



UNIVERSITY OF SEVILLE

VITAMIN D IN THE COVID-19 ERA



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Academic year: 2020/2021

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Faculty of Pharmacy

MASTER'S DISSERTATION

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Bibliographic review



**DECLARACIÓN DE ORIGINALIDAD DEL TRABAJO FIN DE MÁSTER
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ABSTRACT

The rapid global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has re-ignited interest in the possible role of vitamin D in modulation of host responses to respiratory pathogens. Indeed, vitamin D supplementation has been proposed as a potential preventative or therapeutic strategy. Recommendations for any intervention, particularly in the context of a potentially fatal pandemic infection, should be strictly based on clinically informed appraisal of the evidence base. In this narrative review, we examine current evidence relating to vitamin D and COVID-19 and consider the most appropriate practical recommendations.

Although there are a growing number of studies investigating the links between vitamin D and COVID-19, they are mostly small and observational with high risk of bias, residual confounding, and reverse causality. Extrapolation of molecular actions of 1,25(OH)₂-vitamin D to an effect of increased 25(OH)-vitamin D as a result of vitamin D supplementation is generally unfounded, as is the automatic conclusion of causal mechanisms from observational studies linking low 25(OH)-vitamin D to incident disease. Efficacy is ideally demonstrated in the context of adequately powered randomised intervention studies, although such approaches may not always be feasible.

At present, evidence to support vitamin D supplementation for the prevention or treatment of COVID-19 is inconclusive. In the absence of any further compelling data, adherence to existing national guidance on vitamin D supplementation to prevent vitamin D deficiency, predicated principally on maintaining musculoskeletal health, appears appropriate.

KEYWORDS

Vitamin D, Vitamin D Receptor (VDR), hypovitaminosis, COVID-19, Vitamin D2 vegetarianism and veganism.

RESUMEN

La propagación global rápida del síndrome respiratorio agudo severo coronavirus tipo 2 (SARS-CoV-2), responsable de la enfermedad del coronavirus 2019 (COVID-19), ha vuelto a despertar el interés del posible rol de la vitamina D en la modulación de la respuesta del hospedador ante patógenos respiratorios. De hecho, la suplementación con vitamina D se ha propuesto como estrategia de potencial preventivo o terapéutico. Las recomendaciones para cualquier intervención, especialmente en el contexto de una pandemia, deberían estar estrictamente basadas en evaluaciones clínicas informadas de la evidencia existente. En este trabajo se pretende examinar la evidencia actual que relaciona la vitamina D con el COVID-19 y considerar recomendaciones prácticas adecuadas.

Aunque un número creciente de estudios investigan los vínculos entre la vitamina D y el COVID-19 se trata en la mayoría de los casos de estudios pequeños y observacionales de alto riesgo de parcialidad, confusión residual y causalidad inversa. La extrapolación de las acciones moleculares de la 1,25(OH)₂-vitamina D a efecto de niveles incrementados de 25(OH)-vitamina D como resultado de la suplementación con vitamina D es generalmente sin fundamento, ya que se trata de la conclusión automática a la que se llega por los mecanismos causales obtenidos de estudios observacionales que enlazan niveles bajos de 25(OH)-vitamina D a la enfermedad incidente. La eficacia se demuestra en el contexto de estudios de intervención adecuados, aunque tal acercamiento no sea factible.

En el presente, la evidencia parece apoyar la suplementación con vitamina D como prevención o tratamiento para el COVID-19. Ante la ausencia de datos más convincentes, la adherencia a las guías nacionales de suplementación de vitamina D para prevenir su deficiencia, normalmente enfocadas a mantener la salud del sistema músculo-esquelético, parece apropiada.

PALABRAS CLAVE

Vitamina D, Receptor de la Vitamina D (VDR), hipovitaminosis, COVID-19, Vitamina D2, vegetarianismo y veganismo.

INTRODUCTION

Prevalence of vitamin D deficiency and metabolism

Deficiency of vitamin D is very prevalent nowadays, being Europe one of the regions where this condition is higher, reaching 40% of people who are deficient and 13% who are severely deficient. The number of individuals who suffer from this hypovitaminosis varies depending on age, being the children and the elderly the ones whose prevalence is higher. It also depends on ethnicity, since Caucasians are the ones with lower levels of this micronutrient in their plasma (**Amrein et al., 2020**).

For a brief historical outline, vitamin D was discovered in the beginnings of the XX century, being the existence of vitamins previously established by McCollum and Davis in 1913. Despite being identified as such, it was after discovered that it was a hormone since our body can synthesize it through the 7-dehydrocholesterol present in our skin (**De Luca, 2016**).

7-dehydrocholesterol transforms thanks to the sunlight, specifically UVB radiation, into previtamin D₃ and it isomerizes into vitamin D₃ or cholecalciferol later through a thermo-sensitive process (**Bikle, 2014**). For cholecalciferol to turn into vitamin's D active form a hydroxylation needs to happen in the liver by hepatic cytochrome *P*-450s, obtaining 25-dihydroxyvitamin D₃. The transport of vitamin D and its different forms through the organism is realized by the vitamin D binding protein (DBP). Then, this compound suffers another hydroxylation that this time takes place in the kidney and the result of this process is 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), which is the hormonal active form. This step can also happen in other types of cells, due to the presence of 1 α -hydroxylase in them, under specific physiological circumstances such as pregnancy, but it serves as an autocrine/paracrine factor. Nevertheless, since a small intake through diet is necessary in order to reach the recommended daily ingest, we can still consider it as a vitamin instead of strictly a hormone (**Brown et al., 2008; Christakos et al., 2015; De Luca, 2016; Lin et al., 2021; Mizobuchi, 2012**). 1 α -hydroxylase is highly regulated by dietary calcium and parathyroid hormone (PTH) along with other different factors in order to prevent a possible scenario of vitamin D intoxication. The inactivation of 1,25

dihydroxyvitamin D₃ is performed by 24-hydroxylase, which transforms it into calcitroic acid (Brown et al., 2008).

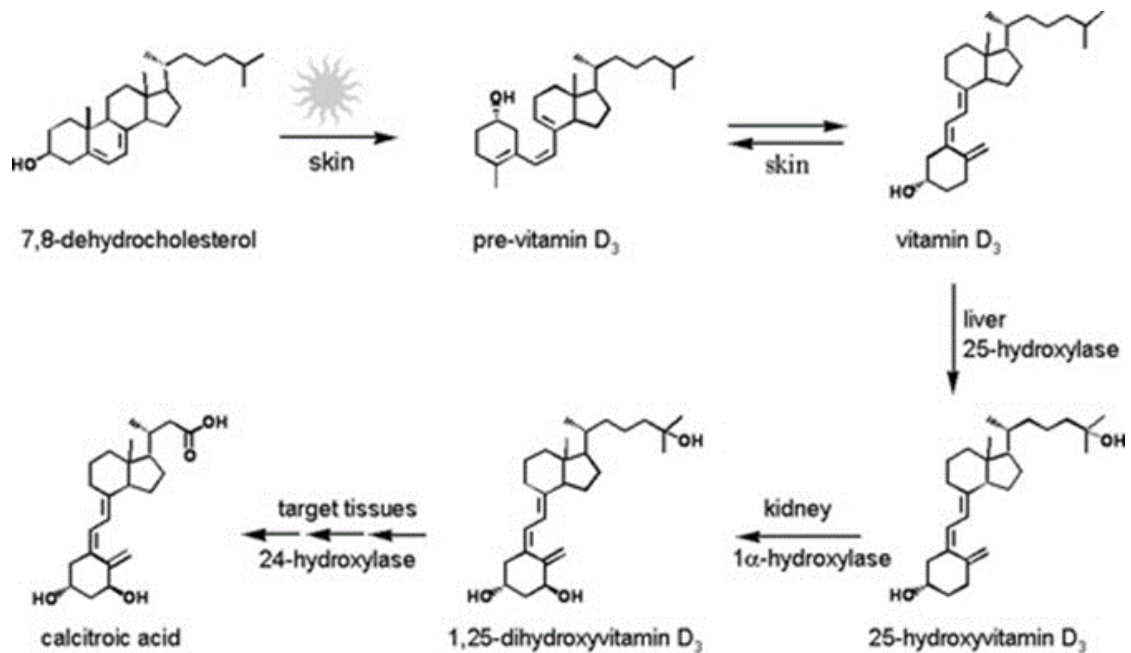


Figure 1: vitamin D biosynthesis in humans (Brown et al., 2008)

Causes of vitamin D deficiency

In addition to the classic action on bone metabolism, a deficient state of vitamin D in the organism has also been associated with several disorders such as diabetes, cancer, immune system dysfunction, hypertension and other cardiovascular diseases, inflammatory state, cognitive alterations and incorrect bone homeostasis, among many other pathological situations (Xu et al., 2020). Recently, hypovitaminosis D has been associated with a major vulnerability to acute respiratory diseases (Bilezikian et al., 2020). Therefore, supplementation could be of use against these types of illnesses, offering a greater resistance by increasing blood concentrations of 25-hydroxyvitamin D (25(OH)D).

As it was said before, vitamin D deficiency is very prevalent worldwide, affecting a great amount of the population of all ages. The possible causes of this are very diverse and we describe some of them in the following **Table 1**, which classifies them into inadequate sun exposure, low intake or certain pathophysiological situations. In Spain, in particular, the lack of vitamin D can be explained by a low external input that is not sufficient to compensate for our synthesis in the organism. It also can be explained by the low incidence of the sun during the winter months or even the use of sunscreen (**Rodríguez-Rodríguez et al., 2019**). Even in the regions with traditionally sunny weather had a prevalence of low concentrations of 25(OH)D in plasma, which led to consider this situation as an epidemic. This situation also happens during summer months in Spain, particularly in the elderly, since southern regions of the country have very high temperatures during the day, reaching an average between 30 and 40°C, and people avoid going out during times when the heat is especially strong, that coincide with a better sun exposure for vitamin D synthesis in the skin (**Navarro-Valverde & Quesada-Gómez, 2014**).

Table 1 “Causes of hypovitaminosis D” (modified from Rodríguez-Rodríguez et al., 2019)

MAIN FACTORS	POSSIBLE CAUSES
Inadequate exposure to sunlight	Recruitment Excessive clothing Solar protection Ambient pollution Exposition through glass Low UV radiation (winter, countries above 35°N, avoiding exposure between 9 and 15 h)
Low vitamin D intake	Low consumption of meat, fish, egg y fortified aliments
Pathophysiological factors	Dark skin Malabsorption syndrome Obesity Hepatic and/or renal failure Exclusive breastfeeding Pregnancy Aging

Skin production of cholecalciferol depends on the radiation that we receive from the sun, being the UVB rays the ones responsible for the synthesis. The solar radiation we receive varies depending on our location on the planet, the latitude in which we are, and it is defined by the zenith angle. The lower the angle, the more radiation you receive, being the equator the zone with the lowest angle on the Earth. This implies that the farther you are from the equator, the angle increases and the incidence of the radiation decreases. The radiation quantity is also less in autumn and winter months because Earth is farther away from the Sun and so, vitamin D production decreases drastically. The time of the day when you are exposed to the sun is also of importance, being the hours around midday when the sun is on its higher point on the sunny the ones in which the transformation of 7-dehydrocholesterol is increased. Aside from latitude, it is important to take into account phototypes associated with each one's skin, the ones that go from I to III are the ones who are prepared to a greater synthesis of vitamin for evolutive adaption of the cells of the epidermis to places which are far from the 0° angle **(Aguilar Shea et al., 2020)**.

Skin production of vitamin D is the most important way to obtain adequate serum levels, so factors that affect this process are going to constitute a bit of a hindrance. Perhaps the aspects that alters the most our own biosynthesis of this hormone are solar protection of factor 30 or higher, dark skin (which is less efficient in the production of vitamin D due to melanin) and air pollution, especially the increasing presence of ozone and nitrogen dioxide, that alter synthesis by absorbing UVB radiation. Sun exposure, as long as it is performed with due caution, does not need to derive on conditions such as melanoma since an exposition from 10 to 15 minutes in noontime (and not in the whole body) should be sufficient for an appropriate daily synthesis and not cause sunburn in white-skinned individuals **(Hosseini-Nezhad & Holick, 2013)**.

Sources of vitamin D

We can also obtain vitamin D through aliments of both animal and vegetal origin in the form of cholecalciferol (vitamin D3) in the former and ergocalciferol or vitamin D2 in the latter (**De Luca 2016**). To be active, vitamin D2 also has to undergo an activation process in the liver and kidney, 25-hydroxylation and 1 α -hydroxylation respectively, the same way as vitamin D3 does. This second structural change is regulated by the levels of calcium and 1,25-(OH)₂D₃ in the blood (**Jones et al., 1998**). The differences between vitamin D3 and D2 are the presence of a double bond and a methyl group in the side chain of the molecule which result in a lower affinity of vitamin D2 for the vitamin D binding protein that lead to a major clearance and different sensibility to certain enzymatic transformations. This explains that vitamin D2 supplementation is less effective than vitamin's D3, unless given on a daily basis (**Bikle, 2014**).

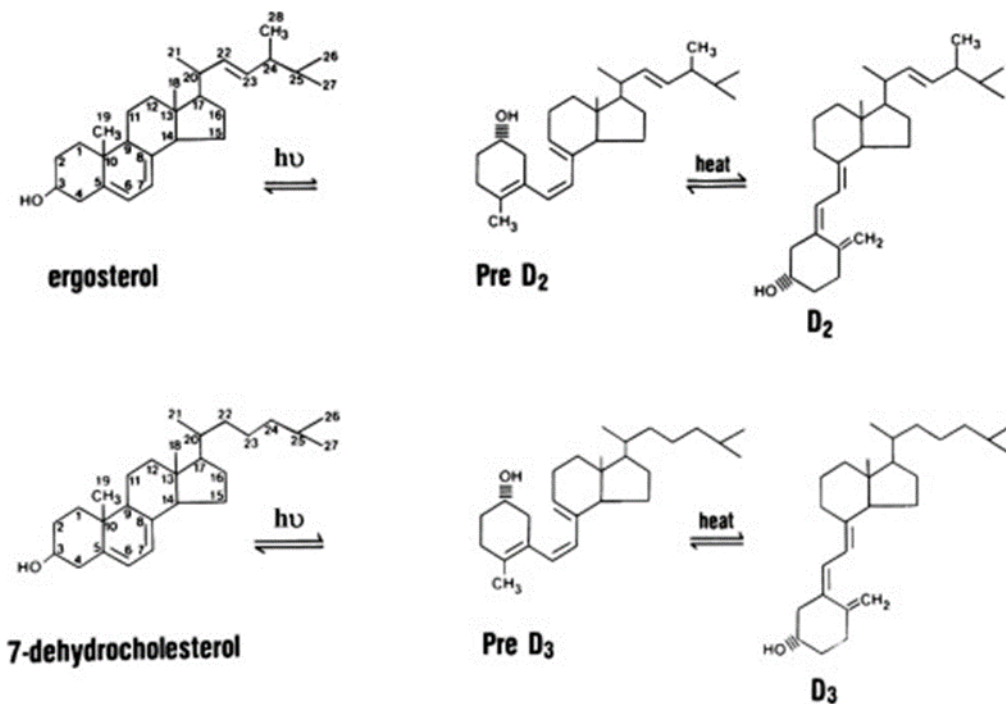


Figure 2: Structure and formation of Vitamin-D3 and vitamin-D2 (**Bikle, 2014**)

The sources of vitamin D are scarce, being sea fish fatty acids the richest in cholecalciferol. Some fishes, like salmon, have enough vitamin D that one ration per day is enough to cover the daily intake of vitamin D (**Rodríguez-Rodríguez et al., 2019**). Other sources of this vitamin in animal products are eggs, milk and other dairy products and entrails. These last ones specifically are very rich but are not often consumed due to their high levels of cholesterol (like eggs or liver). Nevertheless, one of the advantages of vitamin D is that it is very stable during food processing as well as thermostable (**Valero Zanuy & Hawkins Carranza, 2007**).

In vegetables, vitamin D is far more limited and this constitutes a risk factor for people who follow vegan diets. This type of diet has been examined in different studies and most of them concluded that individuals who follow it have lower intake overall of vitamin D than other diets (**Bakaloudi et al., 2020**).

Mushrooms due to its high content in ergosterol (pre-vitamin D₂), can be an important source of ergocalciferol (vitamin D₂) after treatment with UVB radiation (**NIH, 2021; Falcón-García, 2019**). Some cereals or even cocoa shell meal are also good sources of vitamin D when they are exposed to the sun in order to dry them and probably to UVB photo-conversion (**McDowell, 2000**). The possible consequences of veganism on human health will be explored later in this work.

Table 2: “Main sources of vitamin D” (Adapted from Falcon-García, 2019)

Food	Vitamin D in µg/100g	Vitamin D in UI/100g
Cow milk	0,0075-0,001	0,3-0,4
Milk/ reinforced infant formulas	1	40
Butter	0,875	35
Fortified margarine	30	1200
Yoghurt	2,225	89
Cheese	0,3-1,1	12-44
Liver	0,375-1,25	15-50
Yolk	2-2,5	80-100
Mushrooms	0,175	7
Mushrooms exposed to UV light	28,9-31,9	1135-1279
Reinforced cereals	3,325	133
Prawns	3,125	125
Canned tuna, sardines or mackerel in oil	5,6-8,3	224-332
Canned salmon	8,625-9	345-360
Salmon/mackerel	9	360
Fresh herring	40,7	1628
Fresh cod	1,1	44
Cod liver oil	40,7	1628
RDI	20	800

Some countries fortify their foods in certain nutrients to avoid possible situations of deficiency. An example of industry’s take on fortifying foods with vitamin D has recently been evidenced by PLT Health Solutions. The company has received a license from the Natural Health Products (NHP) Directorate of Health Canada to market its Earthlight

Whole Food Vitamin D powder as a help to “maintain/support immune health” and “helps with immune function.”

“Although we may not be able to fully prevent or treat an illness, it is still important to focus on daily eating patterns that are nutrient-rich with foods high in vitamins C and D, in addition to healthy lifestyle practices, such as practicing food safety, washing hands, staying active, getting enough sleep and taking care of one’s mental health to help support the immune system”.

The requirements of vitamin D have changed since its discovery more than a hundred years ago. At the moment the recommended daily intake is 10 µg/day for all ages and 20-25 µg for premature children. The recommendation for people over seventy years old is 20 µg/day (**Rodríguez-Rodríguez et al., 2019**).

Setting the daily dose to take is a key factor since the bioavailability of this vitamin depends on a significant number of factors, such as environment ones, malabsorption problems, use of certain medications or even genetics. This is why it is important to establish a daily intake and investigate the need to modify it if necessary.

Vitamin D receptor and the many functions of vitamin D

The importance of vitamin D for regulation of calcium and phosphate balance in musculoskeletal physiology is well established (**Harvey et al., 2017**). Vitamin D receptors are also expressed by many non-skeletal tissues suggesting a broader role for vitamin D in human health, particularly in modulating immune system activities (**Bikle, 2014; Prietl et al., 2013**).

The vitamin D receptor (VDR) is a nuclear receptor with different functional domains. 1,25 D can do its actions by binding to VDR, forming a complex that dimerizes with the retinoid X receptor. This heterodimer then translocate to the nucleus where it binds vitamin D responsive elements that induce the expression of genes related to vitamin D (**Aranow, 2011**).

This receptor can be found in many different tissues, which means that vitamin D deficiency has consequences beyond the ones that affect our skeletal system. Since the

VDR was discovered in almost every tissue of our body, along with nearly thousands of sites of union for the receptor in the genome, it's interesting to explain some actions that vitamin D performs in our body (**Bikle, 2014**).

Main function of vitamin D

We can find vitamin D receptors on the intestine, inside enterocytes, where they develop the main role of vitamin D: regulation of calcium absorption on this level. This process is dependent on the union of vitamin D with its receptor inside the cells since this union stimulates the production of the channel responsible for the active transportation across the apical membrane. Then, calcium binds to a specific calcium-binding protein and exits the enterocyte across the basolateral membrane, ending in the bloodstream. All this process was discovered thanks to studies using the duodenum but it's known that VDR is present along the entire intestine, both small and large. Also, the channel responsible for the transport of calcium into the cells is more abundant in the distant part of the intestine so it's safe to assume this process occurs throughout the entire organ. Along with this process, calcium is also absorbed by paracellular transport, but the role of vitamin D is not clear and further studies are required (**Christakos et al., 2015**).

On the kidneys, most calcium is absorbed independently of vitamin's D presence but the rest is absorbed in the distant tube through active transport regulated by the presence of vitamin D and the parathyroid hormone (they increased the levels of the pertinent transporter in the membrane, just like happened in the intestine) (**Christakos et al., 2015**).

Calcium and bone homeostasis are closely related. The role of vitamin D receptor is to stimulate bone resorption and to inhibit its mineralization when calcium concentration in plasma is low. This action, however, appears to be redundant since the inactivation of the receptor in mature osteoblasts and osteoclasts didn't have any effects on the metabolism of the skeletal system. It's necessary to develop more studies on this matter (**Christakos et al., 2015**).

The parathyroid hormone (PTH) stimulates the liberation of calcium from the bone in a process dependant on the presence of vitamin D, not being able to do this process in

cases of deficiency. In the same way, without PTH vitamin D can't elevate calcium levels in the bloodstream, unless the dietary intake of this mineral is very high (**De Luca, 2016**).

Vitamin's D role in the utilization of calcium (and also phosphorus), as said previously, is its main function. It helps to prevent diseases like rickets, osteoporosis and osteomalacia indirectly, rising blood levels of this mineral for its use when necessary. An incorrect supplementation of vitamin D can develop into toxic situations like hypercalcemia (**Aguilar Shea et al., 2020; De Luca, 2016**).

Other functions of vitamin D

Apart from its functions related to calcium and bone homeostasis, vitamin D forms part of many other different roles since its receptor can be found in most of the tissues in our body, as said before (**Aguilar Shea et al., 2020**).

Vitamin D receptor also exists in cells that form part of the cardiovascular system, like myocytes, and plays a part in its functions. There are also receptors in the pancreatic beta cells and other target tissues for insulin, like the skeletal muscle tissue or the adipose tissue, and their activity is related to a better activity of those pancreatic cells, their protection against cells of the immune better sensitivity to insulin (**Rodríguez-Rodríguez et al., 2019**). Some studies relate the vitamin D - VDR axis with good homeostasis of the oral epithelium and its immunity since low levels of this vitamin are related to chronic peritonitis (**Khammissa et al., 2018**).

Vitamin D plays a very important role in the immune system and participates in the regulation of innate and adaptive functions. On an innate level, monocytes and macrophages express the VDR, which exerts anti-inflammatory activity on an innate level. Dendritic cells also suffer from modulation by vitamin D, which causes changes in morphology and cytokine production (**Martens et al., 2020**). Vitamin D is also involved in the transcription of cathelicidin and defensin 4, peptides with antimicrobial activity (**Aranow, 2011**).

Regarding adaptive immunity, vitamin D is involved in T-lymphocytes modulation both indirectly and directly. Indirectly, antigen-presenting cells are affected by vitamin D, which decreases their production. This develops into the regulation of lymphocytes T response, lowering their proliferation. Directly, when T lymphocytes are activated they

increase their number of vitamin D receptors and vitamin D inhibits the production of certain cytokines (**Prietl et al., 2013**).

B-lymphocytes have VDR and 1α -hydroxylase which means vitamin D plays an important role in these cells. $1,25(\text{OH})_2\text{D}_3$ induces apoptosis of activated B lymphocytes, which prevents the generation of plasmatic cells and memory cells. Calcitriol also has antiproliferative effects, which was considered a role mediated by T helper cells. Regulation of these lymphocytes may be important in autoimmune diseases (**Martens et al., 2020; Prietl et al., 2013**).

This involvement in the immune function may explain that vitamin D deficiency is involved a less vulnerability towards respiratory diseases and could have a potential role in the new coronavirus disease (**Grant et al., 2020**).

OBJECTIVES

This revision aims to cover the following objectives:

- Explore the prevalence of vitamin's D deficiency in the world and the possible causes for this.
- Explain the metabolism and synthesis of vitamin D.
- Study different dietary sources for vitamin D, both from animal and vegetal origin.
- Explore the relevance and functions of the vitamin D receptor (VDR) on different systems of the organism.
- Give general information about the new SARS-CoV-2: symptoms, possible courses of the disease and recommended sanitary measures for its prevention.
- Make a compilation of relevant articles that relate vitamin D with COVID-19 to ascertain a possible relation between them.
- Explain how vitamin D deficiency may affect the vulnerability to certain respiratory diseases.
- Explore the consequences of vegan diets over the individual vitamin D status.

METHODOLOGY

All the information was searched in the Pubmed and Scopus data bases, different published articles related to the objectives of the review were found. Other information sources were consulted through the University of Seville online catalogue, FAMA such as books. The main criteria used for the inclusion of information in this revision were sources that were in either English or Spanish and with free open access through the resources of the University of Seville. Therefore, texts in other languages different from English or Spanish were excluded and so were the ones without open access.

First, an information search was made to compile information about vitamin D and the VDR. This was carried out by using vitamin D as a keyword in FAMA, where books were consulted, and Pubmed and Scopus, where different relevant studies and reviews were found. To find information about 'vitamin D receptor' a new search was made using it as keyword in both Scopus and Pubmed resulting in several articles found about this issue

Subsequently, a new search was done by using COVID-19 as keyword to search for information in different reviews and articles in Scopus and Pubmed.

Next, different reviews and studies that related to these two topics (vitamin D and COVID) were explored so it was possible to collect relevant information about the relationship that exists mainly between low concentrations of 25(OH)D, which imply vitamin D deficiency, and the gravity or risk of infection of COVID-19.

This compilation of articles and reviews were researched through Scopus following the search criteria "vitamin D" and "COVID" in the title, keywords or abstract. Among the results, the table included those whose abstracts were available so a brief comment about the contents could be made and checked out by everyone. The articles are placed from older to most recent (from December 2019 to June 2021) and language was not a conditional factor, as long as the abstract was in English. Then, three of the most cited ones in Scopus (one review and two studies) were selected to explain its contents and the conclusions that they arrived.

Table 3 “Search in data bases”: different number of articles present in the two main data bases used for this review and included in the table that contains information relating vitamin D and COVID-19.

SEARCH PROFILE	DATA BASE	NUMBER OF ARTICLES
Vitamin D (all open access)	SCOPUS	45,937
COVID-19 (all open access)		118,202
Vitamin D and COVID		994
Vitamin D (all open access)	PUBMED	29,931
COVID-19 (all open access)		113,107
Vitamin D and COVID		660

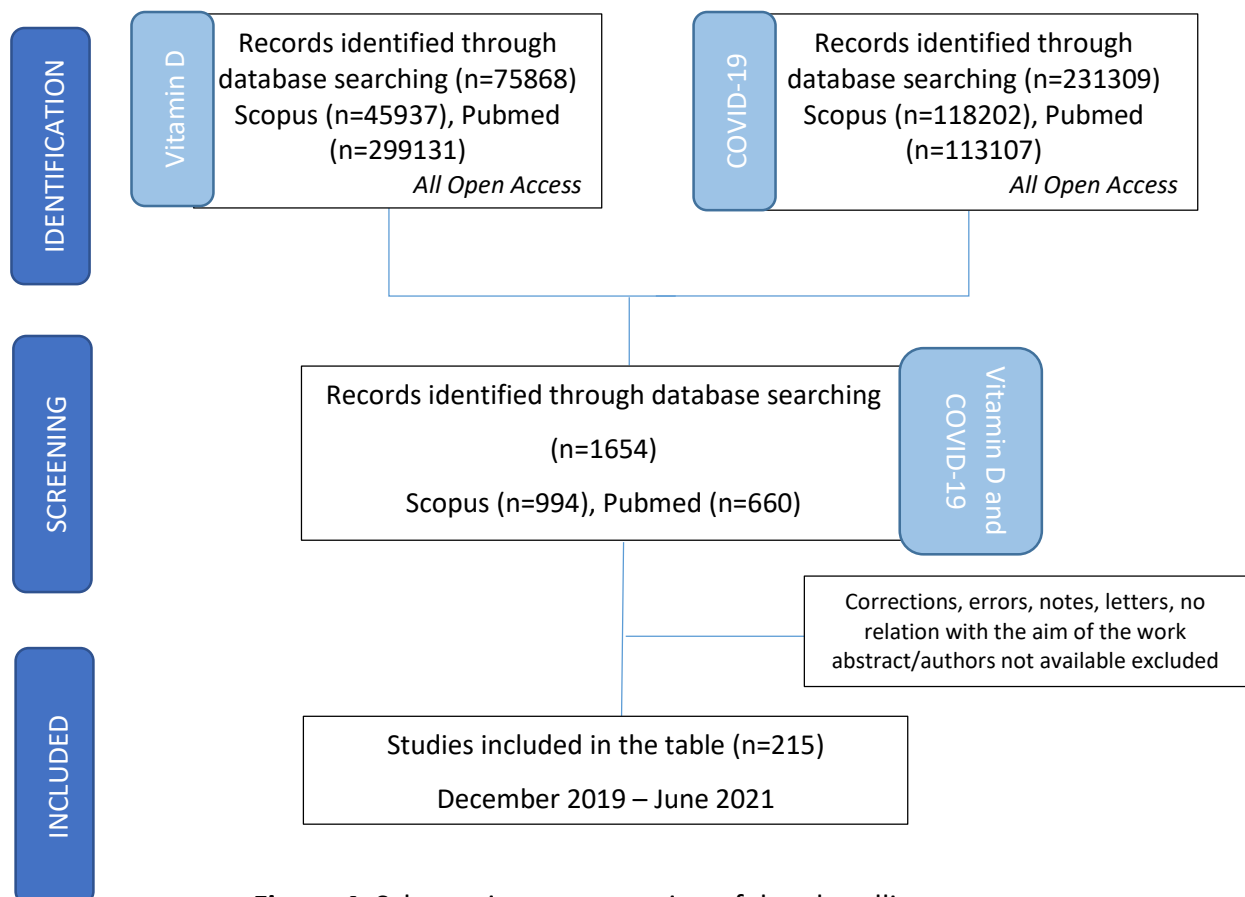


Figure 4: Schematic representation of data handling

Finally, a compilation of relevant information about the relation between vitamin D deficiency and respiratory diseases and the consequences of vegan diets on human health, mainly the nutritional state of the individual, was carried out and how this could affect the risk of getting COVID-19 or the gravity of the disease in case of contracting the illness. For the relation between respiratory diseases and vitamin D deficiency we used the terms “vitamin D” and “respiratory diseases” combined as search criteria in Scopus and then we used “veganism” and “vitamin D” to explore the possible implications of vegan diets over this particular nutrient also in Scopus.

Papers were selected for inclusion in the work based on title and abstract screening followed by full text review, if appropriate. Further relevant studies were identified through cross referencing and author searches.

With regards summarising evidence relating to vitamin D and non-COVID-19 acute respiratory infections, we selected the latest and most comprehensive systematic evidence reviews on the topic.

RESULTS AND DISCUSSION

As can be observed from the Methodology section, this Review has involved an extensive bibliographic consultation that has led to the selection of 215 papers, which have been reviewed in detail and commented (Table 4). Of the 215 papers selected, 105 are research articles, 77 are Reviews and 33 are clinic trials.

From obtained information, a quick analysis could lead us to conclude that hypovitaminosis D is an unfavourable factor against COVID-19 and viral infections; so supplementation with vitamin D would be beneficial. Which is generally true, but it requires a more detailed analysis.

Of all the consulted publications in approximately 90% of them an association between vitamin D deficiency and COVID-19 is described. Since the aims of each article and review vary greatly from one to another it is very tedious and lacking in interest to classify every publication included into a specific category. A good part of them these papers claim that more evidence and studies or trials are necessary in order to prove the relevance of vitamin D in the current pandemic. This is due to the lack of proper randomized controlled trials and observational studies on this matter since this topic is very recent in the current state of affairs and all most of the trials carried out could be considerate inadequate because of, for example, imprecise homogeneity in the groups in which the participants are divided (some groups could have more individuals with certain comorbidities than others or even have different baselines of serum concentrations of vitamin D) spoil the results obtained.

The rest of the articles found about this topic either deny an existent association or claim that proper studies and trials are needed before even claiming that there is a possible link between vitamin D and COVID-19.

Table 4: Revised and commented bibliography

REFERENCE	TITLE	COMMENTARY
Bonvecchio et al., 2019 Archivos Latinoamericanos de Nutrición Volume 69, Issue 4, Pages 259 - 273	Micronutrient recommendations for vulnerable groups in context of undernutrition, during the COVID-19 pandemic in Latin America.	The potential impact of COVID-19 in Latin America could be decreased by following certain dietary measures, such as supplementation with vitamin C, D and zinc in adults.
Palacios et al., 2019 Archivos Latinoamericanos de Nutrición Volume 69, Issue 4, Pages 242 - 258	Nutritional recommendations for healthcare and essential personnel exposed to COVID-19 in Latin America	Supplementation of different micronutrients, including vitamin D, may prevent respiratory infections in adults.
Pereira et al., 2020 Critical Reviews in Food Science and Nutrition DOI: 10.1080/10408398.2020.1841090	Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis	Vitamin D deficiency was not associated with a higher risk of infection by COVID-19, but it was with the severity of the illness.
Nayak et al., 2020 International Journal of Pharmaceutical Research Volume 12, Pages 2437 - 2448	Dietary supplementation and medication of vitamin c and vitamin d in covid-19 – a hypothesis	Vitamin C and D play a role in reducing the risk of respiratory infection and other conditions that are associated with the current pandemic.
Kerget et al., 2020 Tuberkuloz ve Toraks Volume 68, Issue 3, Pages 227 - 235	Evaluation of the relationship of serum vitamin d levels in covid-19 patients with clinical course and prognosis	Quarantine has reduced exposure to sunlight to lower 25(OH)D levels. This status can be responsible for worse outcomes of COVID-19
Adami et al., 2020 Reumatismo Volume 72, Issue 4, Pages 189 - 196	Vitamin d and disease severity in coronavirus disease 19 (Covid-19)	Prevalence of low levels of 25(OH)D is important due to its possible association with inflammatory response and respiratory failure in COVID-19
Jain & Parsanathan, 2020 Journal of the American College of Nutrition Pages 694 - 699	Can Vitamin D and L-Cysteine Co-Supplementation Reduce 25(OH)-Vitamin D Deficiency and the Mortality Associated with COVID-19 in African Americans?	Vitamin D along with L-cysteine correct vitamin D deficiency, therefore, preventing the most severe consequences of the disease

O Shea et al., 2020 Journal of Nutritional Science Volume 9, Article number e40	COVID-19: The older adult and the importance of vitamin D sufficiency	The actions of vitamin D over the immune system lead to a necessity for further studies that establish hypovitaminosis D relation with COVID-19.
Orrù et al., 2020 European Review for Medical and Pharmacological Sciences Volume 24, Issue 15, Pages 8187 - 8193	Inhibitory effects of Vitamin D on inflammation and IL-6 release. A further support for COVID-19 management?	The possible correlation between COVID-19 and vitamin D status has raised insights about the importance of this micronutrient in our health and the possibility of supplementation to fight back the pandemic.
McCartney & Byrne, 2020 Irish Medical Journal Volume 113, Issue 4, Article number P58	Optimisation of vitamin d status for enhanced immuno-protection against covid-19	Respiratory infections are associated with vitamin D deficiency and supplementation has reduced their risk and severity. This could be useful for COVID-19 as well.
Tanner et al., 2020 Current Respiratory Medicine Reviews Volume 16, Issue 2, Pages 93 - 101	Covid-19 susceptibility and severity might be modified by vitamin d status: Theoretical and practical considerations	Vitamin's D role in the immune function may be relevant for COVID-19 infection and there is a widespread deficiency around the world.
Aygun, 2020 Bratislava Medical Journal Volume 121, Issue 12, Pages 870 - 877	Vitamin D may protect against multiple organ damage caused by COVID-19	The immunomodulatory actions of vitamin D may be beneficial against COVID-19's cytokine storm and other organ damage thanks to the presence of its receptor in several tissues.
Laird et al., 2020 Irish Medical Journal Volume 113, Issue 5, Article number P81	Vitamin D and inflammation: Potential implications for severity of Covid-19	Since vitamin D influences the immune system optimising its status has benefits for overall health and against COVID-19
McKenna & Flynn, 2020 Irish Medical Journal Volume 113, Issue 5, Article number P79	Covid-19, cocooning and vitamin D intake requirements	Review that contains information about vitamin D nutrition and how it protects against COVID-19
Smaha et al., 2020 Vnitřní Lekarství Volume 66, Issue 8, Pages 494 – 500	Vitamin D supplementation as an important factor in COVID-19 prevention and treatment: What evidence do we have?	Vitamin's D immunomodulatory actions, along with its deficiency in the world, lead to believe that supplementation may help as prevention and treatment

Ręka et al., 2020 Przegląd epidemiologiczny Volume 74, Issue 4, Pages 583 – 595	Impact of level of vitamin D in the body on the severity of COVID-19 - review of the literature	Correct vitamin D levels are necessary to maintain a correct immune function but there is not enough evidence that those levels are directly related to COVID-19 risk or severity
Ferrari & Locatelli, 2020 International Journal for Vitamin and Nutrition Research Volume 91, Issue 3-4, Pages 200 – 203	No significant association between vitamin D and COVID-19. A retrospective study from a northern Italian hospital	A cohort study was realized to show the possible relationship between vitamin D and COVID-19. Supplementation being beneficial against the disease can't be excluded.
Ye et al., 2020 Journal of the American College of Nutrition DOI: 10.1080/07315724.2020.1826005	Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity?-A Case-Control Study	Supplementation of vitamin D may help reduce the severity of COVID-19 in the elderly
Gavioli et al., 2020 Journal of the American College of Nutrition DOI: 10.1080/07315724.2020.1869626	An Evaluation of Serum 25-Hydroxy Vitamin D Levels in Patients with COVID-19 in New York City	Patients with COVID-19 who had low levels of 25(OH)D were more likely to receive oxygen support therapy than those with adequate levels
Honardoost et al., 2020 Archives of Physiology and Biochemistry DOI: 10.1080/13813455.2020.1792505	Role of vitamin D in pathogenesis and severity of COVID-19 infection	Hypovitaminosis D increases the risk of different comorbidities that cause complications in patients affected by COVID-19. Supplementation may enforce the immune system
Gromova et al., 2020 Farmakoekonomika Volume 13, Issue 2, Pages 132 – 145	COVID-19 pandemic: Protective role of vitamin D	Solving vitamin D deficiency is essential for COVID-19 prevention and relieve the sanitary system by preventing severe cases.
Martín Giménez et al., 2020 Therapeutic Advances in Cardiovascular Disease DOI: 10.1177/1753944720977715	Differences in RAAS/vitamin D linked to genetics and socioeconomic factors could explain the higher mortality rate in African Americans with COVID-19	Predisposition for COVID-19 in the Black population is not only influenced by existing differences in socio-economical status but also with levels of vitamin D and adaptation of RAAS
Mansur,2020 Revista de Nefrologia, Dialisis y Trasplante Volume 40, Issue 4, Pages 330 - 340	Vitamin D, its “non-classic” actions and it utility in the COVID-19 pandemic	The presence of vitamin D deficiency in very different diseases raises a study to try to prevent different conditions

		through supplementation; this includes COVID-19 thanks to its antiviral function.
Vyas et al., 2020 Journal of the American College of Nutrition DOI: 10.1080/07315724.2020.1806758	Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects	COVID-19 associated effects on cardiovascular health and immune function are related to severe vitamin D deficiency
Karonova et al., 2020 Arterial Hypertension (Russian Federation) Volume 26, Issue 3, Pages 295 - 303	Vitamin D deficiency as a factor for immunity stimulation and lower risk of acute respiratory infections and COVID-19	Vitamin D deficiency may be one of the factors related to complications of respiratory diseases so it must be considered as a preventive measure for COVID-19
Roselin & Parameshwari, 2020 International Journal of Research in Pharmaceutical Sciences Volume 11, Issue Special Issue 1, Pages 425 - 429	Role of vitamin d in boosting immunity against covid-19	Vitamin D is essential to strengthen our immune system so it plays an important role against COVID-19
Abrishami et al., 2020 European Journal of Nutrition Volume 60, Issue 4, Pages 2249 - 2257	Possible association of vitamin D status with lung involvement and outcome in patients with COVID-19: a retrospective study	25(OH)D serum levels may provide information about the affection of COVID-19 over the lungs of infected individuals and also the clinical course and outcome of the disease.
Radujkovic et al., 2020 Nutrients Volume 12, Issue 9, Pages 1 – 13, Article number 2757	Vitamin D deficiency and outcome of COVID-19 patients	There is an association between vitamin D deficiency and the severity of COVID-19, but further interventional studies are needed to explore their relationship
Islam et al., 2020 Farmacia Volume 68, Issue 6, Pages 970 - 983	High skin melanin content, vitamin D deficiency and immunity: Potential interference for severity of COVID-19	There is a correlation between vitamin D and melatonin levels and their effects on immunity and possibly in COVID-19
Seijo & Oliveri, 2020 Actualizaciones en Osteologia Volume 16, Issue 2, Pages 1 – 15	Importance of Vitamin D in the time of COVID-19	Vitamin D could have protective effects against COVID-19 thanks to its actions on the immune system. Also, its deficiency is linked to morbidities that worsen the progression of the illness.

Ribeiro et al., 2020 Revista de Saude Publica Volume 54, Article number 53	Does vitamin D play a role in the management of Covid-19 in Brazil?	Vitamin D is important in good immune function but its role in COVID-19 is still unclear due to the lack of randomized controlled trials.
Pigarova et al., 2020 Terapevticheskii Arkhiv Volume 92, Issue 11, Pages 98 – 105	The role of vitamin D in seasonal acute respiratory viral infections and COVID-19	Vitamin D has potential in the prevention of COVID-19 thanks to its role in the expression of antimicrobial peptides and modulatory effects
Glinsky, 2020 Biomedicines Volume 8, Issue 5, Article number 0129	Tripartite combination of candidate pandemic mitigation agents: Vitamin D, Quercetin, and Estradiol Manifest properties of medicinal agents for targeted mitigation of the COVID-19 pandemic defined by genomics-guided tracing of SARS-CoV-2 targets in human cells	The combination of vitamin D, quercetin and estradiol may help against COVID-19 infection by reducing the expression of targets for the virus.
Viani-Walsh et al., 2020 Irish Journal of Psychological Medicine DOI: 10.1017/ipm.2020.107	Vitamin D deficiency in schizophrenia-implications for COVID-19 infection	Respiratory infections are common in schizophrenia along with vitamin D deficiency. The relationship between these two factors and COVID-19 is explored.
Shiravi et al., 2020 International Journal for Vitamin and Nutrition Research DOI: 10.1024/0300-9831/a000676	Vitamin D can be effective on the prevention of COVID-19 complications: A narrative review on molecular aspects	Vitamin D is proposed to avoid potential side effects of COVID-19 due to its effects on the immune system
Baktash et al., 2020 Postgraduate Medical Journal DOI: 10.1136/postgradmedj-2020-138712	Vitamin D status and outcomes for hospitalised older patients with COVID-19	Older adults tend to present vitamin D deficiency and this may be related to worse morbidity of COVID in these patients
Musavi et al., 2020 Archives of Physiology and Biochemistry DOI: 10.1080/13813455.2020.1826530	The benefits of Vitamin D in the COVID-19 pandemic: biochemical and immunological mechanisms	Vitamin D reduces the cytokine storm that happens during COVID-19. The vitamin also affects the renin-angiotensin system (RAS).
Faqihi et al., 2020 Respiratory Medicine Case Reports Volume 31, Article number 101203	Co-infection of SARS-CoV-2 and Bordetella bronchiseptica in a young man with idiopathic non-cystic bronchiectasis and vitamin D3 deficiency	This article studies the use of vitamin D as one of the treatments for the conditions described in the patient and

		proposes further research for vitamin D as a therapy for COVID-19
Salukhov & Kovalevskaya, 2020 Meditsinskiy Sovet Volume 2020, Issue 21, Pages 218 - 228	Vitamin d is a strategic blow to coronavirus infection	The need for prevention and treatment for COVID-19 leads to vitamin D thanks to its action over the immune system and its potential against other viral infections described until now.
Liu et al., 2020 Drug Design, Development and Therapy Volume 14, Pages 3429 - 3434	A single large dose of vitamin d could be used as a means of coronavirus disease 2019 prevention and treatment	The lack of treatment for COVID-19 leads to the proposition of a large dose of vitamin D as a remedy. Moreover, its anticoagulant effect may prevent one of the causes of death of the disease: coagulopathy.
Rastogi et al., 2020 Postgraduate Medical Journal DOI: 10.1136/postgradmedj-2020-139065	Short term, high-dose vitamin D supplementation for COVID-19 disease: A randomised, placebo-controlled, study (SHADE study)	Cholecalciferol supplementation in high dose helped to reduce the percentage of individuals with positive SARS-CoV-2 (meaning a clearance of the virus happened) and their levels of fibrinogen
Alshehri ET AL., 2020 Applied Ecology and Environmental Research Volume 18, Issue 6, Pages 8251 - 8265	Covid-19 infection in inflammatory bowel disease patients treated with tnf-A antagonists: A possible critical enrollment of gut microbiota and vitamin d level – a review	Normal vitamin D levels may be important to maintain gut microbiota so it develops protective functions against COVID in patients with IBD.
Karonova et al., 2020 Jurnal Infektologii Volume 12, Issue 3, Pages 21 - 27	serum 25(OH)D level in patients with CoVID-19	Both vitamin D deficiency and obesity seem to have an influence on the severity of COVID-19 disease
Hedlund et al., 2020 Journal of Biomolecular Structure and Dynamics DOI: 10.1080/07391102.2020.1794973	The latitude hypothesis, vitamin D, and SARS-Co-V2	Respiratory diseases may be related to vitamin D status since the presence of these sickness varies during seasons as well as vitamin D production.
Juneja et al., 2020 International Journal of Research in Pharmaceutical Sciences	Role of vitamin d in prevention of corona virus infection (Covid-19)	SARS-CoV-2 increases the levels of angiotensin II by actions on its receptor, which causes inflammation. Vitamin D

Volume 11, Issue Special Issue 1, Pages 407 - 410		increases the production of the receptor, therefore reducing inflammation.
Grant et al., 2020 Nutrients Volume 12, Issue 4, Article number 988	Evidence that vitamin d supplementation could reduce risk of influenza and covid-19 infections and deaths	Raising blood levels of 25(OH)D helps to prevent COVID-19 and death by it. Treatment with vitamin D3 should be considered in infected patients.
Hribar et al., 2020 Brain Sciences Volume 10, Issue 5, Article number 284	Potential role of vitamin d in the elderly to resist covid-19 and to slow progression of parkinson's disease	Vitamin D supplementation reduces the progression of Parkinson disease but also has positive effects on COVID-19 infection
D'avolio et al., 2020 Nutrients Volume 12, Issue 5, Article number 1359	25-hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2	Levels of 25(OH)D were significantly lower in patients with SARS-CoV-2 which means they could be related and supplementation may have a positive effect.
Crane-Godreau et al., 2020 Frontiers in Public Health Volume 8, Article number 232	Vitamin D Deficiency and Air Pollution Exacerbate COVID-19 Through Suppression of Antiviral Peptide LL37	Through the transcription of genes immune-related genes, vitamin D has been proven to be relevant in respiratory diseases.
Kow et al., 2020 Nutrients Volume 12, Issue 6, Article number 1626	Vitamin d supplementation in influenza and covid-19 infections comment on: "evidence that vitamin d supplementation could reduce risk of influenza and covid-19 infections and deaths" nutrients 2020, 12(4), 988	Discussion on whether vitamin D supplementation in people who are at risk of developing COVID-19 is useful or not.
Hamza et al., 2020 Pakistan Journal of Medical and Health Sciences Volume 14, Issue 2, Pages 462 – 465	Role of Vitamin D in Pathogenesis and Severity of Coronavirus Disease 2019 (COVID-19) Infection	Vitamin's D protective role in respiratory infections is also manifested in COVID-19. Supplementation may boost immune function.
Hastie et al., 2020 Diabetes and Metabolic Syndrome: Clinical Research and Reviews Volume 14, Issue 4, Pages 561 - 565	Vitamin D concentrations and COVID-19 infection in UK Biobank	There is no link between vitamin D and the risk of COVID-19 infection. 25(OH)D levels do not explain either ethnic differences

Kenneth et al., 2020 Clinical Medicine, Journal of the Royal College of Physicians of London Volume 20, Issue 4, Pages E107 - E108	Does Vitamin D deficiency increase the severity of COVID-19?	Vitamin D reduces COVID-19 severity in different manifestations of the disease so supplements can reduce the impact of the pandemic.
Aygun, 2020 Naunyn-Schmiedeberg's Archives of Pharmacology Volume 393, Issue 7, Pages 1157 - 1160	Vitamin D can prevent COVID-19 infection-induced multiple organ damage	The immunomodulatory effects of vitamin D may have protective effects against symptoms of COVID-19 associated with the cytokine storm
Anjum et al., 2020 Pakistan Journal of Medical and Health Sciences Volume 14, Issue 3, Pages 1184 - 1186	Examine the association between severe Vitamin D deficiency and mortality in patients with Covid-19	Vitamin D deficiency causes a major risk of mortality in individuals with COVID-19, especially those who are severely deficient.
Ilie et al., 2020 Aging Clinical and Experimental Research Volume 32, Issue 7, Pages 1195 - 1198	The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality	The number of COVID-19 cases was more abundant in countries where deficiency of vitamin D was more prevalent.
Charoenngam & Holick, 2020 Nutrients Volume 12, Issue 7, Pages 1 – 28, Article number 2097	Immunologic effects of vitamin d on human health and disease	Low levels of 25(OH)D in serum cause different immune-related disorders, like respiratory diseases, so a proper intake of this vitamin is beneficial.
Jayawardena et al., 2020 Diabetes and Metabolic Syndrome: Clinical Research and Reviews Volume 14, Issue 4, Pages 367 – 382	Enhancing immunity in viral infections, with special emphasis on COVID-19: A review	Several micronutrients, such as vitamin D, may positively affect viral infections. They could be useful in both the prevention and treatment of COVID-19.
Song et al., 2020 Chinese Pharmaceutical Journal Volume 55, Issue 13, Pages 1117 – 1121	Evidence-Based Evaluation of Vitamin C and D in the Treatment and Prevention of Acute Viral Respiratory Infectious Disease	After evaluating the evidence that supports the treatment of COVID-19 with vitamin C and D due to their beneficial effects in other respiratory infections there was currently no evidence that supports their use for the current pandemic as proper treatment.

Alexander et al., 2020 Nutrients Volume 12, Issue 8, Pages 1 – 12, Article number 2358	Early nutritional interventions with zinc, selenium and vitamin D for raising anti-viral resistance against progressive COVID-19	Adequate supplementation of micronutrients can be useful in both prevention and outcome of COVID-19 so this ingest should be recommended especially in high-risk areas.
Singh et al., 2020 Aging Clinical and Experimental Research Volume 32, Issue 8, Pages 1609 – 1612	Revisiting the role of vitamin D levels in the prevention of COVID-19 infection and mortality in European countries post infections peak	It appears that there is a negative correlation between vitamin D levels and the number of COVID-19 cases but further studies are required with different subgroups.
Tramontana et al., 2020 Endocrine Volume 69, Issue 2, Pages 237 – 240	The D-side of COVID-19: musculoskeletal benefits of vitamin D and beyond	Adequate 25(OH)D levels in elderly patients are important to achieve good musculoskeletal and respiratory health in COVID-19
Martín Giménez et al., 2020 Life Sciences Volume 254, Article number 117808	Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment	Vitamin D and melatonin could attenuate the pulmonary complications of COVID-19 thanks to their mechanisms against inflammation and oxidative stress.
Brenner et al., 2020 Nutrients Volume 12, Issue 8, Pages 1 – 11, Article number 2488	Vitamin D insufficiency and deficiency and mortality from respiratory diseases in a cohort of older adults: Potential for limiting the death toll during and beyond the COVID-19 pandemic?	Vitamin D3 may reduce COVID-19's mortality since individuals with deficiency had higher mortality than those who did not.
Xu et al., 2020 Journal of Translational Medicine Volume 18, Issue 1, Article number 322	The importance of Vitamin D metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19	Vitamin D has potential for prevention against COVID-19 so this review explores several functions and mechanisms
Singh et al., 2020 Diabetes and Metabolic Syndrome: Clinical Research and Reviews Volume 14, Issue 5, Pages 1033 - 1035	Vitamin D deficiency in patients with diabetes and COVID-19 infection	Vitamin D deficiency is associated with the severity of COVID-19 but there is not enough data related to diabetic patients about the effects of the vitamin on them.
Slominski et al., 2020 Experimental Dermatology Volume 29, Issue 9, Pages 885 - 890	COVID-19 and Vitamin D: A lesson from the skin	Vitamin D supplementation must be taken into consideration in the treatment of COVID-19 especially since the population more vulnerable to the disease is deficient.

Mohan et al., 2020 PLoS Pathogens Volume 16, Issue 9, Article number e1008874	Exploring links between Vitamin D deficiency and covid-19	As an immunomodulator, is relevant to explore the actions of vitamin D against COVID-19, especially since there is no treatment available.
Merzon et al., 2020 FEBS Journal Volume 287, Issue 17, Pages 3693 - 3702	Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study	Low levels of 25(OH)D present in the Israeli population seem to be an independent risk factor for COVID-19.
Pizzini et al., 2020 Nutrients Volume 12, Issue 9, Pages 1 – 9, Article number 2775	Impact of vitamin d deficiency on covid-19—a prospective analysis from the covid registry	Even if vitamin D deficiency is common among patients with COVID-19 there is not enough evidence that proves that it worsens the disease’s outcome.
Shalayel et al., 2020 Pakistan Journal of Pharmaceutical Sciences Volume 33, Issue 5, Pages 2179 - 2186	Vitamin D is a potential inhibitor of COVID-19: In silico molecular docking to the binding site of SARS-CoV-2 endoribonuclease Nsp15	Vitamin D may act as an inhibitor of COVID-19 Nsp15 endoribonuclease binding sites so, its supplementation may be useful to fight the illness.
Whittemore, 2020 American Journal of Infection Control Volume 48, Issue 9, Pages 1042 – 1044	COVID-19 fatalities, latitude, sunlight, and vitamin D	Even though it seemed to be a correlation between a country’s latitude, vitamin D deficiency and COVID-19 fatality, further research is needed to confirm the relation.
de las Heras et al., 2020 Antioxidants Volume 9, Issue 9, Pages 1 – 21, Article number 897	Implications of oxidative stress and potential role of mitochondrial dysfunction in covid-19: Therapeutic effects of vitamin d	COVID-19 is associated with altered mitochondrial functionality and oxidative stress and vitamin D can help normalize these situations in the organism
Macaya et al., 2020 Nutricion Hospitalaria Volume 37, Issue 5, Pages 1039 – 1042	Interaction between age and vitamin d deficiency in severe covid-19 infection	Vitamin’s D deficiency is associated with severe cases of COVID-19 and this could be particularly important in the younger population
Ohaegbulam et al., 2020 American journal of therapeutics Volume 27, Issue 5, Pages e485 - e490	Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series	High dose supplementation of vitamin D is observed to improve the recovery from COVID-19. To ascertain the efficacy of this treatment further studies are needed.

Dos Santos et al., 2020 Archives of Endocrinology and Metabolism Volume 64, Issue 5, Pages 498 – 506	Reasons to avoid vitamin D deficiency during COVID-19 pandemic	Vitamin D supplementation is recommended during the confinement to avoid deficiency but its positive effect against COVID remains unclear
Maghbooli et al., 2020 PLoS ONE Volume 15, Issue 9, Article number e0239799	Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19	Adequate levels of 25(OH)D modulate the immune response and may help to reduce the severity of the morbidities associated with COVID-19
Malek Mahdavi., 2020 Reviews in Medical Virology Volume 30, Issue 5, Article number e2119	A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19	Vitamin D affects unbalanced RAS and ACE2 that happens during COVID-19 so it may have a therapeutic effect against the disease, restoring the balance and preventing lung damage
Žerjavić, 2020 Medicus Volume 29, Issue 2, Pages 219 – 224	COVID-19 and vitamin d – is there a link?	High dose vitamin D supplementation (up to 10,000 IU per day) should be prescribed to achieve antiviral respiratory effects against COVID-19
Isaia & Medico, 2020 Aging Clinical and Experimental Research Volume 32, Issue 9, Pages 1879 - 1881	Associations between hypovitaminosis D and COVID-19: a narrative review	Cross-sectional analyses could not establish a clear relation between hypovitaminosis D and COVID-19, more studies are needed to explore the association between the two and if supplementation may help reduce the negative effects of the disease.
Quesada-Gomez et al., 2020 Journal of Steroid Biochemistry and Molecular Biology Volume 202, Article number 105719	Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020_166	Acute Respiratory Distress Syndrome (ARDS) may be aggravated by vitamin D deficiency so randomized clinical trials are in progress using vitamin D or oral calcifediol in patients with COVID-19 to see the possible benefits of supplementation.
Kaufman et al., 2020 PLoS ONE Volume 15, Issue 9, Article number e0239252	SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels	SARS-CoV-2 positivity is strongly connected with low levels of 25(OH)D so it would be interesting to explore the effects of supplementation in reducing the risk of infection.

Meltzer et al., 2020 JAMA Network Open Volume 3, Issue 9, Article number e202019722	Association of vitamin D status and other clinical characteristics with COVID-19 test results	Vitamin D deficiency is likely associated with an increased risk of COVID-19 in the cohort study, but randomized trials are necessary to determine the real effect of the vitamin over the disease.
Benskin, 2020 Frontiers in Public Health Volume 8, Article number 513	A Basic Review of the Preliminary Evidence That COVID-19 Risk and Severity Is Increased in Vitamin D Deficiency	This review compiles information about the literature existing about vitamin's D effect over COVID-19 and results in a positive view of the supplementation to reduce the risks associated with the disease.
Zhang et al., 2020 Reviews in Cardiovascular Medicine Volume 21, Issue 3, Pages 339 - 344	Vitamin D deficiency in association with endothelial dysfunction: Implications for patients with COVID-19	The role of vitamin D deficiency in worsening the health of COVID-19 patients is still unclear so the review studies the role of vitamin D in endothelial health, which is relevant to the respiratory effects of SARS-CoV-2
Ali, 2020 Journal of Infection and Public Health Volume 13, Issue 10, Pages 1373 - 1380	Role of vitamin D in preventing of COVID-19 infection, progression and severity	Even though there is a need for preventive measures against COVID-19 and some studies suggest vitamin D supplementation, there is not enough evidence that proves its protective role due to several other studies that disprove this statement.
Annweiler et al., 2020 Maturitas Volume 140, Pages 24 – 26	Point of view: Should COVID-19 patients be supplemented with vitamin D?	Positive results in the ongoing trials that study the effects of vitamin D supplementation against COVID-19 would encourage its use as a preventive measure.
Pinzon et al., 2020 International Journal of Nutrition, Pharmacology, Neurological Diseases Volume 10, Issue 4, Pages 229 – 234	Coronavirus Disease 2019 (COVID-19) and Vitamin D Status: Is there any Opportunity for Intervention?	The hospitalized patients due to COVID included in the study had deficient levels of vitamin D. Physicians should take these two factors into account.
Rafiullah, 2020 American Journal of the Medical Sciences Volume 360, Issue 4, Pages 338 – 341	Can a Combination of AT1R Antagonist and Vitamin D Treat the Lung Complication of COVID-19?	AT1R antagonists and vitamin D may protect against COVID by increasing ACE2 protein. ACE2 deficiency caused by the disease causes lung damage.

Taqarort & Chadli, 2020 Nutrition Clinique et Metabolisme Volume 34, Issue 3, Pages 211 – 215	Vitamin D and risk of acute respiratory infections: Influenza and COVID-19	Vitamin D stimulates the immune response and reduces negative responses of the immune system associated with the invasion of pathogens. Its deficiency could be linked to a higher risk of respiratory infections like COVID or influenza.
Daneshkhah et al., 2020 Aging Clinical and Experimental Research Volume 32, Issue 10, Pages 2141 – 2158	Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients	Vitamin D deficiency may be one of the causes for unregulated cytokine response in COVID-19 but the results of the study were insufficient to prove this claim.
Goddek, 2020 International Journal of Infectious Diseases Volume 99, Pages 286 – 290	Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate	Vitamin D3, vitamin K2 and magnesium supplements may prevent the long term health risk of the COVID-19 disease.
Entrenas Castillo et al. 2020 Journal of Steroid Biochemistry and Molecular Biology Volume 203, Article number 105751	“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”	A high dose of Calcifediol or 25-hydroxyvitamin D reduced the ICU admission of patients with COVID-19. Despite this, larger trials with properly matched groups are needed.
Kara et al., 2020 British Journal of Nutrition Volume 124, Issue 7, Pages 736 - 741	'Scientific Strabismus' or two related pandemics: Coronavirus disease and vitamin D deficiency	There is a severe vitamin D deficiency across the world and an association between this and mortality in COVID-19 is possible.
Gündüz & Karaaslan, 2020 Annali Italiani di Chirurgia Volume 91, Issue 6, Pages 673 - 678	Covid-19 reminds us: Community vitamin d deficiency	Comparing vitamin D status between people affected with COVID-19 and those who are not it is noticeable that those affected by the illness had lower levels in serum (<i>In Italian</i>).
Mercola et al., 2020 Nutrients Volume 12, Issue 11, Pages 1 – 24, Article number 3361	Evidence regarding vitamin d and risk of covid-19 and its severity	According to various observational studies, it seems to be a link between a deficiency in vitamin D and the risk of COVID-19 infection. Supplementation of this vitamin as treatment or prevention could be useful, nevertheless, large scale randomized control trials are necessary on this matter.
Hoong et al., 2020 Hormone and Metabolic Research	Are Adequate Vitamin D Levels Helpful in Fighting COVID-19? A Look at the Evidence	There seems to be a link between COVID-19 and vitamin D levels so this association is worthy of exploration.

Volume 52, Issue 11, Pages 775 - 783		
Bilezikian et al., 2020 European Journal of Endocrinology Volume 183, Issue 5, Pages R133 - R147	MECHANISMS in ENDOCRINOLOGY Vitamin D and COVID-19	Vitamin D has the potential to intervene in the cytokine storm that causes some of the most serious complications of COVID-19, like the ARDS. Moreover, it could have effects on the coagulopathy that can course with the illness.
Tan et al., 2020 Nutrition Volume 79-80, Article number 111017	Cohort study to evaluate effect of vitamin D, magnesium, and vitamin B12 in combination on severe outcome progression in older patients with coronavirus (COVID-19)	Supplementation with vitamin D, magnesium and vitamin B12 in older patients to prevent clinical deterioration and oxygen support.
Annweiler et al., 2020 Nutrients Volume 12, Issue 11, Pages 1 – 12, Article number 3377	Vitamin d supplementation associated to better survival in hospitalized frail elderly covid-19 patients: The geria-covid quasi-experimental study	Vitamin D supplementation in elder frail patients was showed to reduce the mortality of COVID-19 in this study.
Mansur et al., 2020 Clinica e Investigacion en Arteriosclerosis Volume 32, Issue 6, Pages 267 – 277	Vitamin D high doses supplementation could represent a promising alternative to prevent or treat COVID-19 infection	Vitamin's D anti-inflammatory and immunomodulatory properties may be beneficial for COVID-19 but more clinical trials are necessary to validate the hypothesis.
Mardani et al., 2020 Virus Research Volume 289, Article number 198148	Association of vitamin D with the modulation of the disease severity in COVID-19	Vitamin D has a modulating effect on lung injuries so its levels were measured, along with ACE concentrations and neutrophil to lymphocyte ratio, in patients with COVID-19 and their levels were altered comparing them to a control group.
Annweiler et al., 2020 Journal of Steroid Biochemistry and Molecular Biology Volume 12, Issue 11, Pages 1 – 12, Article number 3377	Vitamin D and survival in COVID-19 patients: A quasi-experimental study	Vitamin D3 supplementation taken during or just before COVID-19 was associated with a less severe course of the disease in frail elderly patients.

Silberstein, 2020 International Immunopharmacology Volume 88, Article number 106995	Correlation between premorbid IL-6 levels and COVID-19 mortality: Potential role for Vitamin D	IL-6 are higher in COVID-19 patients. Since vitamin D is shown to lower the levels of this interleukin the prescription of this vitamin may be in order to prevent this situation.
Im et al., 2020 International Journal of Infectious Diseases Volume 100, Pages 390 – 393	Nutritional status of patients with COVID-19	Deficiency of vitamin D or selenium is shown to decrease the immune system actions against COVID-19 and worsen the status of the disease.
Lansiaux et al., 2020 Spatial and Spatio-temporal Epidemiology Volume 35, Article number 100362	Covid-19 and vit-d: Disease mortality negatively correlates with sunlight exposure	Sunlight exposure may have a negative correlation with COVID-19 mortality due to its role in vitamin's D synthesis.
Malaguarnera, 2020 Nutrients Volume 12, Issue 11, Pages 1 – 19, Article number 3512	Vitamin d3 as potential treatment adjuncts for covid-19	The use of vitamin D supplementation in SARS-CoV-2 infection is supported by several observational studies since its actions may prevent severe respiratory effects.
Padhi et al., 2020 International Immunopharmacology Volume 88, Article number 107001	Lower levels of vitamin D are associated with SARS-CoV-2 infection and mortality in the Indian population: An observational study	There is an inverse correlation between 25(OH)D levels and SARS-CoV-2 infection rate but these observations need to be validated by more studies.
Evans & Lippman, 2020 Cell Metabolism Volume 32, Issue 5, Pages 704 - 709	Shining Light on the COVID-19 Pandemic: A Vitamin D Receptor Checkpoint in Defense of Unregulated Wound Healing	Paricalcitril, a vitamin D analogue, has been proposed as infusion therapy against the cytokine storm that COVID-19 produces. Vitamin D and the inability of its receptor to activate can worsen respiratory syndrome.
Bae & Kim, 2020 Molecules (Basel, Switzerland) Volume 25, Issue 22	Mini-Review on the Roles of Vitamin C, Vitamin D, and Selenium in the Immune System against COVID-19	Vitamin D, along with vitamin C and selenium, is discussed to have a great impact on the immune system. Their role in COVID-19 is explored in this review.
Santaolalla et al., 2020 Frontiers in Physiology Volume 11, Article number 564387	Association Between Vitamin D and Novel SARS-CoV-2 Respiratory Dysfunction – A Scoping Review of Current Evidence and Its Implication for COVID-19 Pandemic	A search was conducted about different studies to determine the relationship that may exist between COVID-19 morbidity and mortality and vitamin D deficiency. This review resulted

		in the need for more observational studies to clearly establish the connection between the two elements.
Murdaca et al., 2020 Clinical and Molecular Allergy Volume 18, Issue 1, Article number 23	Vitamin D and Covid-19: an update on evidence and potential therapeutic implications	The mechanisms which through vitamin D reduces the risk and mortality of respiratory infections are diverse. Despite this, whether vitamin D is beneficial or not for COVID-19 prevention or treatment is not clear.
Jain et al., 2020 Scientific Reports Volume 10, Issue 1, Article number 20191	Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers	Levels of vitamin D are particularly low among COVID-19 patients and the inflammatory response is higher. This results in increased mortality of the disease, which could be prevented through supplementation.
Pinzon at al., 2020 Tropical Medicine and Health Volume 48, Issue 1, Article number 102	Vitamin D deficiency among patients with COVID-19: case series and recent literature review	In this study, all the participants who had COVID-19, had vitamin D deficiency. Supplementation may be beneficial thanks to the very few risk vitamin D has. Randomized control trials about this recommendation are needed.
Griffin et al., 2020 Royal Society Open Science Volume 7, Issue 12, Article number 201912	Vitamin D and COVID-19: Evidence and recommendations for supplementation	Even if there is no clear correlation between vitamin D deficiency and COVID-19 people who get hospitalized due to the illness should have the levels of the vitamin taken into consideration and the deficiency of the population should be treated.
Grant et al., 2020 Nutrients Volume 12, Issue 12, Pages 1 – 19, Article number 3741	The benefits of vitamin D supplementation for athletes: Better performance and reduced risk of COVID-19	Aside from the benefits that vitamin D has for athletes in improving their condition, the supplementation may offer protection against COVID-19 thanks to its action against other respiratory diseases.
Yilmaz & Sen, 2020 Pediatric Pulmonology Volume 55, Issue 12, Pages 3595 – 3601	Is vitamin D deficiency a risk factor for COVID-19 in children?	Vitamin D values may be associated with COVID-19 since this study of the pediatric population showed that the two factors had a negative correlation.

Annweiler et al., 2020 Trials Volume 21, Issue 1, Article number 1031	COvid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial	Vitamin D supplementation may be effective to improve the outcome of COVID-19. This article studies the effect of a single high dose of cholecalciferol versus a standard dose during 14 days (both oral).
Vassiliou et al., 2020 Nutrients Volume 12, Issue 12, Pages 1 – 9 Article number 3773,	Low 25-hydroxyvitamin D levels on admission to the intensive care unit may predispose COVID-19 pneumonia patients to a higher 28-day mortality risk: A pilot study on a greek icu cohort	Low levels of 25(OH)D upon ICU admission due to COVID-19 seem to be a predisponent factor for mortality according to this observational study.
Ling et al., 2020 Nutrients Volume 12, Issue 12, Pages 1 – 16, Article number 3799	High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with covid-19: A cross-sectional multi-centre observational study	The aim of the study was to predict whether low levels of 25(OH)D could be used as a predictor for COVID-19's mortality. Treatment with cholecalciferol seemed to reduce the risk associated with the disease but larger studies are necessary to determine both of these statements.
Gonçalves et al., 2020 Clinical Nutrition ESPEN Volume 40, Pages 110 – 114	Prevalence of obesity and hypovitaminosis D in elderly with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	There is a high prevalence of ICU admission of elderly patients due to COVID-19 who have obesity and hypovitaminosis D in the study, so they suggest these two factors can be related to the severity of the disease and supplementation of the elderly population should be considered
Name et al., 2020 Frontiers in Nutrition Volume 7, Article number 606398	Zinc, Vitamin D and Vitamin C: Perspectives for COVID-19 With a Focus on Physical Tissue Barrier Integrity	Deficiency of Zinc, Vitamin D or Vitamin C compromises the immune system so supplementation of these nutrients may be in order during the pandemic to offer protection against the disease.
Ahmed, 2020 Frontiers in Immunology Volume 11, Article number 590459	A Network-Based Analysis Reveals the Mechanism Underlying Vitamin D in Suppressing Cytokine Storm and Virus in SARS-CoV-2 Infection	Vitamin D has antiviral effects and the potential for suppressing the cytokine storm that takes place in the organism during SARS-CoV-2 infection
Boulkrane et al., 2020 Frontiers in Pharmacology Volume 11, Article number 604579	COVID-19 Disease and Vitamin D: A Mini-Review	Supplementation of the high-risk population against COVID-19 with vitamin D can be helpful in both the prevention and treatment of the disease.

Ferder et al., 2020 American Journal of Physiology - Lung Cellular and Molecular Physiology Volume 319, Issue 6, Pages L941 - L948	Vitamin D supplementation as a rational pharmacological approach in the COVID-19 pandemic	The inflammatory storm caused by SARS-CoV-2 is one of the causes of mortality of the virus. The modulatory actions that vitamin D exert over the immune system are promising to use it as treatment or prevention in the high-risk population.
Hetta et al., 2021 European Review for Medical and Pharmacological Sciences Volume 25, Issue 4, Pages 2131 - 2145	The interplay between vitamin D and COVID-19: Protective or bystander?	Several studies had linked vitamin D deficiency with a higher risk of viral infection for SARS-CoV-2. Nevertheless, more studies on the matter are needed.
Yisak et al., 2021 Risk Management and Healthcare Policy Volume 14, Pages 31 - 38	Effects of vitamin d on covid-19 infection and prognosis: A systematic review	Different articles showed that blood levels of vitamin D could be linked with different aspects of COVID-19 so supplementation or natural methods to maintain adequate levels are in order to decrease the impact of the pandemic.
Luo et al., 2021 Journal of Nutrition Volume 151, Issue 1, Pages 98 - 103	Vitamin D deficiency is inversely associated with COVID-19 incidence and disease severity in Chinese people	Serum levels of 25(OH)D were significantly lower in patients who had COVID-19 so this could suggest that vitamin D status impacts the severity of the disease.
Rhodes et al., 2021 Journal of Internal Medicine Volume 289, Issue 1, Pages 97 – 115	Perspective: Vitamin D deficiency and COVID-19 severity – plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis	Deficiency of vitamin D has been proposed as one of the determinants of the severity of the new coronavirus disease but the studies to corroborate this claim are still lacking.
Wang et al., 2021 Contemporary Clinical Trials Volume 100, Article number 106176	The vitamin D for COVID-19 (VIVID) trial: A pragmatic cluster-randomized design	The article contains information about how vitamin D3 supplementation seems to reduce hospitalization and mortality of COVID-19
Paiz et al., 2021 Current Tropical Medicine Reports DOI: 10.1007/s40475-021-00236-3	Vitamin D Status: Can It Affect the Risk of Infection and the Severity of COVID-19 Symptoms?	The status of vitamin D could have an influence over the progression of COVID-19 but more studies are needed in order to prove this claim true.
Basaran et al., 2021 Bratislava Medical Journal Volume 122, Issue 3, Pages 200 – 205	The relationship between vitamin D and the severity of COVID-19	Maintaining adequate levels of vitamin D could reduce the inflammation associated with SARS-CoV-2, reducing in this way the severity and the impact of the pandemic.

Verdoia & De Luca, 2021 QJM Volume 114, Issue 1	Potential role of hypovitaminosis D and Vitamin D supplementation during COVID-19 pandemic	The spread of hypovitaminosis D and its possible relation with the current pandemic has impeded this review to compile information about these topics.
Khan et al., 2021 Journal of Diabetes and Metabolic Disorders Volume 20, Issue 1, Pages 931 – 938	Vitamin D and COVID-19: is there a role?	Vitamin's D role against other respiratory disease and immunomodulatory effects has led this review to investigate its possible role in the current pandemic.
Yadav et al., 2021 Indian Journal of Clinical Biochemistry DOI: 10.1007/s12291-020-00950-1	Association of Vitamin D Status with COVID-19 Infection and Mortality in the Asia Pacific region: A Cross-Sectional Study	There is a significant relationship between the number of COVID-19 cases and vitamin D levels. Further trials are needed about this matter.
Martín Giménez et al., 2021 Journal of Current Science and Technology Volume 11, Issue 1, Pages 148 – 157	Covid-19 pandemic and vitamin d deficiency: A different approach with an analysis of the findings and a complimentary proposal	Vitamin D immunomodulatory effects lead to believe that it may have an effect against COVID-19, relating countries with lower levels as those whose mortality due to the disease is higher.
Ferrari et al., 2021 Cell Biochemistry and Function Volume 39, Issue 1, Pages 35 – 47	Is there a link between vitamin D status, SARS-CoV-2 infection risk and COVID-19 severity?	Vitamin D supplementation could be useful against COVID-19 infection since there seems to be a relationship between low levels and the severity of the disease.
Ahmed et al., 2021 Journal of Advanced Biotechnology and Experimental Therapeutics Volume 4, Issue 2, Pages 133 - 148	Prospects of vitamin d in the treatment of covid-19 patient and improving maternal and child health during pandemic	Vitamin D supplementation could play an important role during the pandemic, thanks to its diverse functions, to prevent the disease, especially in vulnerable groups.
Sidiropoulou et al., 2021 International Journal of Molecular Medicine Volume 47, Issue 1, Pages 92 - 100	Unraveling the roles of Vitamin D status and melanin during COVID-19 (Review)	This review studies the relationship between COVID-19 and vitamin D status along with other factors that have an influence on it.
Ünsal et al., 2021 Journal of Endocrinological Investigation DOI: 10.1007/s40618-021-01566-9	Retrospective analysis of vitamin D status on inflammatory markers and course of the disease in patients with COVID-19 infection	High inflammation and worse clinical outcomes for COVID-19 could be related to the low levels of vitamin D detected in the patients.

Bennouar et al., 2021 Journal of the American College of Nutrition Volume 40, Issue 2, Pages 104 - 110	Vitamin D Deficiency and Low Serum Calcium as Predictors of Poor Prognosis in Patients with Severe COVID-19	The severity of COVID-19 seems to be regulated by different factors and two of them could be hypovitaminosis D and hypocalcemia, frequently present among the patients.
Sengupta et al., 2021 Molecular and Cellular Biochemistry Volume 476, Issue 6, Pages 2421 - 2427	Role of vitamin D in treating COVID-19-associated coagulopathy: problems and perspectives	Reducing the risk of COVID-19 through supplements of vitamin D is being studied but more trials related to its effects on coagulopathy are needed.
Panfili et al., 2021 Journal of Endocrinological Investigation Volume 44, Issue 1, Pages 27 - 35	Possible role of vitamin D in Covid-19 infection in pediatric population	Vitamin D is beneficial for immune-related diseases so it could be positive against SARS-CoV-2 infection.
Banerjee et al., 2021 Expert Review of Anti-Infective Therapy DOI: 10.1080/14787210.2021.1905519	Vitamin D and immuno-pathology of COVID-19: many interactions but uncertain therapeutic benefits	Vitamin D role against viral diseases has relevance for the new coronavirus infection and should be investigated for this and future illnesses
Bayramoğlu et al., 2021 European Journal of Pediatrics DOI: 10.1007/s00431-021-04030-1	The association between vitamin D levels and the clinical severity and inflammation markers in pediatric COVID-19 patients: single-center experience from a pandemic hospital	This article studied the role of the anti-inflammatory properties of vitamin D in children and adolescents with COVID-19 and concluded that supplementation in those who are deficient should be considered.
Farid et al., 2021 Irish Journal of Medical Science DOI: 10.1007/s11845-020-02452-8	Active vitamin D supplementation and COVID-19 infections: review	Vitamin D has been suggested as treatment and prevention of COVID-19 by several studies but evidence about whether if this is efficient or not is still needed.
Orchard et al., 2021 Clinical Chemistry and Laboratory Medicine Volume 59, Issue 6, Pages 1155 – 1163	Vitamin D levels and intensive care unit outcomes of a cohort of critically ill COVID-19 patients	This study showed that there were no significant differences between ICU clinical outcomes in patients with COVID-19 with low or normal levels of vitamin D.
Mado et al., 2021 Electronic Journal of General Medicine Volume 18, Issue 2, Article number em283	Is vitamin d supplementation protective against coronavirus disease 2019 (Covid-19)?	Vitamin D affects the immune system in different ways so it has been proposed that it could be positive against COVID-19

Mazziotti et al., 2021 Journal of Endocrinological Investigation DOI: 10.1007/s40618-021-01535-2	Vitamin D deficiency, secondary hyperparathyroidism and respiratory insufficiency in hospitalized patients with COVID-19	Hypovitaminosis D and secondary hyperparathyroidism could affect negatively the outcome of COVID-19
Szeto et al., 2021 Endocrine Research Volume 46, Issue 2, Pages 66 – 73	Vitamin D Status and COVID-19 Clinical Outcomes in Hospitalized Patients	There is no relationship between vitamin D status in prehospitalization and the clinical outcome of COVID-19
Infante et al., 2021 Journal of the American College of Nutrition DOI: 10.1080/07315724.2021.1877580	Low Vitamin D Status at Admission as a Risk Factor for Poor Survival in Hospitalized Patients With COVID-19: An Italian Retrospective Study	In this cohort study low levels of 25(OH)D seemed to increase the risk of in-hospital mortality in patients with COVID-19.
Notz et al., 2021 Clinical Nutrition DOI: 10.1016/j.clnu.2021.03.001	Vitamin D deficiency in critically ill COVID-19 ARDS patients	Low levels of 1,25-dihydroxyvitamin D are associated with a worse clinical case of acute respiratory distress syndrome in COVID-19 patients
Kalia et al., 2021 Journal of Leukocyte Biology DOI: 10.1002/JLB.4COVR1020-698R	Role of vitamin D in regulating COVID-19 severity—An immunological perspective	Several studies have established that exists an association between low levels of vitamin D and the severity of COVID-19 thanks to its immunomodulatory role in respiratory diseases.
Amin & Drenos, 2021 BMJ Nutrition, Prevention and Health DOI: 10.1136/bmjnph-2020-000151	No evidence that vitamin D is able to prevent or affect the severity of COVID-19 in individuals with European ancestry: a Mendelian randomisation study of open data	Vitamin D supplementation has a protective effect against the new coronavirus disease and its deficiency affects the risk and severity of the virus.
Biesalski, 2021 Current opinion in clinical nutrition and metabolic care Volume 24, Issue 1, Pages 18 - 24	Obesity, vitamin D deficiency and old age a serious combination with respect to coronavirus disease-2019 severity and outcome	Supplementation with vitamin D could help as treatment or prophylaxis for COVID-19 thanks to its diverse roles in the organism.
Cereda et al., 2021 Current Opinion in Clinical Nutrition and Metabolic Care Volume 24, Issue 1, Pages 102 - 107	A brief discussion of the benefit and mechanism of vitamin D supplementation on coronavirus disease 2019	Several studies have suggested that vitamin D has a protective role against COVID-19 but more are needed to ascertain whether it prevents the disease, betters the outcome... among other questions.

Giustina, 2021 Endocrine Volume 72, Issue 1	Hypovitaminosis D and the endocrine phenotype of COVID-19	An inadequate vitamin D status could worsen the clinical outcome of patients with COVID-19
Giannini et al., 2021 Nutrients Volume 13, Issue 1, Pages 1 – 15, Article number 219	Effectiveness of in-hospital cholecalciferol use on clinical outcomes in comorbid covid-19 patients: A hypothesis-generating study	Cholecalciferol treatment in patients hospitalized with COVID-19 resulted in more positive outcomes, especially in patients with comorbidities.
Chagas et al., 2021 Sao Paulo Medical Journal Volume 139, Issue 1, Pages 81 - 87	Critical analysis on the use of cholecalciferol as a covid-19 intervention: A narrative review	Several studies report the beneficial effects of vitamin D supplementation against COVID-19 but more data from robust studies are needed.
Livingston et al., 2021 International Journal of Clinical Practice DOI: 10.1111/ijcp.14166	Detectable respiratory SARS-CoV-2 RNA is associated with low vitamin D levels and high social deprivation	Low vitamin D levels are associated with a poorer outcome of the new coronavirus disease, especially in the elderly.
Parsons et al., 2021 BMJ Military Health DOI: 10.1136/bmjmilitary-2020-001686	Does vitamin D supplementation prevent SARS-CoV-2 infection in military personnel? Review of the evidence	The expression of vitamin D receptor in the immune cells reveals the immunomodulatory effects of vitamin D and, therefore, leads to the study of its possible actions against SARS-CoV-2.
Lahoor Basha et al., 2021 Clinical Epidemiology and Global Health Volume 9, Pages 326 – 331	Is the shielding effect of cholecalciferol in SARS CoV-2 infection dependable? An evidence based unraveling	Maintaining adequate levels of vitamin D3 may help the management of the new coronavirus disease.
Abraham et al., 2021 International Journal of Environmental Research and Public Health Volume 18, Issue 2, Pages 1 – 21	Can optimum solar radiation exposure or supplemented vitamin D intake reduce the severity of COVID-19 symptoms?	Vitamin D supplements could reduce the severity of COVID-19 symptoms, especially acute respiratory stress syndrome.
Kumar et al., 2021 Virus Research Volume 292, Article number 198235	Putative roles of vitamin D in modulating immune response and immunopathology associated with COVID-19	Vitamin D exerts its immunomodulatory effects on very different levels so this article explores its potential against COVID-19 in different aspects of the disease.

Hastie et al., 2021 European Journal of Nutrition Volume 60, Issue 1, Pages 545 – 548	Vitamin D and COVID-19 infection and mortality in UK Biobank	The study hasn't found any evidence that supports a possible relationship between low levels of 25(OH)D and COVID-19 but further trials are necessary in order to prove it.
Deluccia et al., 2021 Nutrition Reviews Volume 79, Issue 2, Pages 227 – 234	The implications of vitamin D deficiency on COVID-19 for at-risk populations	The use of supplements of vitamin D due to its possible relationship with the new coronavirus disease is being studied in this article.
Hadizadeh, 2021 Nutrition Reviews Volume 79, Issue 2, Pages 200 – 208	Supplementation with vitamin D in the COVID-19 pandemic?	This review compiles information about the possible influence of vitamin D on COVID-19. It discussed the role of vitamin D in other respiratory diseases and its possible mechanisms of action against the new coronavirus.
Karahan & Katkat, 2021 Journal of Nutrition, Health and Aging Volume 25, Issue 2, Pages 189 – 196	Impact of Serum 25(OH) Vitamin D Level on Mortality in Patients with COVID-19 in Turkey	Vitamin D deficiency was present among a great percentage of the patients with severe coronavirus disease. Low levels of 25(OH)D were independently associated with mortality.
Munshi et al., 2021 Journal of Medical Virology Volume 93, Issue 2, Pages 733 - 740	Vitamin D insufficiency as a potential culprit in critical COVID-19 patients	Vitamin D status could be a factor of prediction of the possibility of a patient with COVID-19 to develop a severe case of the disease.
Kloc et al., 2021 Cellular Immunology Volume 360, Article number 104259	Effects of vitamin D on macrophages and myeloid-derived suppressor cells (MDSCs) hyperinflammatory response in the lungs of COVID-19 patients	Vitamin D could influence the inflammatory response of macrophage and myeloid-derived suppressor cells in COVID-19
De Barros Viana et al., 2021 Reviews in the Neurosciences Volume 32, Issue 2, Pages 235 - 247	COVID-19 in age-related neurodegenerative diseases: Is there a role for vitamin D3 as a possible therapeutic strategy?	Vitamin D supplementation is being taken into consideration due to its possible role in COVID-19 and neurodegenerative illnesses.
Moin et al., 2021 Frontiers in Endocrinology Volume 12, Article number 638621	Vitamin D Association With Macrophage-Derived Cytokines in Polycystic Ovary Syndrome: An Enhanced Risk of COVID-19 Infection?	Vitamin D deficiency and basal macrophage activation that happens during Polycystic Ovary Syndrome increase the risk of a severe COVID-19 infection.

Teymoori-Rad & Marashi, 2021 Reviews in Medical Virology Volume 31, Issue 2, Article number e2159	Vitamin D and Covid-19: From potential therapeutic effects to unanswered questions	Vitamin D supplementation could be beneficial for COVID-19 in both treatment and prevention.
Sulli et al., 2021 Nutrients Volume 13, Issue 3, Pages 1 – 13, Article number 717	Vitamin d and lung outcomes in elderly covid-19 patients	Low levels of 25(OH)D were associated with more lung involvement in the new coronavirus disease. Detection of these low levels in younger patients with severe cases of the illness leads to thinking that it could be a determinant factor.
Lohia et al., 2021 American Journal of Physiology - Endocrinology and Metabolism Volume 320, Issue 3	Exploring the link between vitamin D and clinical outcomes in COVID-19	There was no significant association found between low levels of vitamin D and mortality due to COVID-19 or more risk of its comorbidities.
Lordan, 2021 Nutrients Volume 13, Issue 3, Pages 1 – 25, Article number 740	Notable developments for vitamin d amid the covid-19 pandemic, but caution warranted overall: A narrative review	Patients with severe coronavirus disease tended to have vitamin D deficiency so maintaining good levels may have a positive influence on the disease.
Griffin et al., 2021 Clinical Medicine, Journal of the Royal College of Physicians of London Volume 21, Issue 2, Pages E144 - E149	Perspective: Vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: Implications for COVID-19	The role of vitamin D in respiratory diseases suggests a possible link between its deficiency and the current COVID-19 pandemic. Supplementation should be taken into consideration.
Annweiler & Souberbielle, 2021 Geriatrie et psychologie neuropsychiatrie du vieillissement Volume 19, Issue 1, Pages 20 – 29	Vitamin D supplementation and COVID-19: expert consensus and guidelines	Hypovitaminosis D could be linked with severe cases of COVID-19 since a great percentage of individuals with this illness presented it (<i>In French</i>).
Bleizgys, 2021 International Journal of Clinical Practice Volume 75, Issue 3, Article number e13748	Vitamin D and COVID-19: It is time to act	Vitamin D deficiency is a grave global problem since it could be linked with severe cases of the new coronavirus deficiency.

Name et al., 2021 International Journal of Molecular Medicine Volume 47, Issue 3, Article number 4844	Vitamin D, zinc and glutamine: Synergistic action with OncoTherad immunomodulator in interferon signaling and COVID-19 (Review)	Vitamin D, zinc and glutamine seem to regulate immune responses mediated by IFN signaling and this means they could have potential against COVID-19
Liu et al., 2021 International Journal of Infectious Diseases Volume 104, Pages 58 – 64	Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis	Vitamin's D levels could be associated with an increased risk of COVID-19 infection but further studies are needed on this matter.
De Smet et al., 2021 American Journal of Clinical Pathology Volume 155, Issue 3, Pages 381 - 388	Serum 25(OH)D Level on Hospital Admission Associated with COVID-19 Stage and Mortality	In this study low levels of 25(OH)D upon admission were associated with increased mortality of COVID-19.
Teshome et al., 2021 Frontiers in Public Health Volume 9, Article number 624559	The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis	Low serum levels of 25(OH)D were associated with a higher risk of COVID-19 disease. Sufficient levels decreased said risk.
Nie et al., 2021 Medicine Volume 100, Issue 9, Pages e24517	Oral high dose vitamin D for the treatment of diabetic patients with COVID-19: A protocol for systematic review and meta-analysis	The authors of the article are going to carry out a study of how treatment with vitamin D affects diabetic patients infected with COVID-19.
Feketea et al., 2021 Frontiers in Immunology Volume 12, Article number 648546	Vitamin D in Corona Virus Disease 2019 (COVID-19) Related Multisystem Inflammatory Syndrome in Children (MIS-C)	Supplementation with 25-hydroxyvitamin D3 has favourable effects over Multisystem Inflammatory Syndrome in children, a grave complication of COVID-19.
Hernández et al., 2021 Journal of Clinical Endocrinology and Metabolism Volume 106, Issue 3, Pages E1343 - E1353	Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection	Levels of vitamin D were lower in patients with COVID-19 but there was no apparent relation between this and the severity of the disease.
Murai et al., 2021 JAMA - Journal of the American Medical Association Volume 325, Issue 11, Pages 1053 - 1060	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	A high dose supplementation of vitamin D hospitalized with COVID-19 reduced their hospital stay compared with those who received the placebo.

Meltzer et al., 2021 JAMA Network Open Volume 4, Issue 3, Article number e214117	Association of Vitamin D Levels, Race/Ethnicity, and Clinical Characteristics with COVID-19 Test Results	The risk of COVID-19 was greater in black individuals with low vitamin D but no significant difference was found among white individuals.
Guan, 2021 Chinese Journal of Endocrinology and Metabolism Volume 37, Issue 3, Pages 177 - 179	Can we use vitamin D to prevent and treat COVID-19?	Vitamin D has the potential for treatment and prevention of the new coronavirus illness. The correction of the status of the vitamin is important (<i>In Chienese</i>).
Akbar et al., 2021 Frontiers in Nutrition Volume 8, Article number 660420	Low Serum 25-hydroxyvitamin D (Vitamin D) Level Is Associated With Susceptibility to COVID-19, Severity, and Mortality: A Systematic Review and Meta-Analysis	Low levels of 25(OH)D were associated with high mortality of COVID-19. Other factors that influenced were vitamin D and diabetes.
Easty et al., 2021 Frontiers in Endocrinology Volume 12, Article number 644298	New Roles for Vitamin D Superagonists: From COVID to Cancer	Vitamin D superagonist could play an important role that has not been studied yet against COVID-19
Dramé et al., 2021 Nutrients Volume 13, Issue 4, Article number 1339	Relation between vitamin d and covid-19 in aged people: A systematic review	Vitamin D deficiency appears to be linked with an increased risk of COVID-19, especially in the elderly. It was also associated with worse outcomes of the disease.
Tehrani et al., 2021 Clinical Nutrition ESPEN Volume 42, Pages 313 – 317	Evaluation of vitamin D levels in COVID-19 patients referred to Labafinejad hospital in Tehran and its relationship with disease severity and mortality	There was no statistical difference between levels of vitamin D and COVID-19's outcome. This deficiency affected patients with severe course of the disease.
Carpagnano et al., 2021 Journal of Endocrinological Investigation Volume 44, Issue 4, Pages 765 – 771	Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19	Hypovitaminosis D is prevalent in COVID-19 patients and they have a higher risk of mortality. This deficiency could be a marker of the poor prognosis of the disease.
Katz et al., 2021 Nutrition Volume 84, Article number 111106	Increased risk for COVID-19 in patients with vitamin D deficiency	In this study, vitamin D deficiency was highly linked with a more severe case of the new coronavirus disease.

Charoenngam et al., 2021 Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists Volume 15, Issue 9, Article number e0239799	Association of Vitamin D Status With Hospital Morbidity and Mortality in Adult Hospitalized Patients With COVID-19	There is an independent association between adequate levels of 25(OH)D and decreased risk of mortality from COVID-19 in the elderly and individuals without obesity.
Piroux, 2021 Actualites Pharmaceutiques Volume 60, Issue 605, Pages 52 - 55	Interest of vitamin D in COVID-19	Vitamin's D immunomodulatory effects may have potential against COVID-19, which explains the increased number of purchases and prescriptions of this vitamin.
Abdollahi et al., 2021 Journal of Medical Virology Volume 93, Issue 4, Pages 2359 - 2364	The association between the level of serum 25(OH) vitamin D, obesity, and underlying diseases with the risk of developing COVID-19 infection: A case-control study of hospitalized patients in Tehran, Iran	Vitamin D deficiency and obesity seem to be predisposing factor for the COVID-19 illness.
Cereda et al., 2021 Clinical Nutrition Volume 40, Issue 4, Pages 2469 - 2472	Vitamin D 25OH deficiency in COVID-19 patients admitted to a tertiary referral hospital	Low levels of 25(OH)D were highly prevalent among COVID-19 patients but they weren't associated with clinical outcomes of the disease.
Angelidi et al., 2021 Mayo Clinic Proceedings Volume 96, Issue 4, Pages 875 - 886	Vitamin D Status Is Associated With In-Hospital Mortality and Mechanical Ventilation: A Cohort of COVID-19 Hospitalized Patients	COVID-19 mortality and severity were inversely associated with vitamin D levels. Further observational studies about this are needed.
Turrubiates-Hernández et al., 2021 International Journal of Molecular Medicine Volume 47, Issue 4, Article number 32	Potential immunomodulatory effects of vitamin D in the prevention of severe coronavirus disease 2019: An ally for Latin America (Review)	Vitamin's D immunomodulatory effects suggest that supplementation could help in the prevention of COVID-19
Giustina, 2021 Endocrine Volume 72, Issue 1	Hypovitaminosis D and the endocrine phenotype of COVID-19	Some consequences of COVID-19 infection could be influenced by an incorrect vitamin D status.

Pugach & Pugach, 2021 Wiener Klinische Wochenschrift Volume 133, Issue 7-8, Pages 403 - 405	Strong correlation between prevalence of severe vitamin D deficiency and population mortality rate from COVID-19 in Europe	Prevalence of vitamin D deficiency was associated with higher mortality due to COVID-19. Supplementation could be important in the treatment or prevention of the disease.
Gaudio et al., 2021 International Journal of Environmental Research and Public Health Volume 18, Issue 7, Article number 3491	Vitamin D levels are reduced at the time of hospital admission in sicilian SARS-CoV-2-positive patients	Sicilian patients with COVID-19 had low levels of vitamin D upon hospitalization but there is no clear evidence of a relationship between these two factors.
Demir et al., 2021 Journal of Medical Virology Volume 93, Issue 5, Pages 2992 – 2999	Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease	A big part of COVID-19 positive patients had low levels of vitamin D so, maybe, increasing the levels could be a preventive measure against the disease.
Jayawardena et al., 2021 Diabetes and Metabolic Syndrome: Clinical Research and Reviews Volume 15, Issue 3, Pages 757 – 764	Impact of the vitamin D deficiency on COVID-19 infection and mortality in Asian countries	Vitamin D deficiency is heavily associated with the risk of infection and mortality of COVID-19. Adequate levels seemed to have no relationship with the course of the disease.
Tarazona-Santabalbina et al., 2021 Revista Espanola de Geriatria y Gerontologia Volume 56, Issue 3, Pages 177 – 182	VitaminD supplementation for the prevention and treatment of COVID-19: a position statement from the Spanish Society of Geriatrics and Gerontology	Despite the lack of evidence about its efficacy against COVID-19, daily vitamin D supplementation should be standardized as clinical practice.
Alguwaihes et al., 2021 Aging Clinical and Experimental Research Volume 33, Issue 5, Pages 1415 – 1422	Severe vitamin D deficiency is not related to SARS-CoV-2 infection but may increase mortality risk in hospitalized adults: a retrospective case–control study in an Arab Gulf country	Vitamin D deficiency is associated with a major risk of mortality due to COVID-19 but not with infection risk.
Silberstein, 2021 European Journal of Pharmacology Volume 899, Article number 174031	COVID-19 and IL-6: Why vitamin D (probably) helps but tocilizumab might not	Vitamin D could be more useful than tocilizumab in the downregulation of IL-6, which participates in the cytokine storm during COVID-19
Bassatne et al., 2021 Metabolism: Clinical and Experimental Volume 119, Article number 154753	The link between COVID-19 and Vitamin D (VIVID): A systematic review and meta-analysis	Low levels of 25(OH)D could be related to worse outcomes of COVID-19 but there is still no clear evidence on this matter.

		Calcifediol supplementation may play a protective role over the disease.
Petrelli et al., 2021 Journal of Steroid Biochemistry and Molecular Biology Volume 211, Article number 105883	Therapeutic and prognostic role of vitamin D for COVID-19 infection: A systematic review and meta-analysis of 43 observational studies	Low vitamin D values were associated with a higher risk of COVID-19 infection, severity and mortality.
Ricci et al., 2021 Respiratory Research Volume 22, Issue 1, Article number 76	Circulating Vitamin D levels status and clinical prognostic indices in COVID-19 patients	Assessing vitamin D levels could be useful as prognosis of COVID-19 infection. The deficiency of this vitamin seems to be related to severe cases of the disease.
Al-Daghri et al., 2021 Journal of Translational Medicine Volume 19, Issue 1, Article number 166	Vitamin D status of Arab Gulf residents screened for SARS-CoV-2 and its association with COVID-19 infection: a multi-centre case-control study	Individuals with low 25(OH)D in the Arab Gulf were related to SARS-CoV-2 positivity. However, other factors different than this seemed to be more relevant for COVID-19 so the relationship between vitamin D and the illness should be further studied.
Walrand, 2021 Scientific Reports Volume 11, Issue 1, Article number 1981	Autumn COVID-19 surge dates in Europe correlated to latitudes, not to temperature-humidity, pointing to vitamin D as contributing factor	Low levels of 25(OH)D seemed to be a contributing factor for the severity of the new coronavirus disease.
Jevalikar et al., 2021 Scientific Reports Volume 11, Issue 1, Article number 6258	Lack of association of baseline 25-hydroxyvitamin D levels with disease severity and mortality in Indian patients hospitalized for COVID-19	25(OH)D levels upon hospital admission were not related to clinical outcomes of COVID-19 since treatment with cholecalciferol didn't improve the conditions of the patients, comparing them to those who didn't receive the treatment.

COVID-19 Generalities

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the pandemic that the world is currently experiencing for more than a year now. The first case originated in the Chinese province of Wuhan, from where the virus was then extended through the entire planet, in December of the year 2019 and by March of 2020 the situation was declared as a pandemic by the World Health Organization (**Vabret et al., 2020; Wang et al., 2020**).

Like the rest of the virus of this family, SARS-CoV-2 causes an acute respiratory infection in the host which courses with a variety of symptoms like fever, cough and fatigue. These three are the ones that are more common and make the symptomatology very similar to other respiratory infectious pathologies but this disease can also develop in some patient's dyspnoea in different degrees. Despite their similarities, COVID-19 has a greater chance to develop into severe cases in individuals without comorbidities that require more admissions of said patients to the ICU than in other diseases like pneumonia associated with influenza, even among young people (**Cevik et al., 2020**). COVID-19 can also cause gastrointestinal manifestations such as loss of the sense of smell and taste or diarrhoea and vomits. These extra-respiratory manifestations lead to think that the transmission of the virus could be faecal-oral besides through contact with droplets emitted by sick patients and that explain the contagion of people who are close to them. Some studies suggest airborne transmission as a possible means of transmission (**Vabret et al., 2020; Wang et al., 2020**).

Even though in healthy individuals with a strong immune system the disease may course with no manifestations whatsoever, patients who have different comorbidities or whose health is somehow compromised may have a higher risk of contracting the ailment or develop severe cases of infection that can result in death. Some of the complications that were observed are acute stress respiratory syndrome, acute cardiac diseases or higher sensitivity to other infectious diseases. Besides, the absence of symptoms does not mean that a person cannot be a source of infection for the people that surround them. This is why is very important to adhere to the health recommendations to avoid getting the illness. It is important to notice that COVID-19 was discovered in other tissues

different from the respiratory like in the duodenum. This could be related to other means of transmission (**Vabret et al., 2020; Wang et al., 2020**).

Among the preventive measures for COVID-19, we can find the following recommendations:

- Avoid close contact with people out of your inner circle, guard security distance.
- Wash your hands regularly with soap and water and use a hand sanitizer.
- Use of mask to cover both mouth and nose.
- Clean and disinfect surfaces that are touched frequently.
- In case of need of cough or sneeze, cover yourself to avoid the spread of droplets (**dos Santos, 2020**).

Vitamin D and COVID-19

The rapid global spread of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has renewed interest in the possible role of vitamin D in modulating the immune response to respiratory infections. Indeed, widespread vitamin D supplementation has been proposed as a preventative health measure (**Cobbold, 2020**). However, at present the evidence-base is of insufficient quality to support such recommendations.

Importantly, while the active $1,25(\text{OH})_2$ -vitamin D form has been shown to have a role within the immune system (**Aranow, 2011**), evidence linking low 25(OH)D levels (the main circulating form, which correlates poorly to $1,25(\text{OH})_2$ - vitamin D) with increased risk or severity of COVID-19 has been inconsistent (**Lanham-New et al., 2020**). The non-COVID-19 literature contains numerous examples of 25(OH)D-morbidity associations which could be attributable to confounding or reverse causation (**Harvey & Cooper, 2012**). An example, demonstrated using Mendelian randomisation, is of the observational association between low 25(OH)D levels and obesity, which in causal analyses implicate obesity as driving lower 25(OH) D rather than the other way round (**Vimaleswaran et al., 2013**). Furthermore, 25(OH)D levels are determined by sunlight exposure to the skin, supplement use, diet, and comorbidity (since, in some clinical

contexts, 25(OH)D may be a negative acute phase reactant (**Czarnik et al., 2018**). As such, vitamin D status is closely linked to general health and the potential for confounding in observational studies is high (**Harvey and Cooper, 2012**).

While vitamin D, as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2), has a wide therapeutic window with a relatively low risk of toxicity, the easy availability of high-dose supplements (particularly on the internet) may increase the likelihood of such rare events in the population (**Rizzoli, 2021**). A further consideration in the context of the current pandemic is the potential for adverse health behaviour resulting from a perception of protection gained from taking supplements. Thus, it is important that a strictly evidence-based approach, together with health economic assessment (which is beyond the scope of this review), underpin any health recommendations in relation to the use of vitamin D supplements to prevent or treat COVID-19. In this work, we review the scientific literature relating to vitamin D and respiratory infections, with a particular focus on COVID-19.

A possible relation between vitamin D and COVID-19?

It appears that the outbreak of COVID-19 happened when 25(OH)D levels in blood are low, which coincides with the seasons of the year when the solar radiation that reaches the Earth's surface is at its minimum (**Grant et al., 2020**). It also seems that vitamin D deficiency contributes in the development of acute respiratory stress syndrome (SARS) and increases the fatal cases of the illness, which are related with age and the presence of chronic disease comorbidity (both of them related to low levels of the vitamin) (**Meltzer et al., 2020**).

Another recent study (**McCartney & Byrne, 2020**) highlights the role of dipeptidyl peptidase-4 receptor (DPP-4/CD26) in the molecular virulence mechanism of closely-related COVID-MERS virus. In this respect, human DPP-4/CD26 has recently been shown to interact with the S1 domain of the COVID-19 spike glycoprotein, indicating that it may also be an important virulence factor in COVID-19 infection (**Vankadari & Wilce, 2020**). In this regard, DPP4/CD26 receptor expression has been shown to be significantly reduced *in vivo* upon correction of vitamin D deficiency (**Vankadari & Wilce, 2020**).

Based on this information, researchers call for vulnerable groups (elderly, hospitalizes patients, nursing home residents and others) to receive supplementation with 20-50µg/d of vitamin D to enhance their resistance to COVID-19 (**McCartney & Byrne, 2020; Griffin et al., 2020**).

Although this data does not prove the conclusion that vitamin D prevents COVID-19, its administration could contribute to prevent infections. Vitamin D will most likely be ineffective if given to sick patients; the possible beneficial effects will probably be as prevention, providing some sort of immune-boosting in susceptible individuals. Vitamin D will not be the key element to prevent the coronavirus pandemic, but it can contribute efficiently to prevent and/or difficult infections.

More studies are needed to confirm this hypothesis to substantiate the benefits of vitamin D supplementation against infection, especially in the case of vegetarian and vegan patients who do not consume vitamin-D of animal origin.

Respiratory diseases and vitamin D

Respiratory tract diseases were responsible for more than 2 million deaths in 2013 and they are still a major health problem for the sanitary systems around the world. Different observational studies have detected a connection between low levels of calcitriol, also known as 1- α ,25-dihydroxycalciferol (1,25-(OH)₂D₃), the active form of vitamin D, and greater susceptibility to respiratory infections. This could be explained since vitamin D is relevant in the synthesis of different peptides that have antimicrobial activity in the organism therefore, low levels of 25(OH)D in blood could lead to a lesser protective action against certain pathogens and an individual who is more prone to develop respiratory tract diseases (**Martineau et al., 2017**).

It has been shown that vitamin D supplementation proved to have protective effects against infections but only in weekly and daily administration and not with bolus treatment (**Martineau et al., 2017**). The effects were also bigger in participants who had deficiency at the beginning of the study. As for why bolus treatment was inefficient in the study some of the reasons provided were that this form of administration causes fluctuations in serum calcitriol concentrations that are not observed in the other forms

of administration or that could be a dysregulation in the enzymes that intervene in the metabolism of vitamin D (**Martineau et al., 2017**).

It could be said that vitamin D helps in the prevention of respiratory illnesses and has very few downsides since it is very safe to use and their adverse effects are very rare to occur (**Martineau et al., 2017**).

Therefore, there is a solid rationale to perform studies for vitamin D supplementation in risk-groups such as elderly, hospital inpatients, nursing home residents and obese people, as well as people with darker skin tones. On the other hand, there is mechanistic evidence from *in vitro* experiments that vitamin D inhibits viral replication for other respiratory viruses (**Mock et al., 2020**). There is epidemiological evidence proving that people with viral infections have lower serum levels of vitamin D than controls (**Walrand, 2021**). There is also some randomized control trial (RCT) supporting that supplementation can prevent respiratory tract infections (RTIs) caused by other respiratory viruses, such as RS-virus, rhino-virus and influenza (**Annweiler et al., 2020**). On the other hand, *in vitro* studies have observed that vitamin D can prevent viral replication in respiratory epithelial cells and reduce inflammation in the coronavirus-context (**Bergman et al., 2012; Bergman et al., 2013**).

Since there is no single food, supplement and vitamin that can either treat nor prevent COVID-19, there is a current interest in the scientific community to reinvestigate the role of vitamin D supplementation in reducing the risk of respiratory infections in general, and the new SARS-CoV-2 in particular (**Ilie et al., 2019; Raharusun et al., 2020; Griffin et al., 2020**), as we explored in this work.

Commentary about relevant papers included in Table 4

Evidence that vitamin d supplementation could reduce the risk of influenza and covid-19 infections and deaths (Grant et al., 2020)

This review explored how low levels of 25(OH)D could be related to the prognosis of COVID-19, based on how deficiency of vitamin D could be related to other respiratory diseases like seasonal influenza.

First, the review discusses that the possible peak of influenza in the winter months could be related to a decreased synthesis of vitamin D in the organism. This is because the low incidence of UVB radiation during these months, along with bad weather conditions that make people avoid going outside, reduces skin synthesis of vitamin D, which could even develop into a state of hypovitaminosis if the individual is not careful to take their daily intake of vitamin D through different sources. Some studies claim that supplementation during these specific times could help to prevent influenza.

About vitamin D and COVID-19 there seems to be a disagreement between observational studies and randomized controlled trials (the latter have not reported that this vitamin is able to reduce vulnerability to the disease). The reasons for this are very varied but the most important ones seem to be enrolling individuals with decent concentrations of 25(OH)D and administering them low dosages of vitamin D and not measuring the concentrations achieved before and after the study.

It is important to notice that in elderly patients COVID-19 mortality could also be heavily associated with other diseases and comorbidities such as diabetes, whose prevalence is significantly high in the world. Some chronic diseases have been reported however to course with low levels of vitamin D (and 1,25-dihydroxyvitamin D (calcitriol) intervenes in the immune response of the organism so low levels of this metabolite)

The review establishes the following recommendations:

People who work in hospitals should be supplemented with vitamin D due to the high risk of contagion in this environment. This supplementation should be given to both patients and staff as a prophylactic measure against the illness.

Since there is a lot of data that supports that higher concentrations of 25(OH)D are related to better prevention against acute respiratory tract infections, like influenza, supplementation should be considered, especially in vulnerable groups, before the winter season to raise blood concentrations to either adequate levels or raise them above the average (depending on the baseline state of the individual). The optimal range for protection seems to be from 40 to 60 ng/mL.

High dose supplementation could be beneficial to achieve proper prevention and offer, in exchange, very few problems since vitamin D has low toxicity and it is very safe to use. This does not mean that supplementation should not be supervised by a professional.

It is also important to notice that not all countries have guidelines for recommended daily ingest of vitamin D and that these guidelines tend to change from time to time when new information about nutrients is discovered. Magnesium is also recommended along with vitamin D supplements since it helps activate the vitamin and the enzymes that are involved in vitamin D's metabolism seem to require this mineral.

In conclusion, more studies should be carried out to ascertain if vitamin D is really able to reduce the incidence of COVID-19 and fatal cases that the disease may cause. There also need to be proper guidelines about how the supplementation should be given to people in order to be effective.

25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2 (D'Avolio et al., 2020)

This clinical essay studies the possible involvement of vitamin D in reducing the risk of COVID-19.

Data collection: A PCR analysis was done to a group of patients with some kind of acute respiratory symptoms and a vitamin D analysis within a week of doing the PCR. The control cohort selected for this study was a group of patients with 25(OH)D measurements during the same period of 2019.

The results showed that from a 107 cohort, 27 of the participants had a positive PCR for COVID-19. There was a statistically significant difference between patients with a positive and negative PCR in levels of 25(OH)D, being these lower in the participants with a positive text. This difference was even more significant when comparing the levels with the control cohort.

It is important to notice that 25(OH)D concentrations were significantly lower in participants with a positive text compared with negative ones when the age was above 70 years old. This is significant since age is considered a predictor for the severity of the disease.

Possible biases of this study are:

- Low number of patients from a single hospital.
- No clinical information available for the severity of COVID-19 symptoms for PCR positive or negative patients.

The study calls to pay attention to diet and sun exposure. It should also be considered a reverse causality, in which the viral infection is responsible for the lower levels of vitamin D and not the opposite.

Vitamin D3 supplementation could be useful in the treatment, prevention and/or reducing the symptomatology of the infection. Randomized controlled trials and larger population studies should be performed in order to study these recommendations and the aim of the study.

“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” (Entrenas Castillo et al. 2020)

The aim of this study was to assess the clinical effectiveness of treatment with calcifediol (25-hydroxyvitamin D₃) in hospitalized patients for COVID-19 to evaluate if this treatment could reduce ICU admission and therefore potential risk of death.

The study included 76 patients hospitalized with COVID-19 in the Reina Sofía University Hospital from Córdoba (excluding patients under 18 year’s old and pregnant women). The patients received the best available therapy and the same standard care: a combination of hydroxicloroquine (no longer considered an effective treatment) and azithromycin (and in some cases a broad spectrum antibiotic).

The patients were electronically randomized by independent statisticians into a ratio of 2 calcifediol : 1 no calcifediol (of 76 participants 50 of them were the ones who received the treatment and the rest were not). The effectiveness of calcifediol was measured in both ICU admissions and deaths.

The study took into account the sex and age of the participants as well as several baseline factors that could mark a risk for the disease with no significant difference at baseline.

Among 26 patients not treated with calcifediol 50% of them required ICU admission whereas among the 50 patients treated only one of them required it.

Randomization did not achieve a homogeneous distribution of all the variables that could be considered risk factors, being a statistically significant difference in hypertension and diabetes between the group that received the treatment and the one that did not (which was the one with higher number of patients with these risk factors).

About the number of fatal cases, among the patients treated with calcifediol no one died whereas among the 13 not treat who were admitted in ICU two of them died.

It appears that treatment with a high dose of calcifediol reduced the need for ICU treatment in patients that required hospitalization for COVID-19, despite the significant differences in comorbidities (hypertension and diabetes) between both groups.

Some of the limitations of the study are derived due to it not being double-blind placebo controlled. Obesity was not taken into consideration as a risk factor either and serum levels of 25(OH)D at the beginning of the treatment were not measured (although the majority of the population is deficient during winter months in Córdoba).

Veganism and vitamin D

Vegans have to follow a specific diet in which aliments derived from animals are severely restricted, specifically in strict vegans. This means they have to take their daily intake of vitamin D from plants exclusively, where the sources are really scarce, as it was discussed before. Mushrooms, in particular, are a good font of vitamin D for people who follow a vegan diet, in form of vitamin D₂. By exposing mushrooms to solar light or UVB we can obtain enriched aliments in vitamin D₂ upon 400 IU, which constitutes a recommended intake for people from ages of 51 to 70 years old in the study consulted. Nevertheless, some studies claim that vitamin D deficiency is influenced by other factors

that are more important than diet such as supplementation or consumption of fortified meals or the degree of pigmentation of the skin (**Chan et al., 2009**).

Vitamin D status in vegans appears to be heavily dependent on fortified meals, which are not present in all countries. If this kind of food is not accessible to people who follow this diet, supplementation is often necessary to maintain an adequate status of this micronutrient. Among different risk factors for vitamin D deficiency are high latitudes, dark skin, advanced age, excessive clothing use, and sunscreen use (**Craig, 2009**).

Moreover, vitamin D₂ has less bioavailability than vitamin D₃, so this is another factor to take into account for an increased risk of deficiency in vegans (**Craig, 2009**).

Different studies carried out in Sweden, Finland and Denmark state that the levels of different micronutrients in vegans, being vitamin D one among them, are low in individuals who follow these diets comparing them to omnivores (**Elorinne et al., 2016; Kristensen et al., 2015; Larsson & Johansson, 2002**). Some of them suggest that supplementation of vitamin D should always be associated in this kind of diets to prevent possible situations of deficiency that could be derived from them (**Elorinne et al., 2016; Kristensen et al., 2015**)

Despite this, other studies, like **Rocha et al., 2019**, establish that the multiple health benefits of vegan and vegetarian diets easily surpass the possible risks that could be associated with them and that some situations, such as vitamin D deficiency, are present even in those people who do not follow these types of alimentation (**Rocha et al., 2019**).

The possible connection between vitamin D deficiency and veganism could lead to thinking that there is an increased risk of respiratory diseases in vegan individuals. This could also lead to the possibility of an increased risk of COVID-19 in people who follow this diet but further investigations about the incidence of the new coronavirus disease depending on the diet and nutritional status should be carried out.

To avoid a possible deficiency of vitamin D in people who follow a vegan diet, supplementation through ergosterol should be considered. Certain edible mushrooms are a good source of this compound and they are not fully studied yet. They are great sources of vitamin D thanks to both their taste and their nutritional contents. Supplementation through ergosterol could also be considered for omnivores, since it

appears that exerts a more effective bone remineralization than cholecalciferol and does not have a hipercalcemic effect in the organism. Therefore, obtaining mushrooms with high contents of vitamin D₂ or its metabolites presents a very interesting approach not only for vegans but for omnivores as well (**Falcon-García, 2019**).

CONCLUSIONS

- Vitamin D is essential for the proper function of the organism since it intervenes in different systems due to the presence of the vitamin D receptor in diverse tissues in the body.
- There is a connection between a state of vitamin D deficiency and a greater vulnerability to respiratory diseases such as influenza. This may suggest a connection between this state and higher vulnerability to COVID-19.
- There is a high prevalence of vitamin D deficiency in the world. Countries where the incidence of COVID-19 was greater may suggest that these situations could be related.
- The vitamin D receptor is greatly extended through different tissues in the body and it is involved in very different functions.
- The pandemic caused by SARS-CoV-2 calls for certain measures in order to achieve prophylaxis against the disease, especially in vulnerable population such as the elderly or patients with comorbidities.
- From all the studies reviewed, there seems to be a relation between low vitamin D levels and a higher risk of COVID-19 infection, so its use as a prophylactic treatment should be considered. There is not enough evidence that indicates that vitamin D could be used as a treatment of the illness though.
- Vitamin D supplementation can prevent different pathologies and it is safe enough to be administered to the general population.
- People who follow vegan diets seem to have vitamin D deficiency, though this state is dependent on factors other than diet since individuals with an omnivore alimentation also present this deficiency.
- The majority of existent vitamin D supplementation is from animal origin, which would be discarded by vegans. This opens the possibility of study the supplementation based of vitamin D₂, for which mushrooms treated with UV radiation would be an interesting option.

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