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# Physiological Mini-Reviews

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# A RATIONAL APPROACH BETWEEN VITAMIN D, IMMUNOMODULATION AND THE RENIN-ANGIOTENSIN SYSTEM LINKED TO PREVENTION AND TREATMENT OF SEVERE ACUTE RESPIRATORY SYNDROME BY COVID-19

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## ABSTRACT

A distinctive feature of COVID-19 is its low mortality rate, where the leading cause of decease is related to the development of severe acute respiratory syndrome (SARS). This syndrome involves an exacerbated inflammatory reaction, frequently known as cytokine storm, mainly in the lungs and concomitant over activation of the renin-angiotensin-aldosterone system (RAAS). Consequently, this "explosive cocktail" can lead to death or permanent respiratory sequelae in patients infected with SARS-CoV-2. In this sense, multiple therapeutic strategies have been proposed. Among them, vitamin D stands out as it exerts numerous immunomodulatory effects by acting on various types of immune and epithelial cells, in addition to being able to stimulate the protective arm [(ACE2/Ang- (1-7))] and inhibit the damaging arm (ACE/Ang-II) of the RAAS. Therefore, in the present mini-review, some of the main mechanisms underlying these effects mediated by vitamin D and its receptors are analyzed. Knowledge and translational projection of these mechanisms would positively influence the prevention and treatment of SARS. Thus, current evidence on vitamin D and COVID-19 adds arguments to rational therapy regarding reducing or avoiding disease progression and improving prognosis.

**Keywords:** Vitamin D; 1,25(OH)2D; COVID-19; SARS-CoV-2; severe acute respiratory syndrome

## RESUMEN

Una característica distintiva de COVID-19 es su baja tasa de mortalidad, donde la principal causa de muerte está relacionada con el desarrollo del síndrome respiratorio agudo severo (SRAS). Este síndrome involucra una reacción inflamatoria exacerbada, frecuentemente conocida como tormenta de citoquinas, principalmente en los pulmones y sobre-activación concomitante del sistema renina-angiotensina-aldosterona (SRAA). En consecuencia, este "cóctel explosivo" puede provocar la muerte o secuelas respiratorias permanentes en pacientes infectados con SARS-CoV-2. En este sentido, se han propuesto múltiples estrategias terapéuticas. Entre ellas, destaca la vitamina D que ejerce numerosos efectos inmunomoduladores al actuar sobre diversos tipos de células inmunes y epiteliales, además de poder estimular el brazo protector [(ACE2/Ang-(1-7))] e inhibir el brazo dañino (ACE/Ang-II) del SRAA. Por ello, en la presente mini-revisión se analizan algunos de los principales mecanismos subyacentes a estos efectos mediados por la vitamina D y sus receptores. El conocimiento y proyección traslacional de estos mecanismos influiría positivamente en la prevención y tratamiento del SRAS. Por lo tanto, la evidencia actual sobre la vitamina D y COVID-19 suma argumentos a la terapia racional con respecto a reducir o evitar la progresión de la enfermedad y mejorar el pronóstico.

**Palabras clave:** Vitamina D; 1,25(OH)2D; COVID-19; SARS-CoV-2; síndrome respiratorio agudo severo

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## Introduction

The progress and strictness of the severe acute respiratory syndrome (SARS) observed in patients with coronavirus disease 2019 (COVID-19) is a potentially fatal condition and, at the same time, a determining factor in the prognosis of its pathology [1]. In this sense, Quesada-Gómez and colleagues informed that around 20% of hospitalized patients [both in the intensive care unit (ICU) and not admitted to the ICU] with COVID-19 developed acute respiratory distress syndrome (ARDS) and, despite recent improvements in the strategies of mechanical ventilation and supportive care, around 65% of patients with ARDS died [2].

ARDS is a central component of the pathophysiology of COVID-19, whereby patients with severe disease develop multi-organ dysfunction. The onset of ARDS is frequently rapid and progressive, developing approximately nine days after the onset of severe SARS-CoV-2 [3] infection. The disease has been challenging to manage in terms of morbidity and mortality, high costs and long periods of hospitalization in intensive care. Therefore, early treatment result essential to control the progression of the infection and improve the prognosis of patients with ARDS [4,5].

ARDS develops as a consequence of an exaggerated or uncontrolled inflammatory response known as a “cytokine storm”, resulting from the release of large concentrations of these proteins (IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF- $\beta$ , CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) pro-inflammatory by immune effector cells during SARS-CoV-2 [6] infection. Furthermore, the activation and excessive recruitment of neutrophils into the alveolar interstitium with disruption of the endothelial-epithelial barrier and the consequent alveolar damage exacerbates the pathogenesis of ARDS [7]. Of particular interest, the data obtained to date from patients infected with SARS-CoV-2 confirmed that those who required admission to the ICU had higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNF- $\alpha$  than those that did not require it, which reaffirms the fact that the intensity of the cytokine storm is usually associated with the severity of the disease [8].

Currently, multiple therapeutic behaviors are used -some empirically based and others based on limited evidence- with varying efficiencies for ARDS management, mainly associated with supportive care such as mechanical ventilation and hemodynamic management [9].

Of particular interest, it is known that vitamin D (Vit D) and its receptors (VDR) are present in all living beings that are part of the animal kingdom, playing a fundamental role in the maintenance of bone health and phospho-calcium metabolism. However, the fact that Vit D precursors have also been found in invertebrate organisms such as krill and phytoplankton [10] highlights their importance in regulating numerous additional physiological and homeostatic processes, such as controlling inflammation and oxidative stress [11,12]. Therefore, Vit D could play a leading role in the prevention and treatment of oxidative and inflammatory diseases such as COVID-19 by attenuating several of the underlying mechanisms involved in the pathophysiology of this viral infection.

Vit D deficiency is associated with an increased risk of respiratory infection [13-16]. Likewise, a recent meta-analysis involving around 10,000 individuals from 25 health centers concluded that Vit D supplementation reduced the risk of upper respiratory tract infections by approximately 19%, with patients being severely deficient in Vit D who experienced the greatest benefit [17]. Additionally, Vit D has demonstrated, in *in vitro* models, its ability to inhibit the production and release of cytokines (IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, IL-33, and TNF- $\alpha$ ) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10) involved in the development and progression of ARDS [18].

Indeed, it has been reported that Vit D and VDR signaling may provide some beneficial effects in ARDS through multiple mechanisms, including attenuation of the cytokine and chemokine storm [19], regulation of the renin-angiotensin-aldosterone system (RAAS) [20] and the maintenance of the integrity of the pulmonary epithelial barrier [21], among other aspects, which will be addressed in this min-review.

## Potential therapeutic actions during COVID-19 disease linked to vitamin D and immune-modulation

Unprecedented historical evidence was described more than a century and a half ago. Specifically, in 1849, Dr. Williams reported that in a study of tuberculosis patients, the majority of them showed a "marked and unequivocal improvement" after treatment with cod liver oil (rich in Vit D)[22]. Since then, various Vit D functions related to the regulation of numerous cellular processes have been investigated, concluding that its deficiency is potentially involved in the development of multiple diseases [23].

Additionally, since the discovery of the presence of VDR in a wide variety of cells of the immune system, countless studies on the immunomodulatory effect of VDR, that is, its ability to stimulate (e.g. to accelerate the elimination of a pathogen) or inhibit (e.g. to attenuate uncontrolled inflammation) the immune response according to specific circumstances. In detail, these studies revealed that Vit D would modulate the activity of various immune cells, including monocytes, macrophages, lymphocytes and epithelial cells [24].

In the case of macrophages, it has been observed that low serum concentrations of Vit D in patients with rickets correlate with a decrease in their phagocytic activity, which could be reversed by supplementation with 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-(OH)<sub>2</sub>D<sub>3</sub>), or also called calcitriol, the active form of Vit D [25]. For its part, it has been reported that the antimicrobial activity of macrophages increases in the presence of 25-hydroxyvitamin D<sub>3</sub> (25-(OH)D<sub>3</sub>) after stimulation with antigen ligands. This is because the activation of different macrophage receptors (TLR-2, TLR-4, among others) by foreign agents leads to an increased expression of VDR and of the CYP27B enzyme, which increases both the conversion of 25-(OH)D<sub>3</sub> into its active form 1,25-(OH)<sub>2</sub>D<sub>3</sub> mediated by the CYP27B enzyme, as well as from the expression of antimicrobial peptides such as cathelicidin and  $\beta$ 2-defensin through VDR [26, 27]. Both peptides contribute to hosting defenses by stimulating the expression of antiviral cytokines and chemokines involved in the recruitment of monocytes/macrophages, neutrophils and T lymphocytes, among other immune cells [28]. Another mechanism by which Vit D can promote innate immune function through antimicrobial peptides is closely linked to improving phagocytosis through the induction of autophagy [29]. SARS-CoV-2 uses blocking autophagy to accelerate its replication and infectivity.

By achieving this, the virus induces the expression of the Skp2 protein, which plays a central role in the viral replication mechanism during COVID-19 disease and, in turn, inactivates Beclin 1, a component of the autophagic process [30, 31].

In parallel, 1,25-(OH)<sub>2</sub>D<sub>3</sub> also stimulates the production of Klotho, known to attenuate multi-organ aging and increase longevity, which also promotes autophagy through the maintenance of adequate cellular levels of Beclin 1 [32].

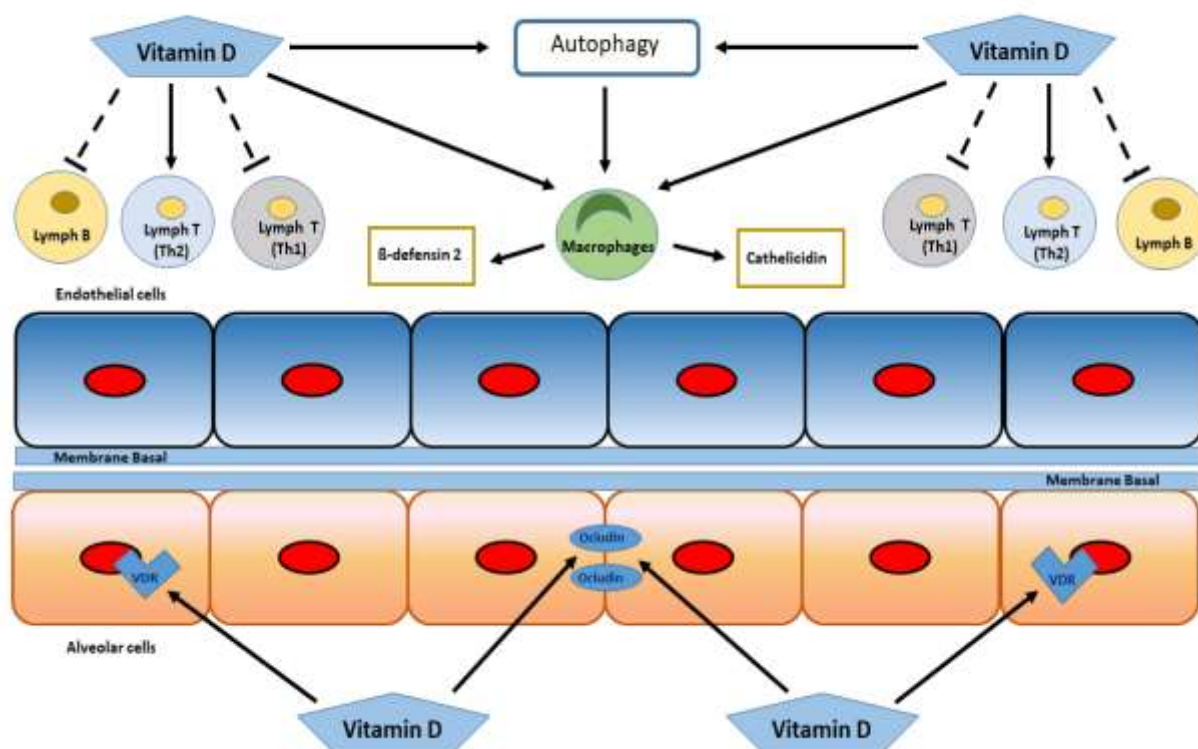
Concerning B lymphocytes, 1,25-(OH)<sub>2</sub>D<sub>3</sub> has been shown to play an important role in the homeostasis of these cells through the inhibition of proliferation and the induction of apoptosis in activated B cells. Likewise, 1,25-(OH)<sub>2</sub>D<sub>3</sub> inhibits the differentiation of B lymphocytes to plasma cells and memory B cells. These mechanisms can prevent or attenuate the pathogenesis of diseases involving B lymphocytes [33].

About T lymphocytes, the biologically active 1,25-(OH)<sub>2</sub>D<sub>3</sub> is capable of modifying the immune response, shifting it from a T helper 1 (pro-inflammatory) profile to a T helper 2 (anti-inflammatory) profile. Additionally, 1,25-(OH)<sub>2</sub>D<sub>3</sub> directly affects the differentiation of regulatory T cells and modulates the functions of dendritic cells [34].

As for the respiratory epithelium cells, they express enzymes capable of converting the precursor 25-(OH)D<sub>3</sub> into its active form 1,25-(OH)<sub>2</sub>D<sub>3</sub>. Therefore, these cells constitute an important source of 1,25-(OH)<sub>2</sub>D<sub>3</sub> that induces the expression of cathelicidin and CD14 by cells of the immune system [35]. Furthermore, type II cuboidal alveolar cells of the lung also express VDR to a large extent. Thus, VDR overexpression exerts a pulmonary anti-inflammatory effect [36,37]. VDR knockout mice experienced more severe acute lung injury than wild-type mice after being treated with lipopolysaccharides (LPS) [38].

Calcitriol/VDR signaling can also protect against acute lung injury by modulating genes that regulate the expression of occludin, a protein responsible for the maintenance of alveolar epithelial tight junctions, avoiding the increased permeability of the epithelial-alveolar barrier stimulated by the inflammatory answer. Therefore, 1,25(OH) 2D is essential to maintain the structure and function of the epithelial barriers of the lung, among other tissues [21].

In this sense, the mechanisms described could represent potential immunomodulatory pathways against the SARS-CoV-2 virus induced by Vit D, outlined in Figure 1.



**Figure 1.** Potential immuno-modulating mechanisms of vitamin D at the endothelial-alveolar barrier level against infection by the SARS-CoV-2 virus. Solid arrows indicate "stimulation", and broken arrows indicate "inhibition."

### Renin angiotensin system linked to COVID-19 pathogenesis and its relationship with the protective role of vitamin D

It has been extensively shown that local or systemic inflammatory responses can activate RAAS. Likewise, the hyper-activation of RAAS induced by SARS-CoV-2 together with the consequent decrease in angiotensin-converting enzyme 2 (ACE2), have been implicated in the pathogenesis of ARDS by COVID-19 [39]. Thus, angiotensin II (Ang-II) generated by angiotensin converting enzyme 1 (ACE) is capable of inducing lung injury, while ACE2 counter-regulates the effects produced by Ang-II by converting Ang II into Ang-(1-7), which in turn activates the Mas receptor to repress the STAT3 signaling pathways and extracellular signal-regulated kinases (ERK), acting as an anti-inflammatory factor. Therefore, the alteration of the balance between the levels of the enzymes ACE and ACE2, affect the endogenous relationship of Ang-II/Ang-(1-7), with elevation of Ang-II, this being a key factor for the development of ARDS in animal and human models [40].

Additionally, it is important to note that SARS-CoV-2 does not enter cells through coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase 4, but rather through the ACE2 [39,40] receptor. In this sense, approximately 83% of the cells that express the ACE2 receptor are a type II

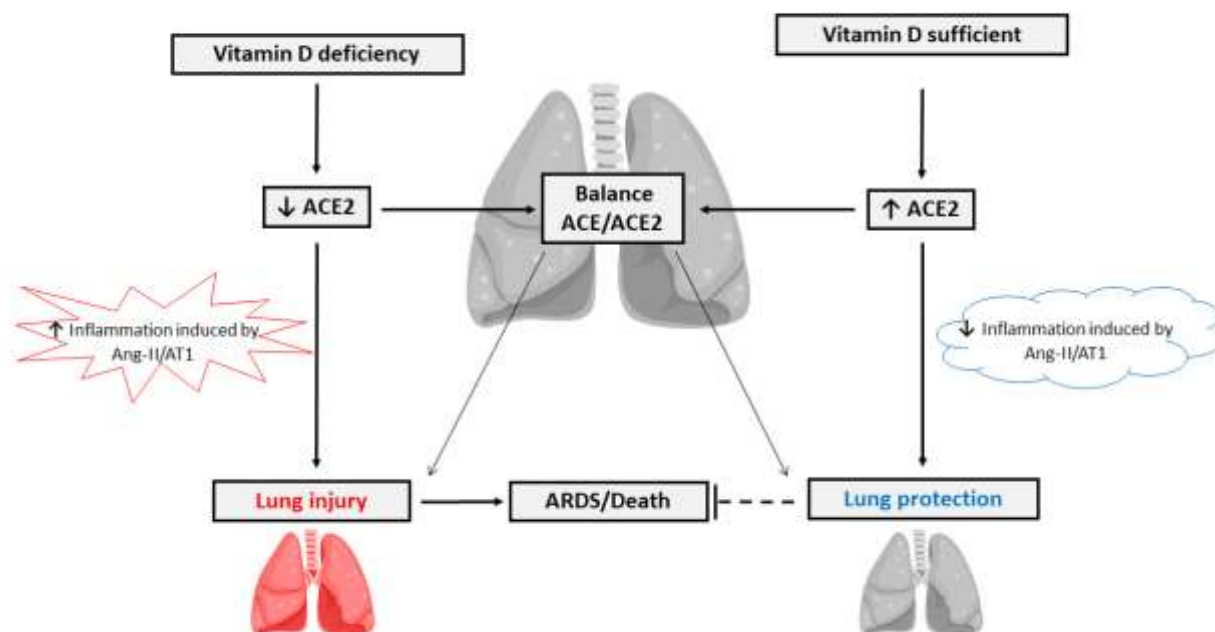
alveolar epithelial cell, which suggests that these cells can serve as a reservoir for viral invasion, further complicating the situation at the pulmonary level [41]. Interestingly, it has been observed that the expression of ACE2 (but not that of ACE) is significantly reduced in lung tissue during SARS-CoV-2 [42] infection. In this way, a crucial lung protection mechanism is lost, and the SARS-CoV-2 infection becomes more lethal, with recruitment, accumulation and exaggerated activation of neutrophils and macrophages, increased vascular permeability due to the breakdown of the barrier epithelial-alveolar (with diffuse alveolar damage and exacerbated edema at the pulmonary level), which will eventually lead to ARDS. In this state, the lungs cannot provide enough oxygen to the blood, which is essential for the proper functioning of vital organs [43]. Additionally, this state of hyper-inflammation and the over-activation of the RAAS are intimately involved in the alteration of the coagulation cascade, which leads to a prothrombotic state, commonly observed in ARDS during SARS-CoV-2 infection [44, 45].

Another consequence of COVID-19 is the potential risk of fibrosis with impaired lung function in recovered patients [46, 47]. In this sense, there is ample evidence that 1,25(OH)<sub>2</sub>D/VDR signaling is a potent negative regulator of RAAS [13, 19, 20]. Renin levels are elevated in VDR knock-out mice. Chronic Vit D deficiency can induce activation of RAAS. 1,25(OH)<sub>2</sub>D can reduce renin, ACE and Ang-II levels, simultaneously increasing ACE2 levels during lipopolysaccharide-induced acute lung injury [48]. Xu and colleagues conducted a study on rat lung endothelial cells to determine whether calcitriol at concentrations of 5, 20, and 100 nM affects lipopolysaccharide-induced acute lung injury. The results indicated that the higher concentration of calcitriol (100 nM) significantly reduced the deleterious effects of lipopolysaccharides on ACE and ACE2 levels, suggesting an essential role for the active form of Vit D in attenuating acute lung injury.

In parallel, and considering that the type 1 Ang-II receptor (AT1) is a downstream effector of ACE, the effects of lipopolysaccharides and calcitriol on its expression were then investigated. In line with the results described above, a significant increase in AT1 mRNA expression was observed in cells exposed to lipopolysaccharides compared to those that were not, while calcitriol reduced the effect of lipopolysaccharides on AT1 mRNA levels in a dose-dependent manner. It should be noted that the mRNA expression of the Ang-II type 2 receptor (AT2), used as a control, was not significantly altered. Therefore, these results confirm that calcitriol can prevent lipopolysaccharide-induced acute lung injury in rat lung endothelial cells, at least partly due to ACE2/Ang-(1-7) axis activation and inhibition of the ACE/Ang-II/AT1R axis of the RAAS [49].

On the other hand, we must consider that 1,25(OH)<sub>2</sub>D also positively regulates ACE2; thus Vit D could facilitate the uptake of viruses in cells that express this enzyme in their membranes. This dual effect means that ACE2 can potentially behave both in a harmful and beneficial way, which generated controversies and intense debates related to using Ang-II antagonists in hypertensive patients [50]. Despite this, most experts concluded that the beneficial effects of ACE2 on the lungs would negate its role in the entry of the virus into these cells [51]. Figure 2 outlines the relationship between Vit D and RAAS in the context of COVID-19.





**Figure 2.** Regulation of the renin-angiotensin-aldosterone system by vitamin D and its protective effects during COVID-19. Solid arrows indicate "stimulation", and broken arrows indicate "inhibition."

### Conclusions and prospect

Numerous studies indicate that Vit D deficiency is associated with increased morbidity and mortality in patients with COVID-19. Furthermore, it has been suggested that Vit D supplementation would reduce the risk of developing SARS in these individuals. However, the underlying molecular mechanisms of Vit D in the prevention and attenuation of this respiratory condition during COVID-19 are still not fully understood, which is crucial to develop better therapeutic management that allows saving the lives of patients infected with SARS-CoV-2.

Currently, several clinical trials are being carried out worldwide to evaluate the effects of Vit D supplementation in patients with COVID-19, both individually and in combination with other active ingredients, comparing the effect of high doses versus standard doses. However, the available evidence does not allow Vit D supplementation as an authorized therapy in patients admitted to health care centers.

Therefore, as a perspective, we propose the challenge of generating new evidence through multicenter clinical studies based on Vit D supplementation to patients with COVID-19 and applying the knowledge of critical analysis in order to obtain successful results.

### Authors' contribution

All authors contributed in the same way in the conception and design of the review, with a substantial contribution on the data, analysis and interpretation of the contents, writing and critical review of the article for its intellectual content.

### Declaration of conflict of interest

The authors declare no potential conflicts of interest concerning the research, authorship and/or publication of this article.

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