COVID-19 and vitamin D. Position paper of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM)

DOI: http://dx.doi.org/10.4321/S1889-836X2020000400009

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INTRODUCTION

Vitamin D exerts its effect mainly through its active metabolite, 1,25-dihydroxycholecalciferol, by binding to a receptor with wide distribution in the different cells of the body. This receptor regulates the expression of genes involved in different biological functions, including organ development, cell cycle control, phosphocalcic metabolism, detoxification, and control of innate and adaptive immunity1,2. Regulation of the vitamin D receptor is determined by interacting environmental, genetic, and epigenetic factors.

Vitamin D increases intestinal absorption and tubular reabsorption of calcium, inhibiting PTH synthesis. This leads to a reduction in bone turnover, which helps maintain its strength and reduce the risk of fractures. In addition, it exerts an intraosseous effect, facilitating the mineralization of the matrix, which prevents the development of rickets in children and osteomalacia in adults. Numerous studies have been published showing an association between low levels of vitamin D and various chronic diseases, such as cancer, diabetes, cardiovascular diseases, multiple sclerosis, and infectious diseases, among others3. These associations can be explained through different pathophysiological mechanisms related to vitamin D deficiency.

In 2020, the pandemic derived from COVID-19 occurred with a high rate of contagion and mortality. The seriousness of the process has made it necessary to apply therapeutic measures without clear scientific evidence4. Many of them have not proved effective in subsequent cohort studies and clinical trials of a different nature, so they have been withdrawn. Some have shown usefulness in certain periods of the disease.

Vitamin D is a hormone whose deficiency has been associated with numerous acute and chronic diseases, both bone and non-bone. However, the studies carried out to demonstrate the causality of the association, in general, have not been positive. The fact that various risk factors associated with the incidence and severity of COVID-19, such as north latitude, advanced age, non-Caucasian races, high blood pressure and diabetes, have also been associated with vitamin D deficiency5, suggests the possible link between COVID-19 infection and vitamin D deficiency.

This leads to the following questions:
- Is there a relationship between vitamin D deficiency and the risk of coronavirus infection?
- Is there a biological explanation for this association?
- Can the administration of vitamin D to deficient individuals prevent infection or alter its severity?
- What is the risk/benefit ratio of its administration?

Is there a relationship between vitamin D deficiency and the risk of SARS-COV-2 coronavirus infection?

Initially, mortality from COVID-19 was reportedly higher in northern latitudes, which could be attributed to decreased production of vitamin D due to the effect of ultraviolet radiation. However, Spain and Italy, located in southern Europe, presented a very high mortality, as well as a high prevalence of hypovitaminosis D4. Ilie et al.7 carried out an ecological study in 20 European countries. They found an inverse relationship of vitamin D levels with the incidence of COVID-19 (r:−0.443; p=0.05) and mortality due to disease (r:−0.4378; p=0.05). In another study carried out in 117 countries, an association between latitude and mortality was observed (p<0.033), after adjusting for age4. Meltzer et al.4, in a 489-patient cohort, with 75% women, found that COVID-19 infection risk was associated with advanced age, non-Caucasian race and vitamin D deficiency. The risk of infection in individuals with vitamin D sufficiency was 12.2%, compared to 21.6% in those with insufficiency (p=0.02). D’Avalio et al.10 reported that patients with positive PCR had vitamin D levels of 11.1 ng/ml, while, among those with negative PCR for COVID-19, the levels were 24.6
ng/ml; p=0.004. Another study linked vitamin D levels with mortality, finding that patients with vitamin D below 10 ng/ml had a 50% chance of dying, compared to 5% of those with a higher level, although the study sample size was small. Hernández et al. found lower levels of vitamin D in hospitalized patients, unrelated to the severity of the disease, although they observed an inverse relationship with the levels of ferritin and D-dimer; both parameters related to the severity of the infection.

The relationship between low vitamin D levels and the risk of infection by COVID-19 has been observed in a recent meta-analysis. Pereira et al. conducted a meta-analysis that included 8,176 patients with COVID-19 infection. These authors did not find a relationship between vitamin D deficiency and an increased risk of infection, but did find a relationship with its severity. A study conducted in England with biobank samples also found no association between vitamin D and COVID-19. It must be taken into account that, in critical patients, there is a high prevalence of vitamin D deficiency, although we do not know if it is an “innocent bystander”, a marker of severity or a real and modifiable risk factor. The stimulation of renal 1α-hydroxylase in the face of inflammatory processes means that the association of various acute processes has the possibility of being an effect rather than a cause, with 25-hydroxyvitamin D levels being a negative acute phase reactant.

So, although the studies carried out have different approaches and their results are not uniform, in general an association, not necessarily causal, is observed between vitamin D deficiency and the incidence and mortality from COVID-19.

### Is there a biological explanation for the association between vitamin D deficiency and incidence and mortality?

Vitamin D can play a protective effect thanks to:
- The maintenance of the integrity of the epithelium.
- The stimulation of the production of antimicrobial peptides.
- The reduction of the inflammatory response.
- Modification of the relationship between ACE/ACE2 by increasing the expression of ACE2.

### Can administering vitamin D to deficient individuals prevent infection or alter its severity?

The evidence to indicate the administration of vitamin D in the prevention or treatment of COVID-19 is scarce and presents numerous limitations. At this time, we do not know the vitamin D threshold that must be reached to achieve the objective, the most suitable metabolite or the doses to be used.

### Can administering vitamin D to deficient individuals prevent infection or alter its severity?

A meta-analysis that included more than 11,000 patients, from 25 clinical trials, showed a beneficial effect of vitamin D in reducing infectious diseases of the respiratory tract. The effect was greater in situations with severe vitamin D deficiency (<10 ng/ml) and with daily or weekly administrations. Taking into account these data, the existence of hypovitaminosis D in patients with COVID-19 and a biological explanation that offers plausibility to a beneficial effect, 18 clinical trials have been proposed that try to demonstrate this hypothesis. The beneficial effects could take place both in the early viremic phases, preventing the development of the disease, and in late hyperinflammatory phases.

However, the evidence available so far is very scarce. Several case/control studies have been published that we can call quasi-experimental and a pilot study from a cohort of patients infected with pneumonia (Table 1). Their sample size is small, except for one of them, which included 1,476 patients. Some favorable results have
Table 1. Vitamin D-COVID-19 studies

<table>
<thead>
<tr>
<th>Autor</th>
<th>Study types</th>
<th>Population (N)</th>
<th>Supplement</th>
<th>Objetive</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risano et al.</td>
<td>Cases/Controls</td>
<td>Patients with disease of Parkinson’s (1,486)</td>
<td>Not established</td>
<td>Incidence of COVID-19</td>
<td>12.4% vs. 22.9% (p=0.010)</td>
<td>Those who receive supplements have less incidence</td>
</tr>
<tr>
<td>Annweiler C et al.</td>
<td>Cases/Controls</td>
<td>Institutionalized (7)</td>
<td>Cholecalciferol 50,000 IU/month (prior 80,000-100,000 IU/2-3 months (prior 80,000 IU single bolus after diagnosis</td>
<td>Mortality</td>
<td>6.9% vs. 31.3% (p=0.017) 18.8% vs. 31.3% (p=0.5)</td>
<td>Those who receive vitamin D in the previous year have less mortality, but not those who receive it after diagnosis. The doses are higher than those usually recommended</td>
</tr>
<tr>
<td>Annweiler G et al.</td>
<td>Cases/Controls</td>
<td>Institutionalized (66)</td>
<td>Cholecalciferol bolus of 80,000 IU before or after diagnosis</td>
<td>Mortality</td>
<td>17.5% vs. 55.6% (p=0.023)</td>
<td>Those who receive vitamin D have less mortality. The doses are higher than those usually recommended</td>
</tr>
<tr>
<td>Tan CW et al.</td>
<td>Cases/Controls</td>
<td>Hospitalized by COVID-19 (43)</td>
<td>Cholecalciferol (1,000 IU/day), magnesium, B12 vitamin</td>
<td>Mortality</td>
<td>17.6% vs. 61.5% (p=0.006)</td>
<td>Those who receive vitamin D need less oxygen therapy and/or admission to the ICU</td>
</tr>
<tr>
<td>Gerecda E et al.</td>
<td>Cases/Controls</td>
<td>Patients with COVID-19: Parkinson’s disease (105), caretakers (92), hospitalized (127)</td>
<td>Cholecalciferol ≥800 IU/day in 38 individuals</td>
<td>Mortality intrahospital</td>
<td>0.9±1.78 (0.64±4.91; p=0.26)</td>
<td>Those who receive vitamin D are more likely to die</td>
</tr>
<tr>
<td>Entreas-Castillo et al.</td>
<td>Clinical trial open pilot, randomized and double blind</td>
<td>Hospitalized by COVID-19 pneumonia (76:50 treated and 26 untreated)</td>
<td>Calciﬂediol 64,000 IU/1st week and subsequently 16,000 IU/week until discharge or admission to the ICU</td>
<td>Admission to ICU</td>
<td>2% vs. 50% (p=0.001)</td>
<td>Those who receive vitamin D are admitted less to the ICU, although the risk factors are not balanced between groups. Doses are higher than recommended.</td>
</tr>
</tbody>
</table>

ICU: Intensive Care Unit.

been obtained, although their limitations should be taken into account. There are no data on baseline and final 25-hydroxyvitamin D values, although they all assess important outcome variables, such as incidence of disease and mortality.

Some studies in an institutionalized geriatric population that analyze the effect of boluses of cholecalciferol (80,000 IU) prior and/or at the time of infection, report a better evolution of the disease and a decrease in mortality, while in other studies of the same characteristics, this effect is observed in individuals who are treated with periodic boluses of cholecalciferol during the year prior to infection. In both cases, the doses used are higher than those recommended. In a study carried out in China with a cohort of asymptomatic patients with COVID-19, the effect of the administration of supplements associating cholecalciferol (1,000 IU), magnesium and vitamin B12 on the evolution of the disease was assessed. Those who received supplements were admitted to the intensive care units (ICU) less and required less oxygen therapy. However, another study, with cholecalciferol, did not confirm these data. The administration of supplements was associated with a tendency to increase mortality, although not statistically significant. However, it is important to mention the methodological limitations of these studies. The only study with calciﬁediol (25-hydroxyvitamin D) has been carried out in Spain and shows a reduction in the severity of the disease and in mortality. Relatively high doses of calciﬁediol were used (0.532 mg, followed by 0.266 mg at 3 and 7 days and subsequently weekly until the patient was discharged), without baseline or during vitamin D treatment determinations, which could raise safety concerns. In fact, with the administration of calciﬁediol (0.266 mg) every two weeks, 25-hydroxyvitamin D concentrations greater than 30 ng/ml are reached in most individuals. Although with this type of dosage, the development of hypercalcemia, around 38% of individuals present concentrations greater than 60 ng/ml. Another study with weekly dosing showed mean concentrations of 93.2±32.4 ng/ml. Although it seems reasonable to use faster and more powerful supplements to achieve sufficient concentrations of vitamin D, it is advisable to carefully consider the dose and frequency of administration.
At the moment, it is not known what is the optimal vitamin D threshold that we must achieve in the prevention or treatment against COVID-19 to reach the objective, as well as the doses that should be used. In a study carried out in China with a small sample size (62 cases and 80 controls), this threshold was set at 16.5 ng/ml\textsuperscript{31}. It seems reasonable to achieve levels above 20 ng/ml and preferably above 30 ng/ml.

In conclusion, we can say that the evidence to indicate the use of vitamin D in preventing and/or treating COVID-19 is scarce and with numerous limitations, with insufficient clinical information to recommend one or another metabolite.

**What is the risk/benefit ratio of its administration?**
Pending the publication of clinical trials that confirm or not its usefulness, the risk/benefit ratio could be favorable to the use of vitamin D in compassionate use (off-label) in the prevention and treatment of COVID-19 in patients at risk, in which it might be reasonable to prevent or treat deficiency, given the known beneficial effect on immunity and respiratory infections.

**Conflict of interests:** José Luis Pérez Castrillón has participated in clinical trials, work groups, training presentations and attendance at medical conferences funded by FAES, Italfármaco and Gebro-Pharma. Enrique Casado has received fees for conferences, scientific advice or funding for conferences from Italfármaco, Gebro, FAES and Angelini.

Luis Corral Gudino has no relevant conflicts of interest for this article. Carlos Gómez Alonso has participated in clinical trials, work groups, training presentations and attendance at medical conferences funded by FAES, Italfarmaco and Gebro-Pharma. Pilar Peris has collaborated as a speaker with Amgen, Lilly, Kyowa Kirin, UCB and Angelini Pharma. Jose A. Riancho has no relevant conflicts of interest for this article.


