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Vitamin D and COVID-19

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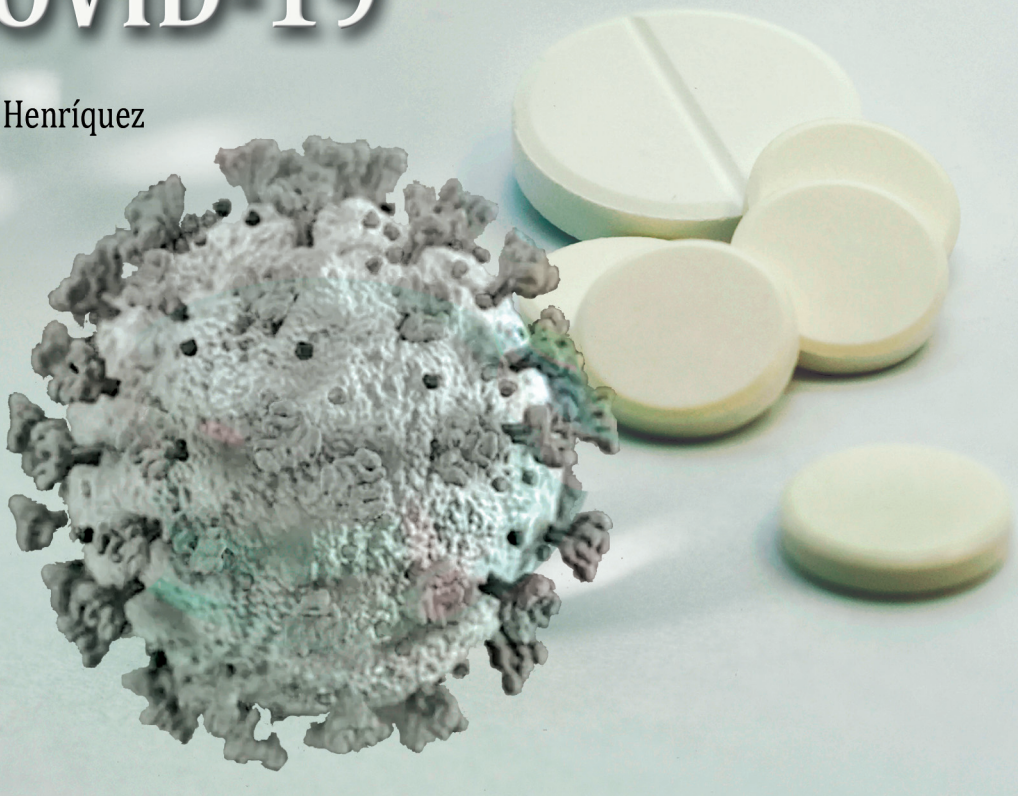

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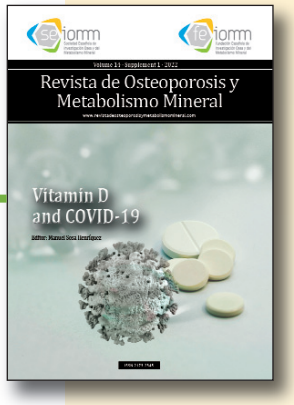

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Vitamin D Update

Sosa Henríquez M
Editor

Vitamin D is recently in the news. Until not many years ago, it was almost exclusively related to bone mineralization. However, the increasingly widespread knowledge that the actions of vitamin D extend to practically all our body cells has led to the discovery and research into the so-called "extra-osseous effects of vitamin D." This research is increasing and becoming better known[1-8]. In fact, vitamin D should be termed hormone D, since its structure, functioning, control and self-regulation mechanisms are more typical of a hormone than a vitamin[9].

Precisely one of these extra-osseous effects is the direct relationship of hormone D with the functioning of the cells responsible for the body's immunity. Thus, low levels of vitamin D have been associated with a higher prevalence of infections and autoimmune diseases and adequate levels have been related to a better clinical course of infectious diseases[1,10,11].

There is a certain ambiguity prevails concerning vitamin D. It is spoken of in general terms and its different metabolites, cholecalciferol, calcifediol and calcitriol are treated indistinctly, calling them all "vitamin D", seeming equivalent and similar in terms of potency or toxicity, which is not true

The whole world is immersed in the COVID-19 pandemic. This has brought about profound changes in both the social sector and, of course, in health care. We have not yet overcome it completely, although everything indicates that, at the time of this writing (October 2021), we are close to overcoming at least its worst stage, thanks to the greater knowledge of the disease and, above all, to the development of vaccines.

In this sense, Dr. Olmos Martínez's article, which opens this supplement, offers a masterful overview of the changes that this pandemic has engendered at all levels, especially in the health sphere. Next, Professor del Pino Montes analyzes the mechanisms by which vitamin D exerts its action in the immune system and, therefore, in close relation to infections. Subsequently, Dr. Hernández Hernández reviews the association between vitamin D and COVID-19 infection, which he does with the authority of having published a study carried out by his working group in the Journal of Clinical Endocrinology and Metabolism[12] which was the most read and cited journal article in 2020. Finally, Dr. Gómez de Tejada describes those documents and guides prepared by some scientific societies and institutions in which they reflect on the need of having and obtaining adequate levels of vitamin D to prevent and treat COVID-19.

However, a certain ambiguity prevails concerning vitamin D. It is spoken of in general terms and its different metabolites, cholecalciferol, calcifediol and calcitriol are treated indistinctly, calling them all "vitamin D", seeming equivalent and similar in terms of potency or toxicity, which is not true[13]. On the one hand, cholecalciferol is the most widely used molecule in the vast majority of clinical trials in which vitamin D has been used as a treatment[14]. In virtually all randomized clinical trials comparing drugs that reduce fracture risk, both the treated and control groups received cholecalciferol. Not one of these trials used calcifediol or calcitriol[15]. Therefore, the clinical evidence goes hand in hand with cholecalciferol.

Furthermore, these molecules do not have the same potency. Calcitriol is so powerful and entails a risk of hypercalcaemia, that its indications approved by the Spanish Agency for Medicines and Health Products (AEMPS) are very scarce, and, in addition, it requires medical inspection approval. Calcifediol is more potent than cholecalciferol and although it does not require inspection, the AEMPS published an alert due to some reported cases of overdose and hypercalcaemia[16]. These side effects, however, do not appear with cholecalciferol.

To sum up, I consider that this collection of articles is of great interest because it deals with a very current topic such as vitamin D in preventing and treating COVID-19, which will help clinicians to gain a better understanding of this broad, complex world of vitamin D.

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Bibliography

1. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-A review of recent evidence. Autoimmun Rev. [2013;12(10):976–89.
2. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev. 2005;26(5):662-87.
3. Dhesi JK, Jackson SHD, Bearne LM, Moniz C, Hurley M V, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing. 2004;33(6): 589-95.
4. Bolland MJ, Avenell A. Do Vitamin D supplements help prevent respiratory tract infections? BMJ. 2017;356:1-2.
5. Quesada Gómez JM, Sosa Henríquez M. Vitamina D: Vitamina D: Más allá del tratamiento de la osteoporosis. Rev Clin Esp. 2008;208(4):173-4.
6. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009;94(1): 26-34.
7. Norman PE, Powell JT. Vitamin D and cardiovascular disease. Circ Res. 2014; 114(2):379-93.
8. Gómez de Tejada Romero M, Sosa-Henríquez M. Acciones extraóseas de la vitamina D. Rev Osteoporos Metab Min. 2014;6(Supl1):11-8.
9. Norman AW. From vitamin D to hormone D: Fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr. 2008;88(2): 491s-499s.
10. DD B. Extra-skeletal actions of vitamin D. Ann New York Acad Sci. 2016;1376: 29-52.
11. Martineau A, Jolliffe D, Hooper R, Greenberg L, Aloia J, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of individual participant data. Thorax 2016; 71(Suppl 3):A60.2-A61.
12. Hernández JL, Nan D, Fernandez-Ayala M, Garciá-Unzueta M, Hernández-Hernández MA, López-Hoyos M, et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. J Clin Endocrinol Metab. 2021;106(3): E1343-53.
13. Navarro-Valverde C, Sosa-Henríquez M, Alhambra-Expósito MR, Quesada-Gómez JM. Vitamin D3 and calcidiol are not equipotent. J Steroid Biochem Mol Biol. 2016;164(2015):205-8.
14. Sosa-Henríquez M, Gómez de Tejada Romero M. La vitamina D en el siglo XXI. Más allá de la osteoporosis. Rev Osteoporos y Metab Miner 2017;9 (Supl 1):3-4.
15. Sosa-Henríquez M G de TRM. N-1-145 - Tratamiento de la Osteoporosis. Medicine 2014;11(60):3545-54.
16. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Vitamina D: casos graves de hipercalcemia por sobredosificación en pacientes adultos y en pediatría. Agencia Española Medicamentos y Productos Sanitarios 2019;Marzo:1-6. Disponible en: http://www.conaf.cl/cms/editorweb/ENCCRV/Nota-Informativa-24.pdf.

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SARS-CoV-2 infection and medical practice

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In January 2020, when a group of researchers from the Chinese province of Wuhan published the outbreak caused by a novel corona virus, few of us imagined the storm that was looming[1]. The experience of epidemic outbreaks due to emerging viral infections that have occurred worldwide in the past twenty years should have warned us that something like this could happen[2-4]. But even the very serious situation of the Ebola virus outbreak in West Africa in 2014 did not alert us, until just a few tragic cases spread across borders, set off alarm bells in Europe[5]. But it seems more incomprehensible that, with the appearance of new viruses of zoonotic origin, such as SARS-CoV-1, MERS, avian influenza viruses (H5N1 and H7N9), or the 2009-H1N1 influenza virus that caused the first pandemic of the XXI century, in the year 2020 we were still ignoring the impending dangers[6].

Just three days after its description, the new agent causing SARS reached Thailand and later the rest of the world. Thus, it was evident that, with globalization, geographical barriers to prevent the spread of biological agents had also collapsed. Two months later the infection broke out in the Italian region of Lombardy, but this did not alarm us either. When this tsunami finally reached Spain, the infection was already difficult to contain. As with natural phenomena, the impact was not felt the same in all regions of our country.

In Cantabria, perhaps due to climate, but also its geoeconomic and social characteristics, the impact was not as violent as in other regions. In any case, more than 400 patients were admitted to Cantabrian hospitals in just two weeks, affected by a syndrome hitherto unknown, even by the most veteran doctors.

The Marqués de Valdecilla University Hospital (MVUH) had designed several containment lines, as barriers to a disaster that was already very close at that time. A plant (equipped with 24 beds) and later another one were enabled to treat these patients. The care of these patients fell on the Departments of Pneumology, Infectious Diseases and Internal Medicine (IMS).

As of mid-March 2020, there were more than 40 patients with SARS-CoV-2 infection admitted to ICU beds. In addition, over the next 7-10 days, the more than 100 non-COVID patients who were admitted to our usual wards at that time were discharged or transferred, in order to be able to use those beds for care. of patients admitted with a confirmed or suspected diagnosis of COVID-19. Initially, the beds on the three Internal Medicine floors were occupied, but a few days later it became necessary to relocate the patients from the floors of other services, to convert them into "COVID floors". Therefore, in the course of a few days, the IMS was completely transformed into a "COVID Service", serving patients who occupied 100% of the available beds on 5 floors of our Hospital (around 200 beds).

All this effort was carried out with the invaluable collaboration of the Admissions Service and all the MVUH nursing staff, which allowed these changes to be made with sufficient agility and efficiency.

In moments of crisis, it is when the seams of an institution come into sharper focus, and just then, our hospital's best asset came out, its human capital. Our IMS, integrated into the new COVID structure, could not assume the enormous burden of care that was arriving, also taking into account that in the first weeks several doctors in our department were infected with SARS-CoV-2 and some of them required hospitalization. hospitable. Then, doctors from other services joined our wards to collaborate in the care of these patients.

It should also be remembered that, during this health emergency, the resident doctors assumed a leading role in containing this avalanche, amply demonstrating the excellent training received and their commendable professionalism. The most novice residents formed pairs with the staff doctors, facilitating the work and mutual security. Not forgetting the nursing staff who showed admirable professionalism and dedication.

We attend dramatic situations from the medical and human point of view. The loneliness of the patients and the impossibility of being surrounded by their relatives in the most difficult moments was one of the most difficult circumstances to bear for the patients, but also for the professionals who cared for them. Therefore, the satisfactory evolution and especially the medical discharge was lived with cheers, and these happy moments helped to mitigate individual tragedies.

Another aspect of care, which is currently of special interest, is the toll that, in terms of morbidity and mortality, patients affected by other diseases had to pay due to the pandemic caused by this new coronavirus.The lower frequency of hospital attendance stimulated by the advice of the health authorities, as well as the fear of

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contagion, the suspension of face-to-face consultations, the delay in diagnostic tests, the blocking of Primary Care or even the modification of perfectly validated protocols in other disorders –in relation to the risk of transmission–, they had collateral effects that we should assess and, as far as possible, improve.

Attention was also restructured in the External Consultations area, reducing face-to-face consultations as much as possible, without canceling the highest priority. The telephone consultations were kept open and once the outbreak was controlled, the usual assistance activity was resumed.

The reviews were mostly carried out remotely, through telephone consultations. The days before, the administrative office of the consultation, contacted patients to inform them that the consultation would be carried out by phone, unless there was some circumstance that did not make it advisable. In this way, during the months of March and April 2020, approximately 50% of the first consultations (all face-to-face) that are usually carried out in our service and more than 70% of the revisions (the majority not face-to-face) were carried out.

Another area that had to be reinforced was continuous care (medical shifts), which were expanded. In addition, the care of patients admitted to our plants was maintained during weekends and holidays, thanks to the fact that a significant part of the professionals who usually cared for these patients came to work in the morning.

This meant an extra effort for the doctors and nursing staff, who were forced to spend many hours in the hospital, with little physical or emotional rest.

The IMS teaching plan also had to be modified during the epidemic outbreak, prioritizing safety over training objectives. Thus, the practices of the Medicine students had to be suspended, although other non-delayed activities, such as theoretical classes or evaluations, continued in a non-face-to-face way.

The MIR (Spanish graduate medical) training was also altered, so that teaching aims had to be modified, prioritizing care of the patients who were arriving and designing new goals in relation to the care of the patient with COVID-19. However, the MIR group also felt that this was a historic opportunity to be part of the health response to a challenge of enormous magnitude.

Finally, continuing face-to-face training was suspended, which was an opportunity to develop other non-face-to-face training modalities, such as online sessions through different platforms (Zoom, Teams) or online seminars (webinars) that various scientific societies, such as the Spanish Society of Internal Medicine (SEMI), the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) and official organizations organized expressly and in which some members of our service participated.

Another noteworthy aspect was the role played by the SMI in research during the COVID-19[7-12] challenge. In this sense, our department led a study on the role of vitamin D in SARS-CoV-2 disease, which had significant scientific and media coverage, and in which we found a high prevalence of vitamin D deficiency in our patients hospitalized for COVID-19[12].

But in this environment of global improvement, some things could also have been done better. The COVID-19 infection in our department left the highest cumulative incidence of SARS-CoV-2 infection cases in the MVUH, with a severe case of bilateral pneumonia, which fortunately resolved after several days of admission and uncertainty. Once again, the slow response to a global threat with the virtual absence of a structural infection prevention plan for healthcare personnel, the late distribution of personal protective equipment (PPE) that arrived by the dropper, the error in Initial Public Health strategy on the restrictive application of diagnostic tests –contrary to WHO recommendations– and surely also a lack of risk perception in the first moments of our own health group, participated in this intolerable number of infected colleagues.

In conclusion, in these lines I have tried to describe the events and sensations that the ICU of our hospital experienced during the first wave of the pandemic. Later other waves have come (we are currently overcoming the 5th), the restrictions, the curfew, mass vaccination, the goodbye to the mandatory mask on the streets and other contradictory messages, but that is another story.

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Bibliography

1. Chen N, Zhou M, Dong X, Qu J, Gong F, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513.
2. Nash D, Mostashari F, Fine A, Miller J, O'Leary D, Murray K, et al. The outbreak of West Nile virus infection in the New York City area in 1999. N Engl J Med. 2001;344:1807-1814.
3. Autochthonous transmission of dengue virus in EU/EEA, 2010-2020 (www.ecdc.eureoa.eu.).
4. Chikungunya situación en las Americas. Organización Panamericana de la Salud 2014.www.paho.org/ Zika strategic response plan 2016. WHO.int.
5. Ebola Outbreak in West Africa 2014-2016 www.CDC.gov.
6. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360:2605-2615.
7. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, et al.; GLUCOCOVID investigators. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: An open-label randomized trial (GLUCOCOVID). Wien Klin Wochenschr. 2021;133:303-311.
8. Cuadrado-Lavín A, Olmos JM, Cifrian JM, Gimenez T, Gandarillas MA, García-Saiz M, et al. Controlled, double-blind, randomized trial to assess the efficacy and safety of hydroxychloroquine chemoprophylaxis in SARS CoV2 infection in healthcare personnel in the hospital setting: A structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21:472.
9. Pardo Lledias J, Ayarza L, González-García P, Salmón González Z, Calvo Montes J, Gozalo Marguello M, et al. Repetición de las pruebas microbiológicas en la sospecha de la infección por SARS-CoV-2: utilidad de un score basado en la probabilidad clínica. Rev Esp Quimioter. 2020;33:410-414.
10. Armiñanzas C, Arnaiz de Las Revillas F, Gutiérrez Cuadra M, Arnaiz A, Fernández Sampedro M, González-Rico C, et al. Usefulness of the COVID-GRAM and CURB-65 scores for predicting severity in patients with COVID-19. Int J Infect Dis. 2021;108:282-288.
11. San Segundo D, Arnáiz de las Revillas F, Lamadrid-Perojo P, Comins-Boo A, González-Rico C, Alonso-Peña M, et al. Innate and Adaptive Immune Assessment at Admission to Predict Clinical Outcome in COVID-19 Patients. Biomedicines. 2021,9:917.
12. Hernández JL, Nan D, Fernandez-Ayala M, García-Unzueta M, Hernández-Hernández MA, López-Hoyos M, et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. J Clin Endocrinol Metab. 2021;106: e1343-e1353.

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Infection, immunity and vitamin D

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The vitamin D system has extraskeletal pleiotropic functions, including the modulation of the adaptive immune response and the enhancement of the innate response[1-3]. This explains why vitamin D influence on infections has been the subject of many analyses. The implication of vitamin D deficiency in tuberculosis has been known for decades. But it has also been associated with other infections, mainly respiratory tract infections and others such as the flu, exacerbations of chronic obstructive pulmonary disease or cystic fibrosis, sepsis or human immunodeficiency virus infection. More recently, there has been interest in knowing its influence on the pathogenesis and possible therapeutic use in SARS-CoV-2 infection[4]. In this article we will review the role of vitamin D in the immune system and its influence on infectious diseases.

As is well known, the biological function of vitamin D depends mainly on its active form 1,25(OH)2D or calcitriol. Binding to the intracellular vitamin D receptor (VDR) induces the expression of target genes. This receptor is present in numerous cells, including a large part of the cells of the immune system. The synthesis of calcitriol requires two steps of hydroxylation of vitamin D3 or cholecalciferol. The first in the liver, where it is transformed into 25(OH)D, calcidiol or calcifediol, and hydroxylation in the 1-alpha position in the kidney to obtain the definitive calcitriol[5].

Relationship between vitamin D and innate immunity

The immune response to the presence of a pathogen requires a rapid response and the innate immune system provides resources to intervene in barriers such as mucosa or skin. Calcitriol enhances innate immune reactions by inducing the transcription of genes that encode proteins with destructive capacity of bacteria, viruses and fungi.

Some immune cells such as macrophages, dendritic cells and cells of the bronchial and pulmonary mucosa have transmembrane "toll-like" receptors (TLR) and recognize the "molecular patterns associated with pathogens" that are part of the structure of infectious agents. This is the starting point for various cell signaling pathways that facilitate the synthesis of cytokines, chemokines, recognition receptors and the so-called "antimicrobial peptides" that have the ability to destroy pathogens. This response increases the competence of both immune cells in their anti-infective action[5]. On the other hand, cells of the adaptive system are activated[1].

This response is magnified by calcitriol, since one of the consequences of TLR activation is the increase in VDR expression. The VDR-calcitriol bond translocates to the cell nucleus where it binds to the retinoic acid receptor and promotes the transcription of genes such as catechillin and several defensins in cells of the immune system and respiratory endothelial surfaces. These are antimicrobial peptides, crucial in protecting this gateway[6].

Modulation of adaptive immunity by vitamin D

Calcitriol acts at different levels endocrine, paracrine and intracrine. As a whole, it decreases Th1 and Th17 responses, increases Th2 and Th8 while promoting T-reg. The result is an anti-inflammatory effect[5].

In a first step, it regulates the Th1 response by inhibiting the production of type 1 proinflammatory cytokines such as IL-12, INF-gamma IL6, IL8, TNF-alpha and IL9. On the contrary, it increases the Th2 response and its production of anti-inflammatory cytokines such as IL4, IL5 and IL10. This regulation of cytokines is mediated by the blockade of NF-Kappa B activation. It induces a change in the polarization of macrophages, passing from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype. It inhibits dendritic cell differentiation by reducing the expression of MHC class 2 molecules, costimulation molecules, and increasing IL12. In this way, by preventing the maturation of dendritic cells, autoimmunity is prevented and immunological tolerance is promoted. Antigen presentation by immature dendritic cells impairs the immune response and induces tolerance.

Concerning B cells, calcitriol inhibits differentiation, proliferation and promotes apoptosis[6].

The global effect of vitamin D as a modulator of the immune system is mainly anti-inflammatory and helps prevent autoimmunity[2].

Infection and vitamin D

If vitamin D participates in this way on the immune system, it is logical to think that its deficiency can limit the defenses against infectious agents[3]. This hypothesis is supported by many epidemiological studies. Studies have focused mainly on respiratory infections (cold, acute respiratory infections, tuberculosis) and viral infections (flu, HIV infection, hepatitis B virus infection, as well as coronavirus infection). See table 1[7].

In an intuitive way, it is easy to associate the nadir of vitamin D levels, during the winter, with the increase in the incidence of influenza and respiratory infections. This hypothesis has been evaluated in various studies, finding an association between vitamin D deficiency and influenza. The influenza virus survives better in environmental conditions of low exposure to ultraviolet light, temperature and humidity. But when attenuated virus has been inoculated into healthy volunteers, the appearance of clinical manifestations is more frequent when

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Table 1. Effect of vitamin D and proposed pathophysiological mechanisms

Infection	Vitamin D effect	Mechanism of action
Flu	Epidemiological studies: relationship between low levels and infection. Treatment (supplementation): possible preventive effect. Conflicting results.	- Enhancement of innate immunity by increasing defensins.
Tuberculosis	Epidemiological studies: relationship between low levels and presence of infection and worse prognosis. Treatment (supplementation): not curative but reduces sputum negativization time.	- Enhancement of innate immunity with increased production of cathelicidin.
Infections acute respiratory	Epidemiological studies: optimal levels prevent the infection. Treatment (supplementation): prevents infections especially in children and young adults.	- Enhancement of innate immunity. Increase defensins in cells of the immune system and of the respiratory epithelium.
HIV	Epidemiological studies: deficit levels are associated an increase in opportunistic infections and a decrease of survival.	- Blockade of calcitriol production by high rate of TNF-alpha. - Enhancement of innate immunity.
COVID19	Epidemiological studies: deficit levels are associated at higher risk of infection. Treatment: probable therapeutic effect improving the prognosis. Preliminary results and pre-print.	- Increased defensins (innate immunity). - Down regulation of the renin-angiotensin system. - Decrease oxidative stress.

it is done in winter and in subjects with poorer vitamin D status[8]. Protection against the influenza virus is related to an action that enhances innate immunity, increasing the production of defensins by cells of the immune system and the respiratory epithelium.

A clear relationship between vitamin D deficiency and the prevalence of tuberculosis or its activity has been confirmed. Mycobacterium tuberculosis has an affinity for the "toll-like" receptors of macrophages, vitamin D would reduce its capacity for growth and replication by increasing the production of cathelicidin by macrophages. From a clinical point of view, recent data indicate that low concentrations of vitamin D would be more of a risk factor than the cause of infection. Supplementation does not manage to cure the active infection, but it can reduce the inflammatory load and improve anthropometric aspects that will help the patient in long-term recovery[9]. In a recent meta-analysis, 8 clinical trials with more than 1,750 patients suffering from active pulmonary tuberculosis and who received, in addition to anti-tuberculous treatment, different vitamin D supplementation regimens were evaluated. In all of them cholecalciferol was used as a form of vitamin D for supplementation in tuberculosis. Negativization of sputum was more frequent among those who received vitamin D. Among other beneficial effects, they found an improvement in lymphocyte count and recovery on chest X-ray[10].

Many studies explore the link with upper respiratory tract infections, which would be consistent in view of its involvement in innate immunity and cellular response in the endothelium of the respiratory tract. Epidemiological data on the status of the vitamin D system and these infections are available, as well as studies on their prevention with different supplementation regimens or higher therapeutic doses[11].

Among the epidemiological studies, a survey carried out in the United Kingdom of almost 20,000 people over 12 years of age should be highlighted. More history of recent respiratory infections was detected in individuals with lower concentrations of 25(OH)VD. After adjusting for confounding factors, the chance of having had an infection was higher when vitamin levels were 10 ng/ml or less when compared to optimal levels[12]. This association is even stronger in certain risk groups such as asthmatics or chronic obstructive pulmonary disease. Similar results are found in various cohorts from various countries, especially from the Anglo-Saxon environment. When hospital data is assessed, it is also reported that hospitalizations for influenza are longer and with a worse prognosis if there is a deficit of 25(OH)VD[9].

To answer the question of whether acute respiratory infections can be prevented with vitamin D supplementation, there are numerous studies available, including some randomized clinical trials versus placebo. In a systematic review that evaluated 30 articles, positive results were only found in a few, especially those that included young patients and healthy adults. The best results have been seen with doses of 400 to 2,000 IU daily. Prevention in school-age children is also effective. It does not prevent respiratory infections in newborns when supplementation is administered to pregnant women.

In patients with previous pulmonary involvement, such as adults with COPD, favorable results are only seen in patients with deficient levels of 25(OH)VD. However, for adults with cystic fibrosis given a single dose of 250,000 IU of vitamin D3, hospitalizations are reduced over the following year[13].

Children are a particularly susceptible population for respiratory infections. In a clinical trial that included children between 3 and 12 months of age, it was found

that the use of high doses of vitamin D (1,200 IU/day) for 4 months had a greater preventive effect on the appearance of influenza A than doses low vitamin D (400IU/day) (26% vs 46%). This article shows that to achieve greater efficacy, higher doses of vitamin D are needed. These high doses seem safe because the adverse effects were not different between the two groups and there were no pharmacological toxicity problems[14].

A meta-analysis has recently been published that includes 46 clinical trials and more than 75,000 patients. In the assessment of the global effect on the reduction of upper respiratory tract infections, a positive effect of vitamin D supplementation was found. The result has a significant difference, although it is of little magnitude (1-2%). One of the limitations they point out is the great heterogeneity of the studies in terms of age, dose of vitamin D, duration of treatment, study follow-up time. However, the authors conclude that daily doses of 400-1,000 IU for 12 months are the most beneficial[15].

It has also been tested on other infections. Supplementation does not modify the frequency or evolution of pneumonia. In the case of some viruses, such as the human immunodeficiency virus, deficient levels of vitamin D are linked to an increase in opportunistic infections and a decrease in survival. In these patients, the high inflammatory load at the expense of TNF-alpha would interfere with the production of 1,25(OH)D, blocking PTH. In patients with hepatitis B virus infection, the prevalence of failure is very high. Lower levels correlate strongly with increased viral load and poor progression to cirrhosis. Two meta-analyses that include nearly 10,000 patients agree that low concentrations of 25(OH)VD increase susceptibility to serious infections, sepsis, and increase mortality[9].

In summary and taking into account all the data, several authors point out that concentrations of 30 ng/ml can be considered effective in preventing infections, especially respiratory ones. Levels above 40 ng/ml do not appear to provide additional benefit. Levels below 20 ng/ml are associated with a higher risk of infections. The safety of supplementation is confirmed in numerous studies. As very infrequent adverse effects, some hypercalcaemia has been reported with no known subsequent complications[7,9,15].

Vitamin D and COVID-19

The literature generated in relation to COVID-19 and possible treatments is enormous. Unfortunately, a pharmacological measure against SARS-CoV-2 is not yet available. Much has been written about the role of vitamin D since, in addition to its influence on the immune system and the response of respiratory cells, there is the fact that vitamin D inhibits the expression of the renin-angiotensin-aldosterone system. In COVID-19, there is a dysregulation of the system with a predominance of angiotensin, which can favor the serious complications of the disease. In addition, vitamin D also reduces thromboembolic events associated with this infection. The anticoagulant effect is achieved by increased expression of anticoagulant glycoproteins, such as defensins, and decreased synthesis of factors essential for coagulation, inhibition of the renin-angiotensin system, and induction of angiotensin-converting enzyme type 2 receptors. An additional effect would be the role it has in reducing the oxidative stress that appears in the infection, downregulating the expression of glutathione[8].

Epidemiological data offer a clear relationship between low levels of 25(OH)D and SARS-CoV-2 infection. In a recent meta-analysis, low levels are associated with an increased risk of infection (OR 1.64) and severity (OR 2.58), but it has not been seen to influence mortality. Some authors propose a new hypothesis to explain this situation and consider the possibility that 25(OH)D is a negative marker of the severity of inflammation. This decrease has been observed in other processes with high inflammation[16].

The use of vitamin D, in the form of supplementation or in higher doses, has been used in clinical trials. The results are variable and do not exceed the results obtained with other drugs such as dexamethasone or tocilizumab. However, given the frequency of low levels in the population at greatest risk, its use is recommended in many protocols considering the few side effects and the cost.

In summary, vitamin D has an immunomodulatory role in the immune system, enhancing innate immunity and the response of the respiratory epithelium to pathogens. Its deficit is associated with an increase in infections, such as tuberculosis, influenza, human immunodeficiency or COVID-19, and its correction has a beneficial preventive effect, especially evident in upper respiratory infections.

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Bibliography

1. Martens P, Gysemans C, Verstuyf A, Mathieu AC. Vitamin D's Effect on Immune Function. Nutrients [Internet]. 2020 Apr 28;12(5):1-22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32353972.
2. Gómez de Tejada Romero M. J. Acciones extraóseas de la vitamina D. Rev Osteoporos Metab Min. 2014;6(Supl 1):11-8.
3. Quesada Gómez JM, Sosa Henríquez M. Vitamina D: Más allá del tratamiento de la osteoporosis. Rev Clin Esp. 2008;208(4):173-4.
4. Bui L, Zhu Z, Hawkins S, Cortez-Resendiz A, Bellon A. Vitamin D regulation of the immune system and its implications for COVID-19: A mini review. SAGE open Med [Internet]. 2021;9:20503121211014070. Available from: http://www.ncbi.nlm.nih. gov/pubmed/34046177.
5. Güerri Fernández RC, Díez Pérez A, Mellibovsky Saidler L, Quesada Gómez JM. [Vitamin D as immunity element against infection]. Med Clin (Barc) [Internet]. 2009 Sep 12;133(9):344-8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19285323.
6. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol [Internet]. 2014;5:151. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24795646.
7. Lang PO, Aspinall R. Vitamin D Status and the Host Resistance to Infections: What It Is Currently (Not) Understood. Clin Ther [Internet]. 2017 May;39(5):930-45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28457494.
8. Taha R, Abureesh S, Alghamdi S, Hassan RY, Cheikh MM, Bagabir RA, et al. The relationship between vitamin d and infections including covid-19: Any hopes? Int J Gen Med. 2021;14:3849-70.
9. Kearns MD, Alvarez JA, Seidel N, Tangpricha V. Impact of vitamin D on infectious disease. Am J Med Sci [Internet]. 2015 Mar; 349(3):245–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25334038.
10. Wu H xia, Xiong X feng, Zhu M, Wei J, Zhuo K quan, Cheng D yun. Effects of vitamin D supplementation on the outcomes of patients with pulmonary tuberculosis: A systematic review and meta-analysis. BMC Pulm Med. 2018;18(1):1-12.
11. Bolland MJ, Avenell A. Do Vitamin D supplements help prevent respiratory tract infections? BMJ. 2017;356:1-2.
12. Ginde AA, Mansbach JM, Camargo CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med [Internet]. 2009 Feb 23;169(4):384-90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19237723.
13. Grossmann RE, Zughaier SM, Kumari M, Seydafkan S, Lyles RH, Liu S, et al. Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation A randomized, controlled trial. Dermatoendocrinol. 2012 1;4:191-197.
14. Zhou J, Du J, Huang L, Wang Y, Shi Y, Lin H. Preventive effects of Vitamin D on seasonal influenza a in infants: A multicenter, randomized, open, controlled clinical trial. Pediatr Infect Dis J. 2018;37(8):749-54.
15. Jolliffe DA, Camargo CA, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. lancet Diabetes Endocrinol [Internet]. 2021;9(5):276–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/ 33798465.
16. Bandeira L, Lazaretti-Castro M, Binkley N. Clinical aspects of SARS-CoV-2 infection and vitamin D : COVID-19 and the endocrine system: special issue for reviews in endocrine and metabolic disorders (Felipe Casaneuva, Editor in Chief) A. Giustina and JP Bilezikian, Guest Editors. Rev Endocr Metab Disord [Internet]. 2021 Sep 24; Available from: http://www.ncbi.nlm.nih.gov/pubmed/34559361.
17. Kaya MO, Pamukçu E, Yakar B. The role of vitamin D deficiency on the Covid-19: A systematic review and meta-analysis of observational studies. Epidemiol Health [Internet]. 2021 Sep 23;e2021074. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34607398.

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Vitamin D Supplements in COVID-19

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Vitamin D is a fundamental hormone for the maintenance of musculoskeletal health and the proper functioning of the immune system[1]. The new coronavirus pandemic, SARS-CoV-2, which emerged in Wuhan at the end of 2019, has hit the world with extraordinary virulence[2]. Several lines of evidence support a potential role for vitamin D in COVID-19. First, a recent meta-analysis has shown a beneficial effect of vitamin D in preventing viral respiratory diseases, especially in those subjects with greater deficiency of this hormone[3]. In addition, vitamin D is crucial in modulating the innate immune system (production of antimicrobial peptides such as cathelicidin and activation of autophagy) and adaptive (inhibition of the activation of Th1 lymphocytes, activation of Th2 lymphocytes, decrease of cells Th17/Treg and inhibition of the proliferation and differentiation of B lymphocytes). Vitamin D deficiency is especially conspicuous in the elderly, in obese individuals and those with chronic diseases such as cancer, diabetes or cardiovascular diseases, which also represent the groups with the highest severity of COVID-19. Finally, vitamin D inhibits proinflammatory cytokine production and its deficiency can induce activation of the renin-angiotensin system (RAS), leading to the production of profibrotic factors and lung damage. This dysregulation of the RAS in COVID-19, mediated by the ACE2 receptor, through which SARS-CoV-2 penetrates the host cell, is responsible for the cytokine storm that precedes the characteristic acute respiratory distress syndrome. of the most serious form of infection by this coronavirus[4].

In this sense, although the studies published to date are heterogeneous in terms of methodology, sample size, inclusion criteria, ethnicity, geographic factors, criteria for defining COVID-19 severity and statistical analysis, the results of the meta-analyses and systematic reviews indicate a significant relationship between vitamin D deficiency and increased risk of SARS-CoV-2 infection and greater severity and mortality of COVID-19[5-10].

The aim of this brief review is to analyze the published works on the potential effect of vitamin D administration (without combination with other nutritional or vitamin supplements) in patients with COVID-19. A PubMed/MEDLINE database search was carried out up to August 1, 2021, using the key terms and operators "COVID-19" OR "SARS-CoV-2" AND "vitamin D supplementation". Observational studies and clinical trials were included, regardless of their design.

Vitamin D in the treatment of COVID-19

Observational studies and clinical trials

Table 1 summarizes the published studies on the use of vitamin D supplements in patients with COVID19[4,11-25]. As can be seen, the studies have been mainly of a prospective and retrospective observational design, in varied populations (hospitalized patients, institutionalized patients), with a highly variable sample size and with a heterogeneous adjustment of the influence of the potential confounding variables on the primary objective. Most used cholecalciferol and three of them calcifediol. For the most part, data were not available on the time from the onset of symptoms of SARS-CoV-2 infection and the start of vitamin D supplementation, nor on baseline 25(OH)D levels or the degree of increase of these after treatment. In addition, the doses of vitamin D were varied considerably (between 25,000 and 400,000 IU) and the time of initiation was also diverse (at diagnosis, admission or in the first days of hospitalization). The therapeutic regimen was also very different between the available clinical studies. The main objectives most frequently analyzed were mortality and the need for admission to the Intensive Care Unit (ICU).

Among all these studies, the so-called GERIA[17] yields some interesting results on the preventive role that could be associated with vitamin D treatment prior to contracting the infection. The GERIA study is a retrospective study that was carried out in 3 groups of geriatric patients with COVID-19 with a poor prognosis. Group 1 included patients who had been supplemented with cholecalciferol during the year prior to the diagnosis of the infection. In group 2, patients supplemented with cholecalciferol a few hours after being diagnosed. Group 3 patients did not receive any supplementation. In conclusion, hospitalized frail elderly patients with COVID-19 who had received regular vitamin D3 supplementation for at least the year prior to COVID-19 diagnosis (50,000 IU/month, or 80,000 – 100,000 IU/2-3 months) presented a less severe COVID-19 and better survival rate. Aware that confirmatory studies are needed, the authors commented that vitamin D3 supplementation may represent an effective, accessible, and well-tolerated method of adjuvant treatment for COVID-19.

Meta-analysis and systematic reviews

Despite the heterogeneity of the studies published to date, the results of the meta-analyses, in general, show a trend towards a beneficial effect of vitamin D supplementation, in terms of reducing the severity of COVID-19 and especially in patients with deficiency of this vitamin[26]. However, in all of them it is pointed out that many unknowns remain to be resolved, especially regarding the type of supplementation, the dose, the most appropriate time of use and the duration of treatment with vitamin D.

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Recently, Pal et al.[27] carried out a systematic review and meta-analysis of 10 observational studies and 3 clinical trials, with a total of 2,933 patients with COVID-19. The most relevant finding of this study was that the improvement in the adverse events of the disease was only observed in the subgroup of patients who received the vitamin D supplement after the diagnosis of COVID-19, but not in those who had previously received it. Rawat et al.[28] carried out a systematic review of quasi-experimental studies and clinical trials only and found no relationship between vitamin D supplementation and the need for invasive ventilation, admission to the ICU or mortality in patients with COVID-19. In any case, they again point out that the aforementioned limitations of the different studies prevent solid conclusions. Clinical trials with uniform methodology need to be carried out with an adequate sample size to resolve this issue.

In the systematic review by Da Rocha et al.[29] only the 3 clinical trials were analyzed, concluding that the evidence for the use of vitamin D in COVID-19 is currently insufficient. Grove et al. reached the same conclusion in a systematic review that evaluated the effect of vitamin D supplementation and vitamin D levels on susceptibility to SARS-CoV-2 infection or COVID-19, including morbidity and mortality variables[30].

The recent review of the Cochrane collaboration[31] published in May 2021 analyzed several relevant aspects of the relationship between vitamin D supplementation and SARS-CoV-2 infection. According to this systematic review, only 2 studies with a total of 213 participants[11,12] compared the effect of vitamin D supplementation (cholecalciferol and calcidiol, respectively) versus placebo or standard treatment on all-cause mortality, in subjects with moderate or severe COVID-19, without finding a clear protective effect. Regarding the need for mechanical ventilation and the duration of admission in this same population, Murai et al.[12] showed a non-significant trend towards a benefit of cholecalciferol supplementation in the first case and no effect in terms of reduction of the average hospital stay. As already shown in table 1, Entrenas-Castillo et al.[11] observed a significant reduction in ICU admission with their calcifediol regimen, while Murai et al.[12] showed a non-significant trend towards the same beneficial effect with cholecalciferol. The authors of the review point out again the heterogeneity and the different methodology, type of supplement, guideline, etc., between the different works. Thus, they conclude that the evidence of a potential benefit of vitamin D supplementation in patients with COVID -19 is currently uncertain. Several clinical trials are underway that will make it possible to answer open questions regarding the usefulness of vitamin D supplementation both in the prevention and treatment of COVID-19 in different population groups (clinicaltrials.gov).

Conclusions

According to the data available to date, vitamin D supplementation could have a beneficial effect on the evolution of COVID-19, although the level of evidence from the studies is insufficient to draw solid conclusions in this regard. Severe COVID-19 particularly affects people at high risk of vitamin D deficiency (the elderly, institutionalized subjects, obese people and patients with comorbidities), so institutional policies aimed at achieving adequate levels of 25(OH) should be promoted. D in these populations. Pending ongoing clinical trials with adequate methodology, treatment with vitamin D supplements may be considered in patients with COVID-19 and vitamin D deficiency.

Table 1. Published studies on the use of vitamin D supplements in patients with COVID-19

Author (ref.)	Study type	N I/C	Age I/C	Target population (COVID-19)	Type vitamin D	Primary objective	Results	Adjustment by confounders	Notes
Entrenas-Castillo[11]	Trial pilot clinical, randomized, open, groups parallel, double masking	76 50/26	53±10	Hospital (pneumonia)	Calcifediol 0.532 mg day 0 and 0.266 mg days 3 and 7 and then weekly until discharge or ICU admission	Entry ICU	1/50 (2%) vs 13/26 (50%) OR 0.03 (0.003-0.25)	DM2, AHT	More AHT and DM in controls. Not double blind. Not able to assess mortality
Murai[12]	Clinical trial Random Multicenter double blind groups Parallel controlled with placebo	235 119/118	56±14/ 56±15	Hospital (moderate-severe)	200,000 UI cholecalciferol	Medium length stay Mortality	HR 1,07 (0.82-1.39) 9/119 (7.6%) vs 6/118 (5.1%)	Arthralgias, HBP, DM2, odynophagia, creatinine and PTH levels	Objective mortality prespecified secondary

Table 1. Published studies on the use of vitamin D supplements in patients with COVID-19 *(cont.)*

Author (ref.)	Study type	N I/C	Age I/C	Target population (COVID-19)	Type vitamin D	Primary objective	Results	Adjustment by confounders	Notes
Lakkireddy[13]	Clinical trial prospective, random, parallel groups, open	87 44/93	45±13	Hospital (slight-moderate)	Cholecalciferol 60,000 IU/day/8 days if IMC 18-25 Kg/m^2 or during 10 days if IMC >25 Kg/m^2	Mortality Inflammatory markers	2/44 (4.5%) vs 5/43 (11.6%) Reduced inflammatory markers	NE	Pilot study
Sabico[14]	Clinical trial random multicenter	73 35/38	54±12/ 46±15	Mild-moderate	5.000 vs 1.000 UI cholecalciferol over 14 days	Symptoms recovery time	Cough: 6.2±0.8 vs 9.1±0.8 (p=0.007) No sense of taste: 11.4±1 vs 16.9±1.7 (p=0.035)	Age, sex, BMI. D-dimer	Severe COVID-19 excluded Only included if 25OHD levels <50 nmol/l
Rastogi[15]	Clinical trial random controled with placebo	40 16/24	NE	Mild or asymptomatic	Cholecalciferol 60,000 IU/day/7 days and then weekly if 25OHD levels >50 ng/ml or 60,000 IU/day/ 7 more days if 25OHD levels <50 ng/ml	% viral RNA negativity Inflammatory markers	10/16 (62.5%) vs 5/24 (20.8%) (p=0.018)	NE	Utility in SARS-CoV2 RNA clearance Only includes subjects with baseline 25OHD levels <20ng/mL
Annweiler C[16]	Retrospective quasi-experimental	66 9/57	88±9/ 87±7	Nursing home	80,000 UI cholecalciferol in the month or week before diagnosis Mortality	Mortality	10/57 (17.5%) vs 5/9 (55.6%) HR 0,11 (0.03-0.48)	Age, sex, medications/ day, condition nutritional and functional, corticosteroids, HCQ, antibiotics, COVID-19 admission	Lower mortality in the group receiving cholecalciferol in the year before, but not after diagnosis

Table 1. Published studies on the use of vitamin D supplements in patients with COVID-19 *(cont.)*

Author (ref.)	Study type	N I/C	Age I/C	Target population (COVID-19)	Type vitamin D	Primary objective	Results	Adjustment by confounders	Notes
Annweiller G[17]	Quasi-experimental retrospective	77 Group (A): 29 Group (B): 16 Group (C) without vitamin D: 32	88 (85-92)	Unit acute geriatric	(A) 80,000-100,000 IU cholecalciferol/2-3 months or 50,000 IU/month in the previous year (B) 80,000 IU within a few hours of diagnosis	14-day mortality	(A) HR 0.07 (0.01-0.61) (B) 0.37 (0-06-2.21)	Age, sex, score of functional capacity, state nutritional, comorbidities, HbA1c, hospital treatment (corticosteroids, antibiotics, drugs for infection respiratory)	Different groups and different doses of vitamin D Mortality reduction only in group A but not in group B
Ling[18]	Transverse	Primary cohort (A): 444 Validation cohort (B): 542	74 (63-83) 76 (61-84)	SARS-CoV-2 + Hospital	(A) Cholecalciferol 40,000 IU/day/7 days at 200,000 IU every 2 weeks (B) 4,000IU/day to 50,000 IU weekly	Mortality	(A) OR 0.13 (0.05-0.35) (B) OR 0.38 (0.17-0.84)	Sex, BMI, race, DM2, 25OHD levels	Opportunistic sampling Not all had 25OHD levels
Giannini[19]	Retrospective cohort	91 36/55	73±13 74±13	Hospital	400,000 IU cholecalciferol (200,000 IU day 0 and 200,000 IU day 1)	ICU admission + Mortality	OR 0.45 (0.20-1.22)	Comorbidities, "propensity score"	Significant result when introducing in the model the "burden of comorbidities"
Jevalikar[20]	Transverse	197 128/69	45±18/ 49±15	Hospital	Cholecalciferol (mean dose of 60,000 IU)	ICU admission Mortality	16/128 (12.5%) vs 13/69 (18.8%) 1/128 (0.8%) vs 3/69 (4.3%)	NE	Includes 17 asymptomatic patients Patients with vitamin D deficiency (25OHD <20 ng/ml)
Hernández[4]	Retrospective case-control	216 19/197	60 (59-75)/61 (56-66)	Hospital (pneumonia)	Cholecalciferol 25,000 IU/month (n=10); 5600 IU/week (n=1) Calcifediol 0.266 mg/month (n=8)	ICU Mortality	1/19 (5.3%) vs 50/197 (25.4%) 2/19 (10.5%) vs 20/197 (10.4%)	Age, tobacco, hypertension, DM2, cardiovascular disease, BMI, calcium levels, filtered out glomerular, immunosuppression, month of determination of 25OHD	Small sample size different doses of vitamin D Significantly lower 25OHD levels in patients admissions vs controls population

Table 1. Published studies on the use of vitamin D supplements in patients with COVID-19 *(cont.)*

Author (ref.)	Study type	N I/C	Age I/C	Target population (COVID-19)	Type vitamin D	Primary objective	Results	Adjustment by confounders	Notes
Cereda[21]	Transverse	324 38/236	69±11/ 71±13	Disease Parkinson (n=105) Careprovi-ders (n=92) Hospital COVID+ (n=127)	Cholecalciferol 25,000 IU/month (800 IU/day in the previous 3 months)	Admissions Hospital mortality	OR 1.30 (0.51-3.32) OR 1.78 (0.69-4.91)	Age, sex, BMI, Parkinson, comorbidities	Not calculation sample size Possible selection bias
Lohia[22]	Multicenter retrospective	26/95 patients with 25OHD <20 ng/ml	64±15	4 Hospitals (COVID-19+)	Vitamin D (specific type not known)	ICU admission Mechanic ventilation Mortality	OR 0.96 (0.35-2.59) OR 0.68 (0.22-2.13) OR 0.86 (0.26-2.80)	Age, sex, BMI, comorbidities	No specified dose or duration of the supplement vitamin D
Alcalá-Díaz[23]	Multicenter re-trospective cohort	537 79/458	67±16 7 /69±15	Hospital (pneumonia)	Calcifediol 0.532 mg day 0 and 0.266 mg on days 3 and 7 then weekly until discharge or ICU admission	30-day mortality	4/79 (5.1%) vs 50/458 (19.6%) OR 0.16 (0.03-0.80)	Age, sex, tobacco, hospital, comorbidities, drugs	Non randomized No basal levels of 25OHD
Cangiano[24]	Prospective cohort	157 (98 COVID+)	89±7	Nursing home	Cholecalciferol 25,000 IU/15 days	Mortality	3/20 (15%) vs 39/78 (50%)	NE	Residents of a geriatric institution Duration of treatment not specified
Nogués[25]	Open cohort	838 447/391	62±16/ 62±17	Hospital (pneumonia)	Calcifediol 0.532 mg day 0 and 0.266 mg days 3, 7, 15 and 30	ICU admission Mortality	20/447 (4.5%) vs 82/391 (21%) OR 0.13 (0.07-0.23) 21/447 (4.7%) vs 62/391 (15.9%) OR 0.21 (0.10-0.43)	Age, sex, 25OHD levels, comorbidity	Non randomized, non placebo controlled

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Bibliography

1. Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020; 12(7):2097.
2. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;382:1199-1207.
3. Jolliffe DA, Camargo CA Jr, Sluyter JD. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021;9(5):276-292.
4. Hernández JL, Nan D, Fernandez-Ayala M, et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. J Clin Endocrinol Metab. 2021; 106(3):e1343-e1353.
5. Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. Int J Infect Dis. 2021; 104:58-64.
6. Teshome A, Adane A, Girma B, Mekonnen ZA. The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis. Front Public Health. 2021;9:624559.
7. Dramé M, Cofais C, Hentzien M, Proye E, Coulibaly PS, Demoustier-Tampère D, et al. Relation between Vitamin D and COVID-19 in Aged People: A Systematic Review. Nutrients. 2021; 13(4):1339.
8. Szarpak L, Rafique Z, Gasecka A, Chirico F, Gawel W, Hernik J, et al. A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19. Cardiol J. 2021;28 (5):647-654.
9. Wang Z, Joshi A, Leopold K, Jackson S, Christensen S, Nayfeh T, et al. Association of vitamin D deficiency with COVID-19 infection severity: Systematic review and meta-analysis. Clin Endocrinol (Oxf). 2021 Jun 23. doi: 10.1111/cen.14540. Epub ahead of print.
10. Sulli A, Gotelli E, Casabella A, Paolino S, Pizzorni C, Alessandri E, et al. Vitamin D and Lung Outcomes in Elderly COVID-19 Patients. Nutrients. 2021; 13(3):717.
11. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. J Steroid Biochem Mol Biol. 2020;203:105751.
12. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA. 2021;325:1053.
13. Lakkireddy M, Gadiga SG, Malathi RD, Karra ML, Raju ISSVPM, Ragini, et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. Sci Rep. 2021;11:10641.
14. Sabico S, Enani MA, Sheshah E, Aljohani NJ, Aldisi DA, Alotaibi NH, et al. Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with Mild to Moderate Covid-19: A Randomized Clinical Trial. Nutrients. 2021;13(7):2170.
15. Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). Postgrad Med J. 2020 Nov 12: postgradmedj-2020-139065. doi: 10.1136/postgradmedj-2020-139065. Epub ahead of print.
16. Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier JM, Lafaie L, Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. J Steroid Biochem Mol Biol. 2020;204:105771.
17. Annweiler G, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, et al. Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 Patients: The GERIA-COVID quasi-experimental study. Nutrients. 2020;12(11):3377.
18. Ling SF, Broad E, Murphy R, Pappachan JM, Pardesi-Newton S, Kong MF, et al. High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with COVID-19: a cross-sectional multicentre observational study. Nutrients. 2020;12:3799.
19. Giannini S, Passeri G, Tripepi G, Sella S, Fusaro M, Arcidiacono G, et al. Effectiveness of in-hospital cholecalciferol use on clinical outcomes in comorbid COVID-19 patients: a hypothesis-generating study. Nutrients. 2021;13:219.
20. Jevalikar G, Mithal A, Singh A, Sharma R, Farooqui KJ, Mahendru S, Dewan A, et al. Lack of association of baseline 25-hydroxyvitamin D levels with disease severity and mortality in Indian patients hospitalized for COVID-19. Sci Rep. 2021;11:6258.
21. Cereda E, Bogliolo L, Lobascio F, Barichella M, Zecchinelli AL, Pezzoli G, et al. Vitamin D supplementation and outcomes in coronavirus disease 2019 (COVID-19) patients from the outbreak area of Lombardy. Italy Nutrition. 2021;82:111055.
22. Lohia P, Nguyen P, Patel N, Kapur S. Exploring the link between vitamin D and clinical outcomes in COVID-19. Am J Physiol-Endocrinol Metab. 2021; 320:E520-E526.
23. Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R, Martin-Escalante MD, Cortes-Rodriguez B, Zambrana-Garcia JL, et al. Calcifediol treatment and hospital mortality due to COVID-19: a cohort study. Nutrients. 2021;13:1760.
24. Cangiano B, Fatti LM, Danesi L, Gazzano G, Croci M, Vitale G, et al. Mortality in an Italian nursing home during COVID-19 pandemic: correlation with gender, age, ADL, vitamin D supplementation, and limitations of the diagnostic tests. Aging. 2020;12:24522-24534.
25. Nogues X, Ovejero D, Pineda-Moncusí M, Bouillon R, Arenas D, Pascual J, et al. Calcifediol treatment and COVID-19-related outcomes. J Clin Endocrinol Metab. 2021 Jun 7:dgab405. doi: 10.1210/clinem/dgab405. Epub ahead of print.
26. Shah K, Saxena D, Mavalankar D. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. QJM. 2021 May 19;114(3):175-181.
27. Pal R, Banerjee M, Bhadada SK, Shetty AJ, Singh B, Vyas A. Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. J Endocrinol Invest. 2021 Jun 24:1-16. doi: 10.1007/s40618-021-01614-4. Epub ahead of print.
28. Rawat D, Roy A, Maitra S, Shankar V, Khanna P, Baidya DK. Vitamin D supplementation and COVID-19 treatment: A systematic review and meta-analysis. Diabetes Metab Syndr. 2021;15(4):102189.
29. da Rocha AP, Atallah AN, Aldrighi JM, Pires ALR, Dos Santos Puga ME, Pinto ACPN. Insufficient evidence for vitamin D use in COVID-19: A rapid systematic review. Int J Clin Pract. 2021 Jul 26:e14649. doi: 10.1111/ijcp.14649. Epub ahead of print.
30. Grove A, Osokogu O, Al-Khudairy L, Mehrabian A, Zanganeh M, Brown A, et al. Association between vitamin D supplementation or serum vitamin D level and susceptibility to SARS-CoV-2 infection or COVID-19 including clinical course, morbidity and mortality outcomes? A systematic review. BMJ Open. 2021;11(5):e043737.
31. Wieland LS. Vitamin D supplementation for the treatment of COVID-19: Summary of a living Cochrane review. Explore (NY). 2021;17(5):481-482.

Rev Osteoporos Metab Miner. 2022;14(Supl 1):S17-19

Guidelines and recommendations from scientific societies and health institutions on COVID-19 infection and vitamin D

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Introduction

The intervention of vitamin D in our immune system activity led to the study of this hormone's effect on SARS-CoV-2 infection from the start of the pandemic. Published studies have already been analyzed in other chapters of this special edition. Some societies and scientific and health institutions have considered this topic, and based on these reflections, offer recommendations to the health community. In this chapter, we present a brief overview.

Spanish Society for Bone Research and Mineral Metabolism (SEIOMM)

As a professional group concerned specifically with the study of bone metabolism and osteoporosis and, therefore, a national reference, a compulsory position document[1] was carried out into the current evidence regarding the role of vitamin D in the context of COVID-19. Published in December 2020, the expert document raised the following questions:

1. Is there a relationship between vitamin D deficiency and corona virus infection risk?
2. Is there a biological explanation for this association?
3. Can administration of vitamin D to deficient individuals prevent infection or alter its severity?
4. What is the risk/benefit ratio of its administration?

After analyzing the published studies and their results, the following responses were:

1. Although not all the data are uniform, there does seem to be a relationship, not necessarily causal, between vitamin D deficiency and the incidence and mortality from COVID-19.
2. Vitamin D can play a protective effect thanks to:
   - Maintaining the integrity of the epithelium.
   - Stimulation of the production of antimicrobial peptides.
   - Reducing the inflammatory response.
   - Modification of the relationship between ACE/ACE2 by increasing the expression of ACE2.
3. The evidence to indicate the administration of vitamin D in preventing or treating COVID-19 is scarce and presents many limitations. Experts indicate that, at this time, the threshold of vitamin D that must be reached to achieve the objective, the most suitable metabolite or the doses that must be used are unknown. Due to the lack of sufficient clinical evidence then, they refrain from recommendations in this regard.
4. Pending the publication of clinical trials that confirm or negate its usefulness, the risk/benefit ratio could be favorable to the use of vitamin D in compassionate use (off-label) in the prevention and treatment of COVID-19 in patients at risk, in which it might be reasonable to prevent or treat the deficiency, given the known beneficial effect on immunity and respiratory infections.

International League of Associations for Rheumatology (ILAR)

In April 2020, the International League of Associations for Rheumatology published a document[2] in which, from the point of view of the rheumatologist, potential targets for COVID-19 treatment were analyzed.

After a brief introduction to the epidemiology of the disease, the risk factors for severe COVID-19 and the clinical manifestations that can mimic other rheumatic diseases, the authors focus on potentially useful drugs for its treatment. Among them, they address treatment with vitamin D supplements. They deem it reasonable to think that vitamin D can boost immunity and help the body in its fight against COVID-19 and its aggressive effects on all organs and systems. Thus, in subjects with laboratory-confirmed vitamin D deficiency, particularly the elderly, obese, those with dark skin, and those living in high latitudes, treatment with high doses of vitamin D should be considered.

Given its protective effects, experts suggest that in subjects at risk with chronic diseases (cancer, cardiovas-

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cular disease, respiratory tract infections, diabetes and hypertension), vitamin D supplementation is associated with an increase in serum levels of 25(OH) vitamin D above 50 ng/ml (125 nmol/l) could substantially reduce the incidence and severity of COVID-19, although they note that more clinical trials and cohort studies are urgently needed to assess its efficacy (and the of other preventive and curative agents) before professional societies can make evidence-based recommendations.

National Institute for Health and Care Excellence (NICE)

The UK's National Institute for Health and Care Excellence (NICE) published its brief guidelines on COVID-19 and vitamin D on December 17, 2020[3]. They offer a series of recommendations on the need to maintain adequate vitamin D levels in the population, especially due to the periods of confinement that prevented sun exposure. But they also recommend that researchers delve into the preventive and therapeutic role of vitamin D in COVID-19.

Among the recommendations, we would highlight:

1. The population (adults, youth, and children over 4 years of age; including pregnant women) should be encouraged to maintain bone and muscle health if sun exposure is poor (for whatever reason) by taking daily supplements of vitamin D (400 IU per day) throughout the year. They should also be taken, regardless of sun exposure, by people with very dark skin due to their low production of vitamin D from the sun; infants from birth to one year of age (in doses between 340 to 400 IU) if they are breastfed or are taking formulas not fortified with vitamin D; children from 1 to 4 years; those whose medical condition implies a lower production of vitamin D.
2. In the autumn-winter months (those that correspond in each hemisphere), these supplements should be taken due to the low production of vitamin D in these times (the entire population).
3. Vitamin D supplementation alone should not be offered for the prevention or treatment of COVID-19, except as part of a clinical trial, due to the limited evidence available at that time.

Spanish Society of Geriatrics and Gerontology (SEGG)

The SEGG published more recently (in February 2021) a position paper[4] in which the role of vitamin D as a modulator of immunity was analyzed, later focusing on its possible actions in COVID-19. They review the studies published to date, and based on them, make the following recommendations for elderly patients hospitalized for COVID-19:

1. Vitamin D should be administered daily until adequate levels are reached and maintained during the hospital stay, since vitamin D behaves as a negative acute phase reactant and consumption by the patient may occur during the course of treating the infection.
2. Although there is no evidence regarding specific doses in the elderly, they recommend their standardization. First of all, vitamin D levels must be determined at the time of hospital admission, and, if necessary, supplementation with vitamin D, suggesting a unique protocol based on experts' opinions. They indicate the recommended doses of both cholecalciferol and calcidiol. The administration of cholecalciferol is recommended in any situation, regardless of the basal levels of 25(OH) vitamin D, and even in the absence of analytical determination. However, calcidiol is only recommended if at the time of diagnosis of COVID-19 we have levels determined and, in addition, these are below 20 ng/ml. In case of obesity or malabsorption, higher doses than those recommended by the authors should be considered.
3. The goal of vitamin D treatment should be to achieve adequate 25(OH) vitamin D levels as quickly as possible and maintain them for at least 3 months.
4. Finally, they recommend paying attention to possible vitamin D toxicity due to the administration of high doses of supplements, especially hypercalcaemia, so blood calcium levels should be monitored regularly during administration.

Vitamin D for all

An open letter published at the end of 2020[5], signed by more than 200 experts and opinion leaders in vitamin D from multiple countries is noteworthy.

It requests that governments and medical groups worldwide increase immediate, widespread determination of vitamin D levels in the population, given the possible benefits that this strategy could have in the fight against COVID-19. The authors highlight the role of vitamin D on immune function, noting that increasing vitamin D levels could help reduce infections, hospitalizations, ICU admissions and deaths from COVID-19.

In order to optimize 25 (OH) vitamin D levels above 30 ng/ml in the adult population, experts recommend an intake of 4,000 IU/day of cholecalciferol (or at least 2,000 IU) without the need for determination of levels, given that this amount is widely recognized as safe by international regulatory authorities such as the European Food Safety Authority (EFSA).

Conclusion

In conclusion, the scientific-health community's recommendations to maintain adequate vitamin D levels in the population in the fight against COVID-19 is well known. Research continues into its implications in the pathogenesis, prevention and treatment of the infection. This demonstrates the importance that vitamin D has for the health of the population.

Conflict of interest: The author declares that she has no conflict of interest.

Bibliography

1. Pérez Castrillón JL, Casado E, Corral Gudino L, Gómez Alonso C, Peris P, Riancho JA. COVID-19 y vitamina D. Documento de posición de la Sociedad Española de Investigación Ósea y del Metabolismo Mineral (SEIOMM). Rev Osteoporos Metab Miner. 2020;12(4):155-9.
2. Misra DP, Agarwal V, Gasparyan AY, Zimba O. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol. 2020;39:2055-62.
3. COVID-19 rapid guideline: vitamin D. London: National Institute for Health and Care Excellence (UK); 2020 Dec 17. www.nice.org.uk/guidance/ng187.
4. Tarazona-Santabalbina FJ, Cuadra L, Cancio JM, Roca Carbonell F, Pérez-Castejón Garrote JM, Casas-Herrero A, et al. Suplementos de vitamina D para la prevención y el tratamiento de la COVID-19: declaración de posición de la Sociedad Española de Geriatría y Gerontología. Rev Esp Geriatr Gerontol. 2021;56(3):177-82.
5. Over 200 Scientists & Doctors Call for Increased Vitamin D Use To Combat COVID-19. https://vitamindforall.org/letter.pdf. Consultado en: Octubre 2021.


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