5; for example, 50 ng · mL^{-1} is equivalent to 125 nmol · L^{-1}.

prevalent in populations across the world: greater than 40% in the general population and up to 76% in those older than 70 years.[46] Vitamin D deficiency in adults older than 60 years have been linked to increased severity of osteoporosis, resulting in greater risk for falls and bone fractures, reduced mobility, and therefore, decreased quality of life. Vitamin D deficiency also increases the risk of cardiovascular deaths, with potential to increase the risk for type 2 diabetes and certain common cancers, notably colorectal cancer.[18]

Deficiencies in vitamin D status can occur along 3 axes: limited sun exposure, reduced ability within the skin to produce vitamin D directly from sunlight, and/or fat malabsorption preventing concurrent absorption of vitamin D. First, serum 25(OH)D trends follow seasonality, with a summer peak and winter trough.[47] Additionally, limited sun exposure due to occupational, disability, or wardrobe reasons can result in inadequate vitamin D from the sunlight.[22,23] Second, individuals with larger quantities of melanin have darker skin, thus decreasing the ability of the skin to produce vitamin D from sunlight.[48] This results in commonly lower serum 25(OH)D levels reported in individuals identified as Black and/or Hispanic, compared with Caucasian or White.[49,50] Finally, vitamin D is a fat-soluble vitamin, so absorption of vitamin D may be inadequate among individuals with conditions resulting in fat malabsorption such as some forms of liver disease, kidney disease, cystic fibrosis, celiac disease, Crohn's disease, an ulcerative colitis.[33,51-54] People with lactose intolerance or those adhering to a vegan or raw diet may also suffer from inadequate vitamin D status, due to lower intakes of dairy products fortified with vitamin D.[55]

Immunomodulatory effects of endogenous vitamin D

Vitamin D is hypothesized to exert immunomodulatory benefits and reduce risk of viral infection and reduce inflammation following infection.[16,56] In general, vitamin D role in immune system function exists as a physical barrier, cellular natural immunity, and adaptive immunity, as grouped in recent reviews.[16,57] Table 2 summarizes the general immunomodulatory effect of serum vitamin D.[16,57] First, vitamin D forms a protective barrier by maintaining tight junctions, gap junctions, and adherens junctions, such that deficiencies in vitamin D leave these junctions structurally prone to disturbance and thereby significantly increasing risk of infection.[58] Second, vitamin D enhances antimicrobial peptides such as human cathelicidin (LL-37) and defensins[59] to enhance cellular immunity. Cathelicidins directly fight against a wide variety of microbes, including gram-positive and gram-negative bacteria, enveloped and nonenveloped viruses, and fungi.[60] In a mouse model, human cathelicidin LL-37 reduced influenza A virus replication[61] and reduced replication of rotavirus in vivo,[62] indicating that optimal vitamin D levels may be proactive in fighting infection. Finally, higher serum 25(OH)D also appears to enhance cellular immunity

Table 2. Immunomodulatory Effect of 25(OH)D

Immune Cell Types	25(OH)D-Induced Effect
Innate immune system	
Physical barrier	Maintenance of tight junctions, gap functions, and adherens junctions[16,118]
	Deficiencies leave these junctions structurally prone to disturbance
Gut microbiome	Reduces gut permeability[58]
	Reduces inflammation[58]
	Influences GM composition[58]
Antimicrobial peptides	Induces formation of antimicrobial peptides[59,119,120]
Adaptive immune system	
CD4+ T cells	Enhances development of Th2 cells
	Downregulated by increased 25(OH)D[121]
CD8+ T cells	Reductions in CD8+ T cells[122–124]
Inflammatory markers	
CRP	Suppresses C-reactive protein in patients with inflammatory bowel disease and other observational studies[9,10]
Th2 cells	Upregulates Th2 cells, which produce IL-17, implicated in the pathogenesis of several autoimmune diseases[125]
TNF-α	Decreases TNF-α in cardiovascular diseases, asthma, autoimmune disorders, sickle cell diseases[126]
IFN-γ	Suppresses pro-inflammatory IFN-γ[126]
IL	Suppresses pro-inflammatory IL-2, IL-6, and IL-17[63,127]
	Increases anti-inflammatory IL-4 and IL-10[63,127]

Abbreviations: CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CRP, C-reactive protein; GM, gut microbiome; IFN-γ, interferon gamma; IL, interleukins; IL-6, interleukin-6; Th2, T-helper type 2; TNF-α, tumor necrosis factor alpha.

via reduction of the cytokine storm induced by the innate immune system during infection.[56,63] Cytokine storms are immune responses that release large amounts of cytokines into the bloodstream disproportional to the viral infection. This disproportional release of cytokines begins to attack healthy tissues, which can lead to liver, blood vessel, kidney, or lung damage. The effect vitamin D levels have on inflammatory markers generated during the cytokine storm is displayed in Table 2.

Pro-inflammatory and anti-inflammatory cytokines are produced via the innate immune system in response to infection.[64] As vitamin D binds to the receptors located on B cells, T cells, macrophages, and dendritic cells, immune responses are activated through upregulation of cathelicidins and defensins peptides.[59,65,66] Cathelicidins and defensins are known for their antiviral effects, which reduce viral replication and decrease the production of pro-inflammatory cytokines.[59] Through this mechanism, vitamin D has been shown to also reduce cytokine storms, which are linked to increased morbidity and mortality in those with RTIs including COVID-19.[67,68]

Proper vitamin D levels can reduce cytokine storms in RTIs and COVID-19 by reducing T-helper (Th) cells inflammatory cytokine production and ultimately resulting in a decrease in tumor necrosis factor-α and interferon-γ.[56,69] In addition to reducing the cytokine storm, vitamin D may increase the expression of anti-inflammatory cytokines, as previously reported in patients with sepsis, asthma, and diabetes mellitus.[70] Higher 25(OH)D is also associated with decreased risk of pneumonia and other RTIs, while

those with vitamin D deficiencies are at a significantly higher risk.[71,72]

VITAMIN D AS A POTENTIAL RISK FACTOR FOR COVID-19

Vitamin D has been hypothesized, as early as March 2020 by Davies et al,[73] to have a contributory part in global COVID-19 outcomes.[73] Since then, multiple retrospective, prospective, randomized controlled trials (RCTs), and case control studies have examined potential relationships between 25(OH)D levels and COVID-19 and have been recently reviewed by Dissanayake and colleagues.[15,74-77] These studies indicate that vitamin D deficiency or insufficiency leads to a greater likelihood of developing COVID-19, increased susceptibility for severe symptoms, and may be related to higher risk of death.[74] This recent evidence suggests vitamin D levels may be a modifiable factor related to the development and severity of the disease.

A database analyzed by Katz et al[78] of cross-sectional patient studies examining the association between vitamin D deficiency and COVID-19 indicated those with vitamin D deficiency were 4.6 times more likely to develop COVID-19 than those who were vitamin D sufficient.[78] A study by Daneshkhah et al[75] analyzed vitamin D data from 10 countries, with CRP and the attendant cytokine storm as primary outcomes. C-reactive protein was found to be inversely proportional to vitamin D levels, implying that patients with deficient vitamin D levels who contracted COVID-19 would be more likely to be affected by unmitigated hyperinflammation and, therefore, experience higher mortality rates.[75] Similarly, Gavioli et al[79] evaluated serum vitamin D levels taken within 3 months of a positive COVID-19 test of 437 COVID-19 patients who were vitamin D deficient (<20 ng $\cdot$ mL^{-1}, n = 177) or vitamin D sufficient (≥ 20 ng $\cdot$ mL^{-1}, n = 260). Low vitamin D levels were associated with the need of oxygen support, and levels less than 10 ng $\cdot$ mL^{-1} were associated with higher hospitalization rates and mortality rates along with a greater need for oxygen support.[79]

A recent study by Meltzer et al[76] assessed 499 patients with vitamin D levels drawn in the last year and had a recent COVID-19 test. Rates of COVID-19 in the vitamin D-deficient group were 21.6% compared with 12.2% in the vitamin D-sufficient group—a significant difference persisting even after adjusting for age and ethnicity.[76] Given these findings, proper vitamin D levels may reduce incidence, severity, and case fatality of COVID-19. Carpagnano et al[77] analyzed retrospective data on patients (n = 42) with acute respiratory failure due to COVID-19, determining that 81% of the patients had low vitamin D levels.[77] Additionally, a survival analysis demonstrated that 20% of cases with severely deficient vitamin D levels (<10 ng $\cdot$ mL^{-1}) resulted in death and 20% transferred to the ICU, versus 3.1% and 12.5%, respectively, in patients with vitamin D greater than 10 ng $\cdot$ mL^{-1}.[77] In a small, clinical case intervention, 4 patients with confirmed COVID-19 diagnosis were provided either a standard dose of cholecalciferol (1000 IU daily) or a high dose of ergocalciferol (50 000 IU daily for 5 days). Those who received the high dose reached normal vitamin D levels and showed signs of improved recovery including shorter length of stay, lower oxygen requirements, and a reduction in inflammatory status marker (IL-6, CRP).[15]

The results of these studies are hypothesis-generating and warrant aggressive pursuit and study. The COVID-19 pandemic has affected older individuals with underlying cardiovascular comorbidities. Besides adult respiratory distress syndrome and acute kidney injury, cardiovascular complications also represent a common consequence of the disease-causing adverse outcomes in these patients. During the COVID-19 pandemic, high incidence of fatalities in older patients occurs. This may be due to the parallel increase in frailty and cardiovascular disease with age, caused by endothelial dysfunction and loss of endogenous cardioprotective mechanisms.[21,80]

The remainder of this review will assess the role of vitamin D in disease processes parallel to those of COVID-19—namely, immune dysfunction, acute RTIs, respiratory distress syndrome, cytokine storm syndrome, and other viral infections.

Autoimmune disorders and immune dysfunction

Some epidemiologic data link inadequate vitamin D status with higher prevalence of autoimmune disorders, such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease.[32] In addition to these correlational relationships, others have implicated vitamin D in the direct control of other inflammatory conditions, such as cardiovascular diseases, cystic fibrosis, and multiple sclerosis.[81-84] For patients with coronary artery disease, for example, low 25(OH)D3 levels significantly correlated with increased activation of inflammatory pathways in epicardial adipose tissue.[83] A study including 16 patients with cystic fibrosis found daily vitamin D supplementation significantly decreased immune activation, and therefore hyperinflammation, in a dose-dependent manner.[81] These studies further confirm a critical role for vitamin D in the modulation of immune system function, by way of decreasing inflammatory status and preventing progression of disease-specific alterations.

Respiratory distress syndrome and respiratory tract infections

Vitamin D is associated with lung maturation and prevention of respiratory distress syndrome, via production and maintenance of surfactant cells.[85] A study of 150 preterm newborns found 25(OH)D deficiency to be an independent risk factor for respiratory distress syndrome, such that high levels of vitamin D reduced the risk of respiratory distress syndrome 3.34 times.[86] Furthermore, in vitro studies showed vitamin D deficiency to directly contribute to inflammation in epithelial cells—a compounding set of risk factors especially in patients at high risk for RTIs.[58]

Given the effect of low vitamin D status on lung maturation, lubrication, and inflammatory responses, its role in RTIs is ostensible. To date, several systematic reviews cite inadequate vitamin D status as a general risk factor for RTIs,[16,56,71] wherein higher serum vitamin D is associated with decreased risk of pneumonia and other RTIs, while those with vitamin D deficiencies are at a significantly higher risk of infection. This risk increases to 20% to 22% among aging patients and/or others with comorbid conditions.[71] Furthermore, a systematic review by Pham et al[17] highlighted the linearity of this inverse relationship. For every 10 nmol $\cdot$ L^{-1} reduction in serum vitamin D concentration, there was a 2% increased risk of acute RTIs. This detriment was most prominent in those with serum concentrations below 37.5 nmol $\cdot$ L^{-1}, suggesting that those most deficient in vitamin D would be most likely to benefit from regular supplementation.[17]

Hyperinflammation and cytokine storm syndrome

In addition to respiratory distress syndrome, the most severe cases of COVID-19 are characterized by a hypoxemic, pro-inflammatory state, and accompanying cytokine storm syndrome—likely mediated by a dysregulated immune response following infection.[12,67] Several studies connect vitamin D deficiency to the advancement of cytokine storm syndrome[87,88] and, thus, have explored its combined impact on COVID-19 incidence, complications, and mortality. Given the anti-inflammatory properties of vitamin D, adequate vitamin D status may not only decrease the likelihood of COVID-19 infection but also directly mitigate its symptoms and prevent mortality.

Viral infection

Another overlapping area of exploration is vitamin D status and other viral infections, including influenza, dengue, hepatitis C, HIV-1, H9N2 influenza, human respiratory syncytial virus, rotavirus diarrhea, and herpes virus.[16]

In particular, the relationship between vitamin D and influenza is of great interest due to the damage placed on the immune system during infection. As such, multiple ecologic and epidemiologic studies suggest correlations between low vitamin D levels and infection.[89-91] For example, one theory is that the spike in influenza during the winter months may be related to the low solar ultraviolet-B (UVB) presence during this season in countries of mid to high latitude.[90] As UVB doses decreased, a great proportion of the population was likely at risk for vitamin D deficiency and, therefore, more susceptible to influenza infection.

These trends were most systematically observed during the 1918-1919 influenza pandemic in the United States. Following the pandemic, the United States Public Health Service collected surveys of 12 communities across the country to establish incidence and case fatality rates and discovered geographical trends associated with the case fatality rates: communities in the southwest had lower case fatality than those in the northeast, presumably due to associations between higher UVB doses and higher vitamin D concentrations.[91,92] Furthermore, groups at high risk for influenza complications included many of whom were also at increased risk of vitamin D deficiency: those older than 60 years, immunocompromised, and with significant comorbidities.[92]

Similar observations in case fatality rate, temporal, and geographic trends have been found with COVID-19: increasing incidence mortality with increasing latitude, a winter peak in infection, and high case fatality rates among the elderly, immunocompromised, or those with comorbid conditions.[47,93,94] Even further, several observational studies have reported a disproportionate infection and mortality rate in men—a group also at significantly increased risk for vitamin D deficiency.[95,96] Given these trends, further exploration of vitamin D and COVID-19 infection, complication, and mortality is warranted.

Advanced age and comorbidities

Finally, COVID-19 is well-known to disproportionately affect older populations and those with metabolic comorbidities.[12,96] One possible reason for the stepwise increase in COVID-19 case fatality rate with increasing age is the parallel increase in chronic diseases and comorbidities. However, advanced age is also associated with other risk factors consistent with vitamin D status. Vitamin D deficiency is common in older adults due to less sunlight exposure, lower intake of vitamin D-rich foods, and a diminished ability for the skin to produce vitamin D.[97]

Inadequate vitamin D status significantly increases incidence and severity of several comorbidities such diabetes mellitus, cardiovascular disease, and other chronic conditions.[98] Furthermore, those with low vitamin D are also at an increased risk of immune system deregulation, which increases in likelihood with age.[56] As previously mentioned, the active metabolite of vitamin D, calcitriol (or 1,25-dihydroxyvitamin D) is required for immune system regulation. However, serum calcitriol concentrations are inversely related to parathyroid hormone concentrations and parathyroid hormone increase with age, leaving patients older than 60 years at significantly increased risk of vitamin D deficiency.[34] Along with increased inflammatory cytokines in aging and vitamin D-deficient populations, these trends may at least partially account for the observed age-related trends in COVID-19.

Vitamin D is also essential to skeletal muscle metabolism and has been hypothesized to help maintain muscle strength and function.[99] The increased risk of vitamin D deficiency in older populations may correspond with an increased risk of developing sarcopenia, the age-related loss of muscle mass, strength, and function.[100,101] While not confirmative, studies in older adults have reported associations between low vitamin D levels and muscle mass and physical performance in elderly populations.[102,103] There have been contradictory results[104]; however,

it is possible that vitamin D plays a role in maintaining muscle mass, strength, and function, which may influence the development of comorbidities and immune dysfunction related to sarcopenia.

VITAMIN D SUPPLEMENTATION AS A PREVENTIVE, NUTRITIONAL STRATEGY

Should vitamin D inadequacy and/or deficiency have a role in increasing incidence, complication, and mortality from COVID-19, supplementation may prevent or mitigate these effects. Supplementation in the form of vitamin D_3 has been found to be more effective in increasing the levels of serum 25(OH)D than supplementing with vitamin D_2,[34] and has frequently been the supplement of choice in intervention studies. Numerous randomized, placebo-controlled trials have assessed the benefit of daily, weekly, or bolus vitamin D_3 supplementation, with the majority recommending a daily supplement regimen ranging from 2000 to 4000 IU to achieve serum levels of over 30 ng $\cdot$ mL^{-1}.[71,72] However, it is important to note that these recommendations are within the context of vitamin D and bone health—dosing and serum levels for immune system maximization have not been previously established.

Vitamin D supplementation has been widely explored in prevention of RTIs, pneumonia, and treatment of other pulmonary diseases sharing similar pro-inflammatory states among those infected with COVID-19. Although individual study results vary, many of these have been the subject of critical review and meta-analysis.

Vuichard Gysin et al[105] evaluated 15 RCTs (753 participants) to examine the protective effect of vitamin D_3 supplementation on new RTIs in healthy individuals.[105] In these studies, vitamin D_3 varied from daily doses ranging from 2.5 to 50 μg (300–2000 IU) to much larger but less frequent weekly or monthly high dosing ranging from 0.25 to 5.0 mg (10 000–200 000 IU). Overall, supplementation was safe, but there was no significant risk reduction with vitamin D_3 supplementation on clinical RTIs in the total sample nor in subgroup analysis of participants who had less than 25 nmol $\cdot$ L^{-1} vitamin D status at baseline.[105] In a much larger and robust analysis using individual participant data, Martineau et al[71] evaluated 25 RCT with 11 321 healthy participants or those under medical care for preexisting pulmonary conditions or immune dysfunction with increased susceptibility to infections. In these studies, vitamin D_3 varied from daily supplementation ranging from 7.5 to 50 μg (300–2000 IU) or less frequent high dosing ranging from 0.75 to 5 mg (3000–200 000 IU) at weekly or monthly intervals.[71,105] Vitamin D supplementation reduced the number of participants obtaining at least one acute RTI.[71] Additionally, benefits of vitamin D supplementation were greater in those with lower baseline vitamin D levels and in those receiving regular vitamin D_3 doses compared with higher bolus doses.[71]

When specifically examining outcomes of COVID-19 after treatment with vitamin D_3, there were mixed results. Supplementation with 60 000 IU daily for 7 days resulted in quicker negativity and lower fibrinogen levels compared with a placebo, but there were no differences in any other inflammatory markers.[106] However, Murai et al[107] found no difference in length of hospital stay, mortality, or ventilation needs after a bolus dose of 200 000 IU compared with a placebo.[107]

In patients with inflammatory pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD),[108,109] vitamin D_3 supplementation on acute complications and disease exacerbation has been reported. In a meta-analysis of 7 RCTs of 955 patients with asthma,[108] vitamin D_3 supplementation significantly reduced the rate of complications requiring treatment with systemic corticosteroids (adjusted incidence ratio 0.74, 95% confidence interval 0.56–0.97).[108] In a meta-analysis of 4 RCTs of 560 patients with COPD,[109] pulmonary complications were reduced in those supplementing

with vitamin D_3, but the benefits were significant only in those having low serum values (<25 nmol · L^{-1}). In both reviews, improvements in complications or exacerbations were observed in those receiving higher, less frequent bolus doses but not smaller daily dosages.[108,109]

Similarly, Han et al[110] reported that high-dose (250 000 of 500 000 IU) vitamin D_3 significantly reduced the average length of stay in ventilated intensive care patients. Length of stay decreased from 36 to 25 days in the group provided 250 000 IUs [25(OH)D average 45 ± 20 ng · mL^{-1}] and to 18 days in the group provided 500 000 IU [25(OH)D average 55 ± 14 ng · mL^{-1}].[110] In a follow-up trial, those in the 500 000-IU supplementation group also had significantly increased hemoglobin concentrations, lowered hepcidin concentrations, and improved iron metabolism—all of which contributed to decreased inflammation and improved immune system response.[111]

FUTURE DIRECTIONS

The data reviewed herein support the relationship between adequate vitamin D status to reduce the risk and complications of RTIs and pulmonary diseases including COVID-19 infection. However, many questions still remain for the general population, for those at high disease risk, and for those with active disease, for which well-designed RCTs are needed. For example, the meta-analyses suggest that serum levels more than 25 nmol · L^{-1} may be protective for the general population, which may be achieved by daily intake of recommended levels (Table 3), but higher supplementation bolus doses (0.25–5 mg) may be needed for those with active disease. Furthermore, type of supplementation may be important to consider, as vitamin D_3 has been thought to be more effective than vitamin D_2 supplementation, possibly due to slight differences in the conversion process.[34] Additionally, many other micronutrients are critical for immune system support and suboptimal levels of these may also coexist with low vitamin D status, especially in vulnerable populations.[112] Of interest, emerging data suggest inadequate magnesium status may be a precursor, as magnesium is required to metabolize vitamin D.[16] Thus, we caution against the conclusion that simple vitamin D supplementation may be an independent protector against COVID-19 infection. Rather, it is plausible that a combination of nutritive strategies will be critical to maintain good immune system function and health status that is preventive of infection, complication, and mortality. Clinicians can take a role in encouraging adequate levels of vitamin D, along with improvement of multiple lifestyle habits. As such,

Table 3. Recommendations for Optimum Vitamin D Level and Supplementation[a]

Life Stage	Daily Dietary Recommendation	Upper Supplementation Limit
0–6 mo	400 IU[b] (10 μg)	1000 IU (25 μg)
7–12 mo	400 IU (10 μg)	1500 IU (38 μg)
1–3 y	600 IU (15 μg)	2500 IU (63 μg)
4–8 y	600 IU (15 μg)	3000 IU (75 μg)
9–18 y	600 IU (15 μg)	4000 IU (100 μg)
19–70 y	600 IU (15 μg)	4000 IU (100 μg)
≥70+ y	800 IU (20 μg)	4000 IU (100 μg)

[a]Reproduced and adapted from *Dietary Reference Intakes for Calcium and Vitamin D*[45] with permission from The National Academies Press.

[b]1 IU is the biological equivalent of 0.025 μg cholecalciferol.

careful consideration of the current evidence, as well as individual assessment must be performed by clinicians before immediate prescription of vitamin D supplementation.

Finally, in addition to addressing inadequacies in vitamin D (and other micronutrients) during the COVID-19 pandemic, we must assume benefits should be additive to other public health recommendations for disease control made by the Centers for Disease Control and Prevention and the National Institutes of Health on hand washing, mask wearing, social distancing guidelines, and established therapeutic treatments. There are a small number of clinical case trials emerging and several clinical trials currently registered to prospectively explore vitamin D supplementation in the prevention of COVID-19 complication and mortality, most in combination with current preventive and/or therapeutic regimens, with results pending.[113-117]

CONCLUSIONS

Vitamin D has a clear immunomodulatory role, such that suboptimal vitamin D status is a significant risk factor for incidence, complication, and mortality due to RTIs, respiratory distress syndrome, deregulated immune response, and other COVID-19-related complications. Finally, current studies on the effect of vitamin D on inflammation, immune system, and RTIs are hypothesis-generating and warrant further exploration. Within the context of the COVID-19 pandemic, vitamin D supplementation for its prevention should be pursued via well-designed randomized trials.

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