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Propiedades terapéuticas, beneficios para la salud y usos de la vitamina D como coadyuvante en el tratamiento contra la COVID-19

Therapeutic properties, health benefits and uses of vitamin D as an adjuvant in the treatment against COVID-19

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RESUMEN

El uso de dosis de vitamina D, especialmente 2000 UI diarias, ha mostrado una mejora significativa en pacientes infectados por SARS-CoV-2, incluyendo aquellos con síndrome respiratorio agudo severo (SARS). Esta terapia ha incrementado la tasa de supervivencia en pacientes críticos y ha disminuido la progresión de complicaciones relacionadas con la COVID-19. Este estudio se fundamenta en investigaciones científicas y académicas recientes de bases de datos como Medline, Pubmed, Hinari y SciELO, además de informes de la Organización Mundial de la Salud y los Centros para el Control y Prevención de Enfermedades. Los hallazgos respaldan el uso de la vitamina D como un agente adyuvante en el tratamiento de la COVID-19, destacando sus propiedades terapéuticas y beneficios para la salud. La vitamina D ejerce su efecto a través de mecanismos inmunomoduladores, incluyendo la promoción de la autofagia, crucial en la respuesta viral, y la mejora de las respuestas inmunitarias innatas y adaptativas en diversas enfermedades. Esto sugiere que la vitamina D no solo podría ayudar en la recuperación de COVID-19, sino también en la prevención de complicaciones severas, reafirmando su papel como un complemento importante en la terapia para pacientes afectados por esta enfermedad.

Palabras clave: vitamina D, SARS-CoV-2, COVID – 19

ABSTRACT

The use of different doses of vitamin D, especially 2000 IU daily, has shown a significant improvement in patients infected by the SARS-CoV-2 virus, including those with severe acute respiratory syndrome (SARS). This therapy has shown an increase in the survival rate in critically ill patients and reduced the progression of medical complications related to COVID-19. The present study was based on recent scientific and academic research, obtained from various databases and sources such as Medline, Pubmed, Hinari, SciELO, as well as reports from the World Health Organization, Ministry of Health and Centers for Control and Prevention of Diseases. The reported results support the use of vitamin D as an adjuvant agent in the treatment of COVID-19, providing therapeutic properties and health benefits. Vitamin D acts through immunomodulatory mechanisms, such as promoting autophagy, which is essential in the fight against viruses, and enhancing innate and adaptive responses in various pathological conditions.

Keywords: vitamin D, SARS-CoV-2 virus, COVID-19

INTRODUCTION

The objective of this work was to compile the available information on the use of vitamin D as an adjuvant in the treatment of patients with COVID-19, as a palpable need to develop therapeutic alternatives due to the collapse of global health systems followed with the arrival of the virus SARS-CoV-2.

The effectiveness of vitamin D in decreasing the mortality risk in infected patients is highlighted, which has prompted academic studies and clinical trials to verify its safety and effectivity as an additional treatment against COVID-19.

This paper addresses topics such as the physicochemical properties of vitamin D, production and metabolism, therapeutic benefits, and the role it has as an adjuvant in the treatment of the disease, as well as the specific immunological mechanism of action against the virus, that it presents.

The topic and chronology were meticulously selected to provide a comprehensive and informed understanding of the research.

MATERIALS AND METHODS

The present research work focused on the collection of information on the use of vitamin D as a complementary treatment against COVID-19, using a descriptive methodology that, as its name indicates, is limited to describing the current information available.

Different stages were followed in order to structure the work. In a first stage, a bibliographic review was carried out using specific descriptors in a wide variety of databases like: Medline, Pubmed, Hinari, SciELO, as well as academic works and data from organizations such as the World Health Organization, the Centers for the Disease Control and Prevention and the Ministry of Health. Updated articles were selected, which in turn were endorsed by health professionals and supported by different sources, limiting them to studies published in the last 10-15 years in Spanish, English and Portuguese, including case-control studies, and clinical trials, observational and descriptive.

In the second stage, the collected data were correlated and analyzed to expand the information. Finally, in the third stage, the objectives were set and a sequence for the subtitles was designed, guaranteeing a coherent progression from the description of basic concepts to the complexity of the topic.

RESULTS

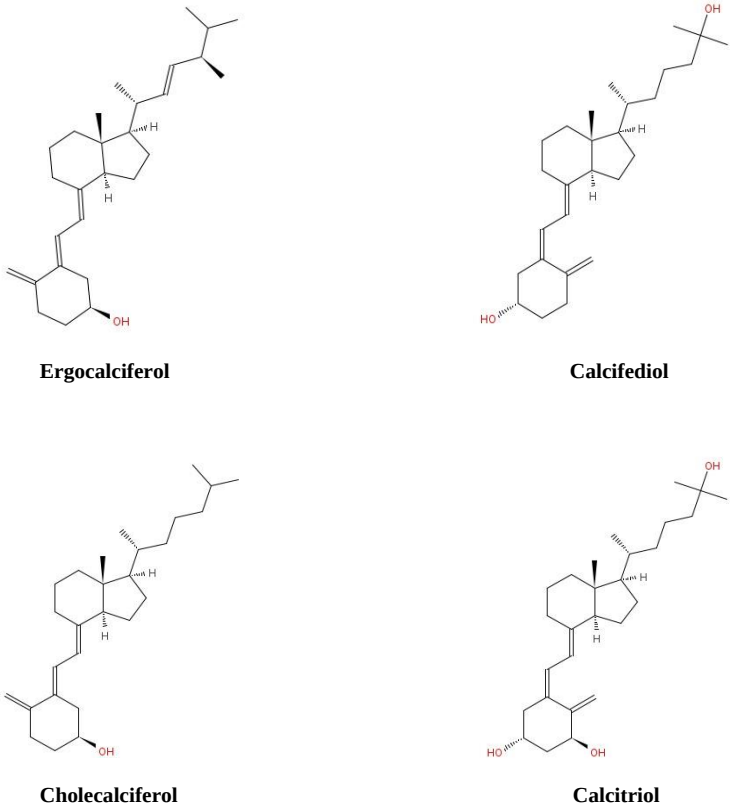
Generalities and physicochemical properties of vitamin D

Vitamin D is a complex prohormone, which has molecular similarities with classic steroids, such as cortisol, aldosterone and estradiol, thanks to its cyclopentaneperhydrophenanthrene ring structure (Zuluaga et al., 2011a). It is mainly obtained

through sun exposure, diet and oral supplements, being synthesized endogenously under the action of ultraviolet radiation from 7-dehydrocholesterol. It is also acquired through diet, whether of animal origin (D3 cholecalciferol) or plant origin (D2 ergo calciferol) (Ramírez et al., 2018). It functions in both an endocrine and autocrine manner, regulating calcium-phosphorus homeostasis, promoting cell differentiation and apoptosis in cells with vitamin D receptors, which prevents diseases such as rickets and osteomalacia (García et al., 2013a). It has the appearance of a white-yellowish crystalline powder, with solubility in ether and chloroform. A relative thermos sensitivity, being stable to heat in crystallized form, but susceptible to isomerization in oily solution (Rodríguez Sangrador, 2007a; 2007b).

Figure 1

Chemical structures of the vitamin D family.



Note. Adapted from Influence of sun exposure and diet on vitamin D nutritional status in adolescent and elderly women: Optiford-European Union study (p. 12), by M. Rodríguez Sangrador, 2007, Complutense University of Madrid

Sources for obtention of vitamin D

Vitamin D belongs to the group of steroids and is obtained both endogenously and exogenously. Endogenous synthesis occurs from 7-dehydrocholesterol, which is converted to cholecalciferol in the skin by ultraviolet radiation (Pérez Castrillón, 2020a). Sun exposure provides a significant amount of vitamin D, even in elderly people with low levels of 7-dehydrocholesterol, and a good diet also contributes to achieving adequate levels, but in a less efficient way. The cutaneous synthesis of vitamin D is highly influenced by several factors. Starting from the concentration of 7-dehydrocholesterol in the epidermis, that decreases with age,

making it difficult to achieve optimal levels of vitamin D (Valero and Hawkins, 2007b). Another notable point is the amount of melanin in the skin, this also has an influence, since people with darker skin tones need longer sun exposure to produce the same amount of cholecalciferol as those with lighter tones, because melanin absorbs solar photons (Valero and Hawkins, 2007c). Other factors that can affect the synthesis of vitamin D include the intensity of sunlight, which varies with time of day, season, and latitude (Valero and Hawkins, 2007d).

Foods from animal origin contain cholecalciferol, while vegetables contain ergo calciferol; both forms must be metabolized to be activated (Valero and Hawkins, 2007a). Given the scarcity of foods rich in vitamin D, foods such as milk, juices, bread, margarine, cereals and flour have been fortified. Being indicative of the need to implement alternatives for those with fat absorption difficulties (Sevillano Segura, 2016b; U.S. Department of Health & Human Services, 2021). Daily intake recommendations vary, from 600 IU/day for those under 70 years of age to 2000 IU/day for those at highest risk of deficiency (Pérez Castrillón, 2020b; Sevillano Segura, 2016c). To achieve optimal levels of 25(OH) vitamin D, a daily supplementation of 20-25µg is recommended, with an approximate ratio of 2.5nmol per 100IU (2.5µg) of vitamin (Sevillano Segura, 2016d).

Endogenous and exogenous metabolism of vitamin D

Vitamin D is obtained mainly from the diet and endogenous production by photochemical conversion from 7-dehydrocholesterol in the epidermis. This endogenous synthesis is induced by exposure to ultraviolet B (UVB) rays from sunlight (Zuluaga et al., 2011b). During exposure to ultraviolet light, photons are absorbed by 7-dehydrocholesterol, forming precholecalciferol, which is rapidly converted to cholecalciferol (Valero and Hawkins, 2007g). It must be converted into the active form, that will be transported by vitamin D binding protein (DBP) for activation in the liver and subsequently in the kidney (Zuluaga et al., 2011d). 25-hydroxyvitamin D3 is the main circulating form and the best indicator of vitamin D levels (Zuluaga et al., 2011g). 1,25-dihydroxyvitamin D3 is the hormonally active form responsible for most biological effects, and its production is also found in other tissues (Zuluaga et al., 2011i).

Vitamin D is inactivated in the liver and is eliminated mainly through the bile (Valero and Hawkins, 2007h). The skin production of this vitamin decreases with age and is influenced by factors such as the amount of melanin in the skin, geographical latitude, and the season of the year (Busturia Jimeno, 2012). The absorption of vitamin D from the diet occurs at the duodenum and jejunum through a passive diffusion mechanism (Rodríguez Sangrador, 2007c). Once absorbed, it binds to DBP and enters the blood circulation (Rodríguez Sangrador, 2007d). Additionally, certain medications and adipose tissue can affect the metabolism and bioavailability of the vitamin (Flores, Macías Morales & Rivera Pasquel, 2012a).

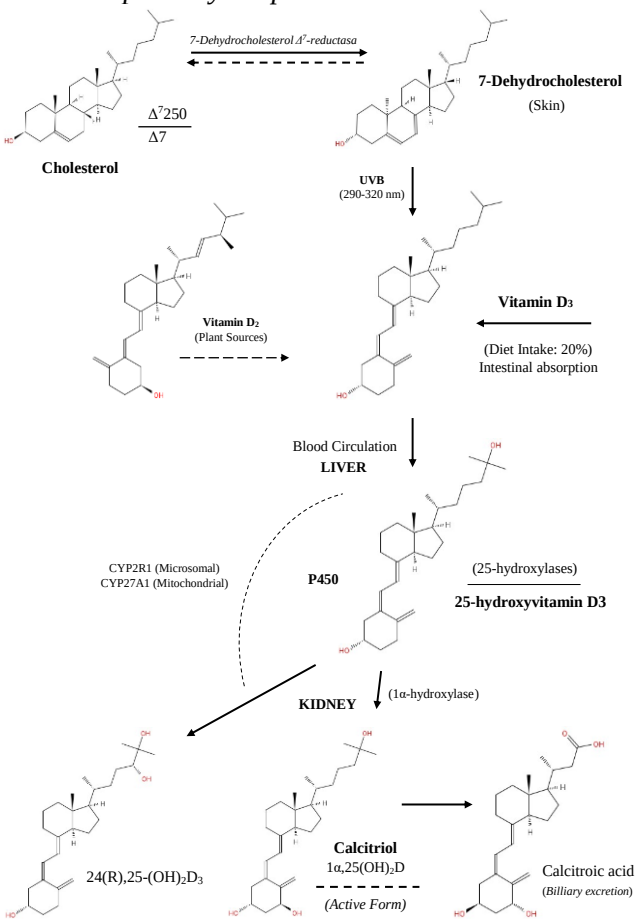
Therapeutic properties and health benefits

The action of vitamin D is mediated by the vitamin D receptor (VDR), which binds to specific DNA sequences and regulates gene transcription. It is estimated that RVD can regulate between 100 to 1,250 genes (Higdon and Delage 2017a). The 1,25-dihydroxyvitamin D Receptor (VDR) regulates the expression of genes related to the biological activity of vitamin D, as part of the family of nuclear hormone receptors (Zanchetta & Fradinger, 2009a). The actions of vitamin D, including non-genomic ones, are carried out through the VDR located in the plasma membrane, which is widely distributed in 36 different tissues (Zanchetta & Fradinger, 2009b).

Multiple physiological functions are attribute to vitamin D and the deficiency of it is associated with several diseases, for example bone disorders (Vásquez Awad et al., 2017a). The causes of deficiency can be extrinsic (inadequate intake or low sun exposure) or intrinsic (diseases that affect the absorption or metabolism of the vitamin) (Varsavsky et al., 2017a, 2017b). Despite discrepancies between standardization of optimal levels, vitamin D insufficiency is considered to be between 50 and 75 nmol/L, while levels below 50 nmol/L indicate definetely a deficiency. Although more research is needed, higher levels of vitamin D are associated with greater protection against respiratory viral infections (Flores, Macias Morales & Rivera Pasquel, 2012d).

Figure 2

Metabolic pathways to produce Vitamin D.



Note. Adapted from Effects of vitamin D on health, immune response, and neurodevelopment in children (1st ed., pp. 13-43) by F. Macías Morales & Rivera Pasquel, 2012, Mexico: National Institute of Public Health.

Musculoskeletal and Cardiovascular system

Vitamin D continues to be widely used in the preservation of bone mass and as an adjuvant in the treatment of osteoporosis (Vásquez Awad, 2013b). It improves bone quality through several mechanisms, such as decreasing bone resorption and increasing cortical bone formation (Vásquez Awad, 2013c). Low levels of vitamin D are associated with chronic diseases like metabolic syndrome, type 2 diabetes and cardiovascular disease. Vitamin D can influence endothelial function, lipid metabolism and the regulation of the immune response, which may have implications in the prevention of cardiovascular diseases (Vásquez Awad, 2013e, 2013f, 2013g).

Cancer

It has been suggested that vitamin D may influence the reduction of cancer risk, regulating cellular processes related to apoptosis, proliferation, and differentiation (Vásquez Awad, 2013h). However, the evidence is still limited, and the mechanism is not fully described or understood (Vásquez Awad et al., 2017c).

Multiple sclerosis

Vitamin D may play a role in the prevention of multiple sclerosis by inhibiting the activity of CD4 T lymphocytes and modulating the immune response (Vásquez Awad, 2013i).

Renal system

Calcitriol, the active form of vitamin D, plays a crucial role in renal calcium handling, regulating the reabsorption and homeostasis (Zanchetta & Fradinger, 2009d, 2009e).

Immune system

Vitamin D can induce the expression of antibacterial proteins and regulate the immune response, influencing the cells of both the innate and adaptive immune system (Vásquez Awad et al., 2017e; Vásquez Awad, 2013j). Another piece which plays an important role in the inmune response and genetic polymorphisms, es the vitamin D receptor, that can influence susceptibility to viral infections (Bilezikian et al., 2020h, 2020i).

Other functions of vitamin D

Calcitriol has effects on cell proliferation and differentiation, regulation of immune function and fetal development, with vitamin D receptors being identified in various organs and tissues (Rodríguez Sangrador, 2007f, 2007g, 2007h).

Benefits of the use of vitamin D, as an adjuvant in the treatment against COVID-19

To understand how the action mechanism of vitamin D works as an adjuvant in the treatment against Covid-19, it is necessary to know the mechanisms that the virus uses to damage the human body. Infection with the SARS-CoV-2 virus causes a pathophysiological phenomenon known as "pulmonary cytokine storm", which is the causal agent of most cases of mortality and morbidity, as it is the result of an imbalance in the immune system. innate causing a large release

of proinflammatory cytokines and chemokines, leading to an abnormal activation of adaptive immunity resulting in acute respiratory distress syndrome (ARDS). (Bilezekian, J. et al, 2020k).

The SARS-CoV-2 virus enters cells to bind to the ACE2 receptor, which is found in type II alveolar cells. This binding causes a systemic inflammatory response to be generated, beginning with a storm of proinflammatory cytokines (IFN-a, IFN -g, IL-1b, IL-6, IL-12, IL-18, IL - 33, TNF - α, TGFb, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10). Causing a cascade of inflammation in the lower respiratory tract, bringing with it acute respiratory distress syndrome (Oliva Marín, 2020a). Another effect of the virus binding to the ACE2 receptor is the negative regulation of cellular expression, causing it to stop exercising its protective functions. Leading to the accumulation of angiotensin II, since one of the functions of the receptor is to catalyze the cleavage of angiotensin II into angiotensin. This accumulation and uncontrolled activity of angiotensin II is believed to be responsible for acute lung injury in COVID-19 disease, unfavorable myocardial remodeling, increased vascular permeability, peripheral vasoconstriction, inflammation, oxidative stress, and pulmonary fibrosis, which are the causes of severe respiratory symptoms due to COVID-19 (Oliva Marín, 2020b; Seijo and Oliveri 2020a).

At least 3 mechanisms have been proposed for how vitamin D can fight infection and reduce the risk of developing serious complications caused by COVID-19. These 3 mechanisms are based on acting on physical barriers, innate immunity and adaptive immunity. On the other hand, vitamin D helps maintain integrity after binding to its receptor by stimulating the genes that encode proteins responsible for maintaining cellular junctions, such as occludins (tight junctions), connexins 43 (gap junctions) and E -cadherin (adherent junctions) (Mansur, 2020a). Epithelial and endothelial cell junctions guarantee the permeability and integrity of the alveolar wall.

The SARS-CoV-2 virus, as a virus with destructive action, causes tissue alteration, on cell junctions needed to reduce cell progression and superinfection with other microorganisms such as bacteria and to avoid pneumonia (Seijo and Oliveri 2020b).

Vitamin D induces the differentiation of monocytes and macrophages, improving both phagocytic and chemotactic capacity. Additionally, when toll-like receptors are present, innate immune response cells, such as macrophages; bind to pathogen-associated molecular patterns (PAMPs), generating a response that causes greater expression of VDR and CYP27B1, increasing the capacity of macrophages and monocytes to transform 25(OH)D into 1,25(OH)D. Which are responsible, together with the VDR, for interacting with vitamin D response elements (VDRE) of cellular DNA, positively regulating the expression of genes such as nucleotide-binding oligomerization domain containing protein 2 (NOD2), which is an important receptor that recognizes intracellular PAMPs and enhances the expression of β-defensin, hepcidin antimicrobial protein (HAMP), cathelicidin (CAMP), and β-defensin 4 (DEFB4) (Seijo and Oliveri 2020c; Bilezekian, J. et al, 2020l).

All these molecules participate in the destruction of infectious agents, altering their capsids, blocking viral invasion of cells, reducing the amount of intracellular iron, which is vital for the survival of viruses, preventing cell death of the epithelium of the respiratory tract. respiratory and neutralizing the activity of endotoxins. In this way, the VD regulates the production of antimicrobial peptides that allow the immune response to be modulated by reinforcing the function of lung epithelial cells (Seijo and Oliveri 2020d; Bilezekian, J. et al, 2020m).

Stimulating innate immunity, Vitamin D also manages to promote the homeostasis of cellular oxidation and reduction, that is, it manages to stimulate the production of reactive oxygen species nitric oxide and superoxide. Vitamin D is important to produce these reactive oxygen species, which maintains normal mitochondrial function and inhibits oxidative stress pathways (Seijo and Oliveri 2020f). Which brings us to autophagy, a mechanism that cells use to maintain their homeostasis since through this process they manage to degrade and eliminate all damaged proteins and organelles. This process is also a defense mechanism against viral infections since with autophagy; Viral particles can be encapsulated and, through lysosomal degradation, destroyed to subsequently carry out antigen presentation and activate the adaptive immune response (Bilezekian, J. et al, 2020n).

Through studies it has been proven that 1,25(OH)D can induce autophagy in monocytes, the mechanism by which it does so is through the inhibition of the protein kinase 2 associated with the S phase Skp2, this protein It has been seen that it is synthesized by the SARS-CoV-2 virus, which manages to block the autophagy process and thereby promote its accelerated replication (Seijo and Oliveri 2020g). Vitamin D stimulates the promotion of enzymes autophagy stimulants such as Beclin 1 and PI3KC3, which produce the elongation of the autophagosome and its fusion with the lysosome. In addition, vitamin D stimulates the formation of autophagosomes that facilitate viral elimination indirectly. Through the induction of cathelicidin expression, which will subsequently stimulate Beclin 1 (Bilezekian, J. et al, 2020ñ; Rodríguez et al. 2020a). The vitamin can influence the activation of adaptive immunity, due to its inhibitory and anti-inflammatory action. By having the ability for dendritic cells to present antigens, decreasing the activation of T lymphocytes (Bilezekian, J. et al, 2020o).

Secondly, Vitamin D influences the different populations of T lymphocytes, favoring the proliferation of Th2 lymphocytes and Treg lymphocytes, which in turn stimulates the production of anti-inflammatory cytokines. In addition, Vitamin D inhibits the proliferation of Th1 and Th17 lymphocytes, causing a decrease in the production of pro-inflammatory cytokines. This activation and inhibition of T lymphocytes helps prevent the cytokine storm, mainly responsible for the complications caused by the SARS-CoV-2 virus (Seijo and Oliveri 2020h). In addition to the 3 mechanisms mentioned above, vitamin D is capable of exerting effects on the renin-angiotensin-aldosterone system. These effects are of utmost importance since large amounts of angiotensin II

contribute to the appearance of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Rivera, Medina, Vargas, Gómez & González, 2020). VD increases ACE2 levels, decreasing the levels of Ang I and Ang II and causing greater synthesis of Ang 1.9 and Ang 1.7, which counteracts the harmful effects at the lung level (Seijo and Oliveri 2020i).

Although vitamin D is known to participate in the maintenance of bone health and calcium-phosphorus metabolism. However, various functions of this hormone have recently been discovered, especially as an immunomodulator, promoting antiviral immunity, which is important due to its role in COVID-19 infection (Bilezikian et al., 2020p; Panfili et al., 2020a). In addition to the immunomodulatory role of vitamin D, it is known that VDR activation can regulate the expression of more than 900 genes, many of which are involved in innate and adaptive immunity (Panfili et al., 2020b). On the other hand, VDR is expressed on almost all immune cells, including activated CD4+ and CD8+ T cells, B cells, and antigen-presenting cells such as macrophages and dendritic cells. The receptor acts as a modulator of innate and adaptive immunity. In turn, it is known that vitamin D improves the expression of two antimicrobial peptides called cathelicidin and β-defensin, and that they play a key role in innate immunity. These peptides are involved in direct microbicidal effects in addition to pleiotropic effects in the induction of immunomodulatory responses to pathogenic stimuli (Panfili et al., 2020c).

In particular, the human cathelicidin peptide LL37 exhibits a variety of effects by interacting with formyl peptide receptor type 1 (FPRL1), recruiting neutrophils, monocytes, and T cells to infectious sites. Promoting apoptosis of infected cells by showing potent antiviral effects on a variety of viruses, including HIV-1, influenza viruses, HSV1-2, rhinovirus and HCV. Several studies reported a high prevalence of vitamin D deficiency among HIV-infected people. More specifically, faster HIV progression and severity, lower CD4+ counts, increased risk of mortality, and increased vulnerability (Panfili et al., 2020d).

Another property of vitamin D relevant to antibacterial and antiviral mechanisms is the promotion of autophagy. Autophagy is a fundamental biological process that maintains cellular homeostasis through the encapsulation of damaged organelles and misfolded proteins in the intracellular membrane (Bilezikian et al., 2020q). Autophagy is also an essential mechanism through the which cells cope with viruses. Autophagic encapsulation of viral particles packages them for lysosomal degradation and subsequent antigen presentation and adaptive antiviral immune responses. Therefore, autophagy facilitates, but does not guarantee, a hostile cellular antiviral environment (Bilezikian et al., 2020r). Beyond the immediate regulation of pathways associated with the induction of autophagy, vitamin D may also stimulate the formation of autophagosomes to facilitate viral clearance indirectly through the induction of cathelicidin expression, which in turn stimulates factors key to autophagy such as Beclin 1 (Bilezikian et al., 2020).

Vitamin D may play a crucial role in maintaining an appropriate balance between autophagy and apoptosis to maximize antiviral responses to infection (Bilezikian et al., 2020t). It promotes self-tolerance by changing cytokine patterns from a Th-1 to a Th-2 environment, resulting in a reduction of Th1 and Th17-stimulating cytokines with a depletion of the Th-17 cells themselves that are related to tissue damage, inflammation and a positive regulation of type 2 regulatory cells (T reg) (Panfili et al., 2020e). Finally, 25-hydroxyvitamin D and 1,25(OH)2D modulate T cell immunity, reducing type 1 proinflammatory cytokines (IL-8, IFN-γ, IL-12, IL-6, TNF -α and IL-17) and the increase in type 2 anti-inflammatory cytokines (such as IL-4, IL-5 and IL-10). Specifically, 1,25(OH)2D inhibits plasma cell proliferation and immunoglobulin secretion and induces B cell apoptosis.

A devastating pathophysiological aspect of SARS-CoV-2 infection is the so-called "pulmonary cytokine storm", one of the main causes of morbidity and mortality. Cytokine storm is the result of a dysviosis of the innate immune system with an avalanche of proinflammatory cytokines and chemokines, leading to abnormal activation of the adaptive immune pathway (Bilezikian et al., 2020u). The serious damage caused by coronaviruses such as SARS-COV-2 is due to their infection of the upper and lower respiratory tract with rapid virus replication, massive infiltration of inflammatory cells producing an increase in proinflammatory cytokines and chemokines that lead to acute illnesses and respiratory distress syndrome (Bilezikian et al., 2020v). Approximately 5 percent of patients infected with Covid-19 will develop ARDS, due to a dysfunctional immune response, resulting in a "cytokine storm" and subsequently multi-organ failure (Slominski et al., 2020a).

The main proinflammatory elements in a cytokine storm are IL-1β, IL-6, TNF-α, INFγ and IL-17. The important master regulation of proinflammatory responses is NF-κB, while Th17 responses are related to the retinoic acid receptor (RORγ). Oxidative stress may be another etiological factor in the development of ARDS. It can be triggered by a virus and can activate toll-like receptors (TLRs) with subsequent release of cytokines (Slominski et al., 2020b).

Oxidative stress induced by a viral infection or cytokine storm can amplify the damage inflicted on target organs. Breaking this vicious and self-amplifying cycle without toxic side effects and an impairment of the host antiviral response would represent a logical management of COVID-19 (Slominski et al., 2020c). That said, it is known that active forms of vitamin D, including classical calcitriol [1,25(OH)2D3] and hydroxyderivatives of CYP11A1, can inhibit the production of proinflammatory cytokines from a cytokine storm with a mechanism of action involving negative regulation of NF-κB and inverse agonism at RORγ. Counteracting oxidative stress by activating TNF α and p53-dependent pathways. Therefore, it is possible that hydroxide derivatives of vitamin D3 are candidates for the treatment of COVID-19, because if they target both the cytokine storm and oxidative stress, they could have antiviral effects (Slominski et al., 2020d).

COVID-19 has been associated with cardiovascular sequelae, including myocardial injury, type 1 myocardial infarction, acute coronary syndromes, cardiomyopathy, arrhythmias, thrombotic complications, and cardiogenic shock. Myocardial injury, with elevation of cardiac biomarkers, as well as electrocardiographic or echocardiographic changes, are common and reported in between 20 and 30 percent of hospitalized patients with COVID-19 (Bilezikian et al., 2020w). It has been associated with cardiovascular sequelae, including myocardial injury, type 1 myocardial infarction, acute coronary syndromes, cardiomyopathy, arrhythmias, thrombotic complications, and cardiogenic shock. Myocardial injury, with elevation of cardiac biomarkers as well as electrocardiographic or echocardiographic changes, is common, reported in 20-30 percent of hospitalized patients with COVID-19 (Bilezikian et al., 2020w).

Cardiomyopathy has been reported in 7-33 percent of critically ill COVID-19 patients. Cardiac arrhythmias, including new-onset atrial fibrillation and atrial flutter, heart block, and ventricular arrhythmias have been reported in 17 percent of hospitalized patients and 44 percent of ICU patients (Bilezikian et al., 2020x). On the other hand, the various cardiovascular risk factors that have been correlated with increased mortality from COVID-19 are also more evident in experimental and clinical studies of Vitamin D deficiency (Bilezikian et al., 2020y).

Vitamin D deficiency may predispose to hypertension and other types of conditions by upregulating the RAAS and increasing vascular resistance and vasoconstriction. While direct causal evidence for a role of vitamin D deficiency in SARS-CoV-2-related heart disease is not available, extrapolation of evidence from previous animal and human studies allows speculation about several plausible mechanisms (Bilezikian et al., 2020z).

Academic studies and research regarding the use of Vitamin D in the treatment of COVID-19

The relationship between low levels of Vitamin D and the severity of COVID-19 has generated a series of investigations, in order to validate this hypothesis. When analyzing the epidemiological data, a correlation was observed between COVID-19 mortality and latitude, suggesting a relationship with sun exposure and the endogenous synthesis of Vitamin D, as exposed before (Cortina-Gutiérrez et al., 2020a). Age is another factor that correlates with the decreased of vitamin D levels, which mathces with severity and mortality in older patients (Cortina-Gutiérrez et al., 2020b).

Studies done in the Philippines, have shown a significant inverse correlation between clinical severity and Vitamin D levels. Lower levels were associated with severe cases (Mansur, 2020d). Similarly, in Indonesia and Iran, higher mortality was observed among patients with lower Vitamin D levels (Mansur, 2020d). In studies carried out in Mexico, although no statistically significant differences were found, it was observed that most deceased patients had vitamin D deficiencies. At the same time, it was determined that most hospitalized patients had lower levels of vitamin D, revealing that the majority of deaths corresponded to subjects with low

levels or deficiencies of vitamin D3, as well as the majority of those hospitalized (Rodríguez et al., 2020f).

A six-week prospective observational study conducted in India found that patients with lower levels of vitamin D showed greater disease severity and therefore higher mortality rates (Jain et al., 2020a). Jain et al., in their studies, demonstrated that patients with low concentrations of vitamin D3 had higher levels of pro-inflammatory interleukins such as IL-6 and serum ferritin (Jain et al., 2020e).

A meta-analysis showed a beneficial effect of Vitamin D in reducing respiratory infectious diseases, especially in those who had a severe deficiency and to whom the vitamin was administered daily or weekly (Pérez Castrillón et al., 2021a). Although various clinical trials have been proposed to investigate this hypothesis, more studies are still required to confirm the beneficial effects and determine the appropriate doses of supplementation (Pérez Castrillón et al., 2021b).

Table 1

Vitamin D studies in patients infected with COVID-19. This table has been adapted from COVID-19 and Vitamin D. Position paper of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) by Pérez Castrillón et al., 2021, Revista de Osteoporosis y Metabolismo Mineral, 12(4) , (pp. 155-159)

AUTOR	TYPE OF STUDY	POPULATION	SUPPLEMENT	OBJETIVE	RESULTS	COMMENT
Fasano *et al.*	Cases/Controls	Patients with Parkinson's diseases (1,486).	Not established	Incidence of COVID-19.	12.4% vs 22.9%	Those who receive supplements have less incidence.
Annaweiler C *et al.*	Cases/Controls	Institutionalized (7).	Cholecalciferol 50,000 IU/month (previous) 80,000-100,000 IU/2-3 months (previous) 80,000 IU single bolus after diagnosis.	Mortality	6.9% vs 31.3% 18.8%vs31.3%	Those who receive Vitamin D in the previous year have less mortality, but not those who receive it after diagnosis.
Annaweiler G *et al.*	Cases/Controls	Institutionalized (66)	Cholecalciferol bolus of 80,000 IU before and after diagnosis.	Mortality	17.5% vs 55.6%	Those who receive Vitamin D have less mortality.
Tan CW *et al.*	Cases/Controls	Hospitalized for COVID-19 (43).	Cholecalciferol (1,000 IU/day), magnesium, Vitamin B12.	Mortality	17.6% vs 61.5% admission to ICU	Those who receive Vitamin D need less oxygen therapy or ICU admission.
Entrenas-Castillo *et al.*	Open, randomized, double-blind pilot clinical trial.	Admitted for COVID-19 pneumonia (76; 50 treated and 26 untreated).	Calcifediol 64,000 IU/first week and subsequently 16,000 IU (week until discharge or admission to the ICU.	Admission to ICU.	2% vs 50%	Those who receive Vitamin D are admitted to the ICU less, although the risk factors are not balanced between groups.

A study carried out in France, on the other hand, evaluated whether the constant administration of Vitamin D could influence the survival of elderly patients hospitalized with COVID-19. Dividing them into three groups: those who received supplements regularly one year in advance (Group 1), those who received supplements after diagnosis (Group 2) and those who did not receive supplementation (Group 3) (Annweiler et al., 2020a).

The results showed that the mortality proportion of patients with severe COVID-19 was lower in Group 1 compared to Group 3. However, Group 2 did not show significant improvements compared to the group without supplementation (Annweiler et al. , 2020c). It was concluded that supplementation after diagnosis did not show significant benefits, while a regular Vitamin D supplementation could be associated with a decrease in the severity of COVID-19 and a better survival rate, during hospital stay (Annweiler et al., 2020e).

A study done in Spain, showed that the administration of calcifediol helped to improve the progression of the disease and reduced the number of admissions to the Intensive Care Unit (ICU), reducing mortality (Entrenas Castillo et al., 2020c). Despite certain comorbidities such as high blood pressure and diabetes mellitus, calcifediol was shown to significantly reduce the need for ICU admission in patients with COVID-19 (Entrenas Castillo et al., 2020f).

DISCUSSION

During the execution of this research work, different clinical studies were analyzed, where hundreds of patients were subjected to treatments with Vitamin D. It is worth mentioning that these trials were carried out around the world in people infected with SARS-CoV-2, with different doses and schedules of Vitamin D, to evaluate the evolution of each of them.

The most relevant studies were those where patients infected with SARS-CoV-2 who presented hypovitaminosis or plasma concentrations of vitamin D $\leq$ 20 ng/mL, had worse disease progression and a higher mortality rate than those with desirable concentrations, that is, greater than 30 ng/mL. This is because, adding the hypovitaminosis of Vitamin D, with latitude, a worse evolution of the COVID-19 disease can be observed. For example, in countries further away from the Equator, that is, to the north, the intensity of UV rays is lower and therefore the endogenous production of the vitamin decreases considerably. Another important factor for the decrease in serum Vitamin D is age. It was observed that elderly patients developed greater complications caused by this disease.

Mansur J., in 2020, found in publications from countries such as: Switzerland, Ireland, Belgium, the United Kingdom, Philippines, Israel and the United States, significant differences were found between patient groups and control groups.

Studies carried out in the Philippines present an inversely significant relationship between the severity of the evolution, the clinical picture and plasma concentrations of vitamin D in 212 patients. Where the serum average was 31.2 ng/mL in mild patients, 25.4 ng/mL in moderate patients, 20.2 ng/mL in severe patients and 17.1 ng/mL in critical patients. Of these, 47 cases were mild (representing 85.5 percent) and only 2 were critical (3.6 percent), within the deficient group (less than 20 ng/mL) only 1 of the cases (1, 4 percent) were mild and 25 of them (32.5 percent) were critical. On the other hand, in Indonesia, in 780 confirmed cases, 46.7 percent of those deficient in Vitamin D died, 49.1 percent of those deficient in Vitamin D (between 20 and 30

ng/mL) and only 4.2 percent of those had a plasma level greater than 30 ng/mL. Finally, in Iran it was reported that 20 percent of those hospitalized died with less than 30 ng/mL and 9.7 percent with a higher value.

At the same time, Rodríguez et al., in 2020, carried out a study at the Central Military Hospital of Mexico of a retrospective observational, case-control, analytical and cross-sectional type that included hospitalized patients with a diagnosis of SARS-CoV-2 infection or with suspicion of COVID-19 in whom the serum concentration of Vitamin D was determined before hospital admission. This was with the objective of investigating whether there was any direct relationship between serum vitamin D levels before hospital admission and the mortality rate of the patients. To standardize Vitamin D levels as: optimal, insufficient and deficient, the group of researchers in charge was based on the levels presented by the Endocrinology Society of the United States (SEO). Among the results observed, the SEO obtained that 20.3 percent of patients with COVID-19 had levels lower than 8 ng/mL (that is, they presented Vitamin D hypovitaminosis).

Consequently, the mortality rate presented was 20.5 percent, and although there was no statistically significant difference between the mortality of the patients and the categorization of Vitamin D levels. It could be observed that patients with optimal levels (≥ 30 ng/mL) none died, while the majority of patients who died (77.1 percent) had deficient levels (<20 ng/mL). Within the group of patients who died, they had lower levels of vitamin D (13.60 ± 6.36 ng/mL) compared to patients who survived (17.30 ± 7.44 ng/mL). Additionally, patients who had plasma levels less than 8 ng/ml had a 3.69 times greater risk of dying compared to those who had levels above 8 ng/ml. In relation to the above, it was observed that infected patients who required hospitalization for COVID-19 presented, on average, deficient levels of Vitamin D (16.54± 7.37 ng/mL), among which only 4.1 percent of hospitalized patients, presented optimal levels.

During the research, the role of Vitamin D in the cytokine storm in people with COVID-19 was also evaluated. Likewise, in 2020 Daneshkhah et al. observed that patients with a marked Vitamin D deficiency (≤15 ng/mL) had higher levels of proinflammatory markers and/or cytokines than control groups with desirable concentrations.

Furthermore, patients with low plasma concentrations had a significant increase in “C-reactive protein” which, in turn, also increased the probability of triggering cytokine storm and this, consequently, drastically increased the probability of developing a severe course due to COVID-19.

The use of Vitamin D as an adjuvant in the treatment and medical management of patients infected by SARS-CoV-2 has shown, in the majority of studies carried out around the world, a beneficial and immunomodulatory effect for the improvement and evolution of the patients with COVID-19, especially when given daily in small doses, rather than in boluses or occasionally in higher concentrations.

CONCLUSIONS

According to current literature, the role of Vitamin D in the evolution of COVID-19 has led to considering its use as a complementary treatment, with studies showing a correlation between vitamin D deficiency and a severe evolution of the disease.

Although some studies have been limited by the size of the sample, a significant difference is observed between patients with normal levels of vitamin D and those with deficiency; they were more resistant and had greater survival, requiring less oxygen supply or admission to intensive care.

Regarding the administration of Vitamin D supplements, there are divergences in the results: while some studies show improvements with post-diagnosis administration, others do not find significant benefits. Some authors report not having found any benefit, which suggests that more studies should be carried out with larger samples and more risk factors should be considered.

In summary, although vitamin D supplementation after COVID-19 diagnosis may not represent a significant improvement, maintaining adequate vitamin D levels before infection appears to reduce complications and risks of severe illness from COVID-19, according to the results of clinical trials.

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