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The relationship between 25(OH) vitamin D levels and COVID-19 onset and disease course in Spanish patients

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ABSTRACT

Objective: Currently, there are no definitive data on the relationship between low levels of vitamin D in the blood and a more severe disease course, in terms of the need for hospital admission, intensive care unit (ICU) stay, and mortality, in patients with coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

We aimed to study the association between levels of circulating 25-hydroxyvitamin D (25(OH)D) and adverse clinical outcomes linked to SARS-CoV-2 infection.

We further aimed to observe the incidence of low, below-average, and normal levels of 25(OH)D in patients hospitalized for COVID-19 between March 12, 2020, and May 20, 2020, and assess whether these values differed between these patients and a normal population. Finally, we determined whether the need for transfer to the intensive care unit (ICU) and the mortality rate were related to low levels of 25(OH)D.

Study Design: Retrospective observational study.

Setting: Quironsalud Hospitals in Madrid, Spain.

Participants: We analyzed 1549 patients (mean age, 70 years; range, 21–104 years); 835 were male (53.9 %; mean age, 73.02 years), and 714 were female (46.1 %; mean age, 68.05 years).

Subsequently, infected patients admitted to the ICU (n = 112) and those with a fatal outcome (n = 324) were analyzed.

Procedures: Serum concentrations of 25(OH)D were measured by electrochemiluminescence.

Results: More hospitalized patients (66 %, n = 1017) had low baseline levels of 25(OH)D (<20 ng/mL) than normal individuals (45 %) ($p < 0.001$).

An analysis by age group revealed that COVID-19 patients between the ages of 20 and 80 years old had significantly lower vitamin D levels than those of the normal population ($p < 0.001$).

Patients admitted to the ICU tended to have lower levels of 25(OH)D than other inpatients ($p < 0.001$); if we stratified patients by 25(OH)D levels, we observed that the rate of ICU admission was higher among patients with vitamin D deficiency ($p < 0.001$), indicating that higher vitamin D levels are associated with a lower risk of ICU admission due to COVID-19.

ICU admission was related to sex (higher rates in men, $p < 0.001$) and age ($p < 0.001$). When using a logistic regression model, we found that vitamin D levels continued to show a statistically significant relationship with ICU admission rates, even when adjusting for sex and age. Therefore, the relationship found between vitamin D levels and the risk of ICU admission was independent of patient age and sex in both groups. Deceased patients (n = 324 tended to have lower levels of 25 (OH)D that normal population of the same age ($p < 0.001$).

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Conclusion: Vitamin D deficiency in patients with COVID-19 is correlated with an increased risk of hospital admission and the need for critical care. We found no clear relationship between vitamin D levels and mortality.

1. Introduction

A new and highly contagious disease caused by a novel coronavirus, known as coronavirus disease 2019 (COVID-19), has triggered an unprecedented pandemic in our society since it first emerged in late 2019. Given the great impact that this disease has on human health and the economy, all types of interventions leading to an improvement in the clinical state of patients and that reduce the risk of clinical exacerbation and mortality should be considered.

Following the rickets epidemic of the 19th century caused by vitamin D deficiency due to insufficient exposure to the sun, vitamin D insufficiency (i.e., deficiency and insufficiency) was once again considered to be a globally recognized pandemic with severe consequences for human health [1]. Prolonged vitamin D deficiency causes rickets in children and osteomalacia in adults, while insufficient levels of vitamin D are an important contributing factor in osteopenia and osteoporosis, loss of bone mass, muscle weakness, falls, and fractures. In addition to these classical effects, vitamin D deficiency has been associated with an increased risk of developing chronic and degenerative diseases including certain types of cancer, autoimmune disorders, infectious diseases, arterial hypertension, and cardiovascular disease, among others [1].

The discovery of vitamin D receptors (VDRs) together with the presence of the enzyme 1-alpha-hydroxylase not only in the kidneys but throughout the body, has contradicted previous ideas that the effects of vitamin D were limited to the bones and muscles.

Currently, there is no definitive evidence linking low circulating vitamin D levels and a severe clinical course in COVID-19, the disease caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection, in terms of both overall hospitalization and intensive care unit (ICU) admissions as well as fatal outcomes in these patients, despite robust data implicating vitamin D in infectious diseases and immune processes [2,3].

1.1. Vitamin D activity as an immunomodulator and in prevention of infection

Vitamin D can reduce the risk of infection by acting as a physical barrier or by improving the innate immunity of cells. The cells that make up the immune system (i.e., macrophages, monocytes, dendritic cells, T and B cells) have VDRs and enzymes that enable them to synthesize 1,25-dihydroxyvitamin D (1,25D) [4–6].

Innate immunity is enhanced through the production of antimicrobial peptides such as cathelicidin and beta-defensin 2. These antimicrobial peptides are generated by vitamin D. Here, it is worth noting that cathelicidin works against bacteria, viruses, fungi, and Koch bacilli via membrane disruption. Additionally, cathelicidin contributes to the suppression of the cytokine storm that occurs with infections, such as SARS-CoV-2, by inhibiting the production of T helper cell type 1 (Th1) cytokines such as interferon-γ and tumor necrosis factor-α (TNF-α) [7].

Numerous studies have shown that people with chronic illnesses have lower levels of 25-hydroxyvitamin D (25(OH)D) than healthy subjects. Vitamin D status has been associated with viral infections such as dengue fever, hepatitis, herpes virus, HIV, influenza, respiratory syncytial virus, and rotavirus and with upper respiratory tract infections, enteric infections, urinary tract infections, pneumonia, otitis media, vaginosis, and sepsis.

1.2. Vitamin D and viral respiratory infections

1.2.1. Flu (seasonal influenza)

It has been reported that one-third of patients hospitalized with confirmed influenza develop pneumonia, particularly children and elderly individuals. It has been argued that the increased incidence of influenza infection in the winter months may be related to decreases in sun exposure and vitamin D levels coupled with the longer survival of the virus at low temperatures.

VDRs are mostly distributed among respiratory epithelial cells and immune cells (i.e., B cells, T cells, macrophages, monocytes). 25(OH)D, the major circulating form of vitamin D, can be converted to its active form (1,25-dihydroxyvitamin D) within the bronchial epithelium and in immune cells. Serum levels of 25(OH)D must be above a certain threshold to increase levels of 1,25-dihydroxyvitamin D and improve the immune response to viral respiratory infections [8].

The Grassroots Health Study is a survey-based initiative that studied 12,605 participants for the presence or absence of influenza-like syndrome in the first 6 months of life as well as the vitamin D levels of the participants. Participants with 25(OH)D levels of at least 60 ng/mL had a 43 % lower risk of contracting an influenza-like disease than those with levels below 20 ng/mL ($p < 0.0001$) [9].

1.2.2. Coronavirus (CoV) infection

Influenza and coronaviruses (CoVs) primarily cause infections in the winter months; these illnesses may be severe and lead to death by pneumonia. Regarding the current pandemic, it has been hypothesized that areas populated by individuals with low average 25(OH)D levels may have higher rates of incidence and mortality [10].

One of the ways in which CoVs disrupt the pulmonary epithelium is by producing Th1 cytokines as part of the innate immune response to viral infection. Similarly, it has been reported that interferon-γ is responsible for acute lung injury in late-stage SARS-CoV infection [11] and that the so-called cytokine storm causes complications in these viral infections, although it has also been described that COVID-19 is associated with an increase in Th2 cytokines (IL-4 and IL-10) [12].

Our aim in performing this study was to determine whether low circulating vitamin D levels, compared to the normal vitamin D levels, facilitate disease transmission and influence the disease course, possibly leading to an increase in ICU admissions and fatal outcomes.

2. Methods

The study was conducted according to the Declaration of Helsinki and with the approval of the Ethics Research Committee of Fundación Jiménez Díaz (EO154−20-FJD) and II FJD (Instituto Investigación Fundación Jiménez Díaz).

2.1. Study design and participants

During the study period (March 12, 2020 to May 20, 2020), a sample of patients admitted to one of the Quironsalud Hospitals in the region of Madrid (Fundación Jiménez Díaz, Hospital General de Villalba, Quironsalud Madrid, Hospital Universitario Infanta Elena and Hospital Rey Juan Carlos) were enrolled, and their 25(OH)D levels were measured at the time of admission. All patients were diagnosed with SARS-CoV-2 infection detected by polymerase chain reaction (PCR) or RT-PCR (Viasurer®, SARS-CoV-2, Real Time PCR Detection Kit).

Prior treatments and associated diseases were not evaluated in the patients studied. We analyzed 1549 patients (mean age, 70 years; range, 21–104 years); of these, 835 were male (53.9 %; mean age, 73.02 years), and 714 were female (46.1 %; mean age, 68.05 years).

Subsequently, patients admitted to the ICU (n = 112, mean age:) and infected patients with a fatal outcome (n = 324) were analyzed.

2.2. Laboratory analysis

25(OH)D levels were measured by an electrochemiluminescence immunoassay (Elecsys, Roche). The intra-assay variability of the measured serum level of 25(OH) was ≤ 8.9 %, and the inter-assay variability was ≤ 10.8 %.

2.3. Statistical analysis

The values found for our patients were compared to those of the overall Spanish population [12–15]. Vitamin D levels and age groups were compared using the chi-squared test. In our cohort of patients with COVID-19, comparisons of vitamin D level, age and sex between patients admitted to the ICU and those that were not admitted were made. A Student's *t*-test was used to compare age and vitamin D levels, and the chi-squared test was used to compare sex and ranges of vitamin D levels. A multiple logistic regression model was adjusted with vitamin D, age and sex as the predictors and admission to the ICU as a response.

We used Student's t-tests to compare mean values for each group. P value<0.01 indicated statistical significance.

Comparisons of vitamin D levels between patients admitted to the ICU and those not requiring ICU admission were performed on mean values ± standard deviation with Student's t-tests and by comparing means and interquartile ranges with the Mann-Whitney *U* test.

The chi-squared test was used to compare differences between values for normal patients and patients with deficient levels of 25(OU)D (<20 ng/mL).

We used a multivariate logistic regression model, with ICU admission as the dependent variable (admitted vs. not admitted), while the independent variables were vitamin D level, sex, and patient age.

Vitamin D levels were also compared between surviving patients and those with fatal outcomes. The mean age of the living patients were 67 years, and 82 years the mean age of the deceased patients.

Vitamin D levels were compared between deceased patients and the normal population of the same age. Comparisons were performed of mean values ± standard deviation with Student's *t*-test and by comparing means and interquartile ranges with the Mann-Whitney *U* test.

Comparisons of the mortality rates based on vitamin D levels was performed using Student's *t*-test and the Mann-Whitney *U* test.

3. Results

3.1. Vitamin D levels of admitted patients

Table 1 shows the vitamin D levels of non-COVID-19 patients (1811), [13] compared with the vitamin D levels of admitted COVID-19 patients (1549).

The frequency of low levels of vitamin D (< 20 ng/mL) is higher in COVID-19-admitted patients than in a group of 1811 people from a non-COVID-19 population [13].

We also performed an analysis of vitamin D levels by age group (Table 2), compared with a group of 465 non-COVID-19 normal individuals [14,15].

The prevalence of 25(OH) vitamin D levels lower than 10 ng/mL in hospitalized patients without ICU admission was 25.1 %, and it was 32.9 % in ICU patients.

All the groups of COVID-19 patients between the ages of 20 and 80 years old had significantly lower vitamin D levels than those of the normal population [14,15] ($p < 0.001$).

3.2. Association between vitamin D levels and ICU admission

We performed a comparison of mean values of vitamin D levels +/- standard deviation between the ICU admission and non-ICU admission patients with Student's *t*-test and by comparing means and interquartile ranges with the Mann-Whitney *U* test (Table 3).

We also used a multivariate logistic regression model, using ICU admission as the dependent variable (admitted vs. not admitted) and vitamin D level, sex, and patient age as the independent variables (Table 4).

Both analyses revealed differences in vitamin D levels between patients who were admitted to the ICU and those who were not. Specifically, patients requiring ICU admission tended to have lower levels of circulating vitamin D.

We also evaluated ICU admissions according to different ranges of vitamin D levels, sex, and age. Number counts and percentages are provided for patients with and without ICU admission. These frequencies were compared using the chi-squared test (Tables 5 and 6).

These results suggest that higher vitamin D levels are associated with a lower risk of ICU admission. We believe it is of interest to determine whether these groups (ICU admission vs. no ICU admission) showed differences in characteristics such as age and sex. We then compared patients not admitted to the ICU and those who did require intensive care in terms of their sex and age. We observed that patients requiring ICU admission showed differences in sex and average age when compared to those not requiring ICU admission.

Given that patient age and sex are associated with a higher or lower likelihood of ICU admission, it may be worthwhile to perform a comparison of vitamin D levels adjusting for these variables. To do this, we used a multivariate logistic regression model. Under this model, the dependent variable was ICU admission status (admitted vs. not admitted), while the independent variables were vitamin D, sex, and patient age (Table 7).

This table shows the results of this analysis, including the odds ratio (OR), 95 % confidence interval (95 % CI), and p value, revealing statistically significant results for the variables sex and age. Therefore, the relationship found between vitamin D levels and the risk of ICU admission was independent of patient age and sex in both groups. The

Table 1
Patient frequencies for each range of vitamin D levels in COVID-19 patients compared with the normal population.

Vitamin D	Non-COVID-19 (n = 1811)	COVID-19 (n = 1549)	p
<20 ng/mL	815 (45 %)	1017 (66 %)	<0.001
20–30 ng/mL	688 (38 %)	318 (20 %)	<0.001
>30 ng/mL	308 (17 %)	214 (14 %)	<0.001

The prevalence of 25(OH) vitamin D values lower than 10 ng/mL in the group of all hospitalized patients was 27.8 %.

Table 2
Comparison of mean vitamin D levels by age group in COVID-19 patients compared with non-COVID-19 patients.

Age group	Non-COVID-19 (N = 465)	COVID-19 (n = 1549)	p
20–59	(n = 81) 19.2 ± 2.0	(n = 398) 15.8 ± 9.2	<0.001
60–70	(n = 31) 27.2 ± 2.0	(n = 347) 17.3 ± 10.6	<0.001
>70	(n = 353) 22.7 ± 10	(n = 804) 19.5 ± 13.2	<0.001

Results are expressed as the mean+/- standard deviation.

Table 3
Comparison of vitamin D levels between patients admitted to the ICU and those not requiring ICU admission.

Nº ICU (No ICU) (n = 1437)	ICU (n = 112)	p
18.4 ± 12.1	14.2 ± 7.4	<0.001
15.8 (14.7)	12.9 (7.8)	0.002

Table 4
Comparison of vitamin D levels between patients admitted to the ICU and those not requiring ICU admission, adjusting by age and sex.

Non-ICU (n = 1437)	ICU (n = 112)	p
14.9 (14.4, 15.4)	12.7 (11.2, 14.4)	0.003

Table 5
Vitamin D ranges, sex, age, and ICU Admission.

Vitamin D ranges	No ICU admission (n = 1437)	ICU admission (n = 112)	p
<20 ng/mL	926 (64 %)	91 (81 %)	<0.001
20–30 ng/mL	300 (21 %)	18 (16 %)	
>30 ng/mL	211 (15 %)	3 (3%)	
Male	760 (53 %)	75 (67 %)	0.005
Age	71.2 ± 16.2	59.1 ± 10.7	<0.001

Table 6
ICU admission according to vitamin D range adjusted by age and sex.

Variable	OR (95 % CI)	p
Vitamin D range		
<20 ng/mL	Reference	
20–30 ng/mL	0.75 (0.42, 1.25)	0.282
>30 ng/mL	0.24 (0.06, 0.65)	0.016
Age	0.96 (0.95, 0.97)	<0.001
Female	0.70 (0.46, 1.06)	0.099

Table 7
Multivariate logistic regression model (ICU admission status vs vitamin D levels, sex and age).

Variable	OR (95 % CI)	p
Vitamin D	0.97 (0.94, 0.99)	0.007
Female	0.70 (0.46, 1.06)	0.097
Age	0.96 (0.95, 0.97)	<0.001

Table 8
Comparison of vitamin D levels in deceased patients with the normal population over 70.

Normal population over 70 (n = 336)	Deceased due to COVID-19 (n = 324)	P-value
23.4 ± 10.0	19.2 ± 13.8	<0.001

Table 9
Comparison of vitamin D levels between living and deceased patients.

Values for 25(OH)D:	Living (n = 1225)	Deceased (n = 324)	p
Student *t* -test	17.8 ± 11.3	19.2 ± 13.8	0.091
Mann-Whitney U test	15.0 (13.2)	16.2 (19.2)	0.063

OR is less than 1, indicating that higher vitamin D values are associated with a lower risk of ICU admission.

3.3. Association between vitamin D levels and mortality

The mean age of the living patients was 67 years, and the mean age of the deceased patients was 82 years. Vitamin D levels were compared between deceased patients and the normal population of the same age (Table 8).

Compared with normal population of the same age, deceased patients have a significant low level of vitamin D ($p < 0.001$).

Vitamin D levels were also compared between surviving patients and those with fatal outcomes, as shown in Table 9. Comparisons were performed of mean values ± standard deviation with Student's *t*-test and by comparing means and interquartile ranges with the Mann-Whitney *U* test. Table 10 shows the values adjusted for age and sex.

Neither of the two tests revealed differences in vitamin D levels between those who survived the disease and those who did not, even when the data were adjusted by age and sex. This suggests that these variables are unrelated, or at least that there is no clear relation between vitamin D level and mortality.

Similarly, a chi-squared test revealed no statistically significant differences in mortality rates between groups based on levels of circulating vitamin D.

4. Discussion

Some retrospective studies [3] have shown a correlation between vitamin D levels and COVID-19 positivity, as well as the clinical course of the disease, although others have failed to find such a correlation. Despite reports concluding that low vitamin D levels facilitate SARS-CoV-2 infection with a more severe disease course, these findings are based on studies with small sample sizes, and there are certain inconsistencies between them [3]. However, there is insufficient evidence on vitamin D levels and COVID-19 severity and mortality, thus suggesting the need for further research involving larger cohorts to test this hypothesis [10].

Iddir et al. [16] stated that the relationship between low vitamin D levels and the development of the disease is not clear, and they recommended performing a case control study to observe the frequency of vitamin D deficiency among patients with poor COVID-19 outcomes. They did not endorse the use of vitamin D for the treatment or prevention of COVID-19 infections but instead stressed the need for more robust research that can address the early correlations noted above.

Three recent meta-analyses enrich this information. Pereira et al. [17] published the first systematic review that reports the relationship between vitamin D levels and COVID-19 severity. This review also has its limitations. They identified that the results of the studies included in their review were not stratified according to the sex of the participants. Moreover, the studies showed various methodological divergences that prevented exploration of the heterogeneity of the meta-analyses and prevented subgroup analyses due to confounding variables. Furthermore, most of the studies chosen presented a high risk of bias. This is because the studies were conducted using hospital-based samples, and the data in these studies were taken from secondary recordings in patient records. It should also be considered that confounding factors, such as age, sex, and the presence of comorbidities, were not used in most of the studies. Such variables are determinants of COVID-19 severity. Thus, it is necessary to consider these aspects in future studies on this topic.

Petrelli et al. [18] found that among subjects with deficient vitamin D values, the risk of COVID-19 infection was higher than that among those with replete values (OR = 1.26; 95 % CI, 1.19–1.34; P < .01). Vitamin D deficiency was also associated with worse severity and higher mortality than replete values (OR = 2.6; 95 % CI, 1.84–3.67; P < .01 and OR = 1.22; 95 % CI, 1.04–1.43; P < .01, respectively), even though they did not compare the data among people with worse severity and people

Table 10
Comparison of vitamin D levels between living and deceased patients adjusted by age and sex.

Living (n = 1225)	Deceased (n = 324)	p
14.9 (14.3, 15.4)	14.1 (13.1, 15.3)	0.613

who died. Reduced vitamin D values resulted in a higher infection risk, mortality and severity of COVID-19 infection. Vitamin D supplementation may be considered a preventive and therapeutic measure.

Aya Bassatne et al. [19] showed that while the currently available evidence, largely from poor-quality observational studies, may indicate a trend for an association between low serum 25(OH)D levels and COVID-19-related health outcomes, this relationship was not found to be statistically significant, and it was concluded that none of the outcomes evaluated in this systematic review revealed clear and strong evidence for a cause/effect relationship of vitamin D status and COVID-19 health-related outcomes. Clear evidence-based recommendations on vitamin D supplementation and timing and dosing regimens can only be determined based on results from several ongoing randomized controlled trials examining the effects of vitamin D on COVID-19-related health outcomes.

Recently, a large review of the relationship between low levels of vitamin D and COVID-19 published in November 2020 [20] found inconsistent results in several studies. At that time, the impact of vitamin D deficiency on the occurrence of COVID-19 and the severity of the disease was not clearly defined, probably because the number of patients included in the review (20 patients, 107 patients, 49 patients, 449 patients) was small. Studies investigating vitamin D and COVID-19 are currently underway and more are likely to follow in the future.

J Elliot et al. reviewed COVID-19 mortality in the UK Biobank cohort [21]. Using the community-based UK Biobank cohort, they examined risk factors for COVID-19 mortality in comparison with non-COVID-19 mortality. They investigated demographic, social (education, income, housing, employment), lifestyle (smoking, drinking, body mass index), biological (lipids, cystatin C, vitamin D), medical (comorbidities, medications) and environmental (air pollution) data from the UK Biobank (N = 473,550) in relation to 459 COVID-19 and 2626 non-COVID-19 deaths prior to 21 September 2020.

In multivariable regression, alongside demographic covariates, factors including being a healthcare worker or current smoker, using oral steroids, or having cardiovascular disease, hypertension, diabetes, or an autoimmune disease at enrollment were independently associated with COVID-19 mortality. Penalized regression models selected income, cardiovascular disease, hypertension, diabetes, cystatin C, and oral steroid use as jointly contributing to the COVID-19 mortality risk; black ethnicity, hypertension and oral steroid use contributed to the COVID-19 but not non-COVID-19 mortality. Age, male sex and black ethnicity, as well as comorbidities and oral steroid use at enrollment, were associated with an increased risk of COVID-19 death.

These results suggest that previously reported associations of COVID-19 mortality with **low vitamin D,** body mass index, air pollutants, and renin-angiotensin-aldosterone system inhibitors may be explained by the aforementioned factors.

A total of 1547 hospitalized patients were included in this study, and this large number helped us to assume more consistency in our results. We found that low 25(OH)D levels were associated with more severe disease, possibly requiring hospital admission, including some cases that required admission to the ICU. The 25(OH)D values of patients with COVID-19 were lower than those corresponding to the normal population.

We also found that deceased patients were more likely to have low 25 (OH) levels compared with the normal population of the same age. However, we failed to find a higher rate of mortality among patients with low levels of vitamin D compared with the rest of the patients admitted to the hospital with COVID-19. The fact that this study did not gather data on drug intake, including vitamin D supplements, or the comorbidities presented by these patients impeded us from further defining this parameter.

Several strategies for the treatment of COVID-19 have been introduced in recent months, some of which have a scientific basis and others even with empirical evidence in support of their effectiveness. These strategies call for the use of antiretroviral drugs, corticosteroids, and immunomodulators, among others.

Despite their low evidence levels, certain clinical studies [22,23] have reported findings in support of the benefits of vitamin D treatment in the general population and/or for patients exposed to SARS-CoV-2.

Some authors suggest maintaining 25(OH)D levels of at least 30 ng/mL or even 40–50 ng/ml or, alternatively, maintaining levels within the range of 40–70 ng/ml to minimize the risk of infection [24]. For the present pandemic, Grant [9] suggests a vitamin D dose of 10,000 μL/d administered over 1 month to rapidly raise vitamin D levels to the range of 40–60 ng/ml, continuing with 5,000 μL/d in subsequent months. Any dosage capable of raising 25(OH)D to these levels (e.g., daily, weekly) may be sufficient.

Despite the small sample sizes used, other studies have found that treatment consisting of ultrahigh doses of calcifediol improves the prognosis of patients with this disease. A previous study compared two groups of patients with COVID-19, the first group comprising 26 patients who did not receive vitamin D supplements. Fifty percent of these patients required ICU admission, while another 50 patients were treated with ultrahigh doses of calcidiol. Only 1 patient required urgent ICU admission ($p < 0.001$). Two patients in the first group died, and all patients in the second group survived [25].

There is a need for clinical trials in larger, appropriately compared samples to provide evidence of a definitive response to vitamin D supplementation.

5. Conclusions

Our findings support the position that vitamin D deficiency in patients with COVID-19 is correlated with an increased risk of hospital admission and the need for critical care, although vitamin D levels do not influence the rate of mortality. Further clinical research is required to expand the evidence base and include an analysis of comorbidities. Clinical trials performed to test these findings should be case-controlled and properly compared to test the relevance of vitamin D levels as a risk factor for infected patients and the application of vitamin D in therapy [20,24].

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Authorship

All listed authors meet the ICMJE criteria.
We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the manuscript has been read and approved by all named authors.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

Authors roles

Study design: Manuel Diaz Curiel, Alfonso Cabello. Data collection: Manuel Diaz Curiel, Marjorie Andrade Poveda, Antonio Romero, Sara Haili. Data Analysis: Ignacio Mahillo Fernández, Manuel Diaz Curiel. Drafting the manuscript: Manuel Díaz Curiel, Marjorie Andrade, Ignacio Mahillo Fernández. Manuscript revision: Manuel Díaz Curiel, Rosa Arboiro Pinel, José Luis Mansur.

All authors approved the final content of the manuscript. MDC takes responsibility for the integrity of the data analysis.

Declaration of Competing Interest

No conflict of interest exists.

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References

[1] M. Díaz Curiel, R.M. Arboiro Pinel, Prevalencia de hypovitaminosis-D en nuestro medio, Rev. Osteoporos Metab. Miner. 9 (Supl 1) (2017) S10–15, https://doi.org/10.4321/S1889-836X2017000200003.

[2] G.K. Schwalfenberg, A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency, Mol. Nutr. Food Res. 55 (2011) 96–108, https://doi.org/10.1002/mnfr.201000174.

[3] J.L. Hernández, D. Nan, M. Fernandez-Ayala, M. García-Unzueta, M.A. Hernández-Hernández, M. López-Hoyos, P. Muñoz-Cacho, J.M. Olmos, M. Gutiérrez-Cuadra, J. J. Ruiz-Cubillán, J. Crespo, V.M. Martínez-Taboada, Vitamin D status in hospitalized patients with SARS-CoV-2 infection, J. Clin. Endocrinol. Metab. (October (27)) (2020) dgaa733, https://doi.org/10.1210/clinem/dgaa733. Online ahead of print. PMID: 33159440.

[4] J.R. Mora, M. Iwata, U.H. Von Adrian, Vitamin effects on the immune system: vitamins A and D take centre stage, Nat. Rev. Immunol. 8 (September (9)) (2008) 685–698, https://doi.org/10.1038/nri2378.

[5] José Luis Mansur, Carlos Tajer, Javier Mariani, Felipe Inserra, León Ferder, Walter Manucha, Suplemento con altas dosis de vitamina D podría representar una alternativa promisoria para prevenir o tratar la infección por COVID-19, Clin. Investig. Arterioscler. (2020), https://doi.org/10.1016/j.arteri.2020.05.003.

[6] T.L. Van Belle, C. Gysemans, C. Mathieu, Vitamin D in autoimmune, infectious and allergic diseases: a vital player? Best Pract. Res. Clin. Endocrinol. Metab. 25 (4) (2011) 617–632, https://doi.org/10.1016/j.beem.2011.04.009.

[7] JoséL. Hernández, Daniel Nan, Marta Fernández-Ayala, et al., Vitamin D status in hospitalized patients with Sars-CoV-2 infection, J. Clin. Endocrinol. Metab. (2020), https://doi.org/10.1210/clinem/dgaa733. -10-27.

[8] Maryam Ebadi, Aldo J. Montano-Loza, Perspective: improving vitamin D status in the management of COVID-19, Eur. J. Clin. Nutr. 74 (2020) 856–859, https://doi.org/10.1038/s41430-020-0661-0.

[9] (https://www.grassrootshealth.net/project/our-scientists/).

[10] William B. Grant, Henry Lahore, Sharon L. McDonnell, Carole A. Baggerly Christine, B. French, Jennifer L. Aliano, Harjit P. Bhattoa, Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections, and deaths, Nutrients 12 (2020) 988, https://doi.org/10.3390/nu12040988.

[11] M. Theron, K.J. Huang, Y.W. Chen, C.C. Liu, H.Y. Lei, A probable role for IFNgamma in the development of a lung immunopathology in SARS, Cytokine 32 (2005) 30–38, https://doi.org/10.1016/j.cyto.2005.07.007.

[12] José Manuel Quesada-Gomez, Manuel Díaz-Curiel, in: M.F. Holick (Ed.), Consequences for the Health of People in Mediterranean Countries. From: Nutrition and Health: Vitamin D, C Springer Science+Business Media, LLC, 2010, https://doi.org/10.1007/978-1-60327-303-9_23.

[13] J.M. Olmos, J.L. Hernández, P. García-Velasco, J. Martínez, J. Llorca, J. González-Macías, Serum 25-hydroxy vitamin D, parathyroid hormone, calcium intake, and bone mineral density in Spanish adults, Osteoporos. Int. 27 (1) (2016) 105–113, https://doi.org/10.1007/s00198-015-3219-6.

[14] I. González-Molero, S. Morcillo, S. Valdés, V. Pérez-Valero, P. Botas, E. Delgado, D. Hernández, G. Olveira, G. Rojo, C. Gutiérrez-Repiso, E. Rubio-Martín, E. Menéndez, F. Soriguer, Vitamin D deficiency in Spain: a population-based cohort study, Eur. J. Clin. Nutr. 65 (2011) 321–328.

[15] J.M. Quesada, W. Coopmans, B. Ruiz, P. Aljama, I. JAans, R. Bouillon, Influence of vitamin D on parathyroid function in the elderly, J. Clin. Endocrinol. Metab. 75 (2) (1994) 494–501.

[16] M. Iddir, A. Brito, G. Dingeo, S.S. Fernandez Del Campo, H. Samouda, M.R. La Frano, M. Mohan, J.J. Cherian, A. Sharma, Exploring links between vitamin D deficiency and COVID-19, PLoS Pathog. 16 (September (9)) (2020), e1008874, https://doi.org/10.1371/journal.ppat.1008874. PMID: 32946517; PMCID: PMC7500624.

[17] F. Petrelli, A. Luciani, G. Perego, G. Dognini, P.L. Colombelli, A. Ghidini, Therapeutic and prognostic role of vitamin D for COVID-19 infection: a systematic review and meta-analysis of 43 observational studies, J. Steroid Biochem. Mol. Biol. (March (25)) (2021), 105883, https://doi.org/10.1016/j.jsbmb.2021.105883. Epub ahead of print. PMID: 33775818; PMCID: PMC7997262.

[18] M. Pereira, A. Dantas Damascena, L.M. Galvão Azevedo, T. de Almeida Oliveira, J. da Mota Santana, Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis, Crit. Rev. Food Sci. Nutr. (November (4)) (2020) 1–9, https://doi.org/10.1080/10408398.2020.1841090. Epub ahead of print. PMID: 33146028.

[19] Aya Bassatne, Maya Basbous, Marlene Chakhtoura, Ola El Zein, Maya Rahme, Ghada El-Hajj Fuleihan, The link between COVID-19 and VItamin D (VIVID): a systematic review and meta-analysis, Metabolism (March (24)) (2021), 154753, https://doi.org/10.1016/j.metabol.2021.154753 [Epub ahead of print] PMCID: PMC7989070.

[20] J.P. Bilezikian, D. Bikle, M. Hewison, M. Lazaretti-Castro, A.N. Formenti, A. Gupta, M.V. h V Madhavan, N. Nair, V. Babalyan, N. Hutchings, N. Nápoles, D. Accili, N. Binkley, D.W. Landry, A. Giustina, Mechanisms in endocrinology: vitamin D and COVID-19, Eur. J. Endocrinol. 183 (November(5)) (2020) R133–R147, https://doi.org/10.1530/EJE-20-0665. PMID: 32755992 DOI: 10.1530 / EJE-20-0665.

[21] Centre for Guidelines Methods and Economics Team (UK), Evidence Reviews for the Use of Vitamin D Supplementation As Prevention and Treatment of COVID-19: Vitamin D for COVID-19: Evidence Review A, National Institute for Health and Care Excellence (UK), London, 2020. Dec. PMID: 33378142.

[22] Joshua Elliott, Barbara Bodinier, Matthew Whitaker, Cyrille Delpierre, Roel Vermeulen, Ioanna Tzoulaki, Paul Elliott, Marc Chadeau-Hyam, COVID-19 mortality in the UK Biobank cohort: revisiting and evaluating risk factors, Eur. J. Epidemiol. (February (15)) (2021) 1–11, https://doi.org/10.1007/s10654-021-00722-y. Online ahead of print.

[23] C.W. Tan, L.P. Ho, S. Kalimuddin, B.P.Z. Cherng, Y.E. Teh, S.Y. Thien, et al., A cohort study to evaluate the effect of combination Vitamin D. Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients [preprint], Infect. Dis. (except HIV/AIDS) (2020), https://doi.org/10.1101/2020, 06.01.20112334.

[24] N. Ali, Role of vitamin D in preventing of COVID-19 infection, progression and severity, J. Infect. Public Health (2020), https://doi.org/10.1016/j.jiph.2020.06.021.

[25] M. Entrenas Castillo, L.M. Entrenas Costa, J.M. Vaquero Barrios, J.F. Alcala Diaz, J. L. Miranda, R. Bouillon, J.M. Quesada Gómez, Effect of Calcifediol Treatment and best Available Therapy versus best Available Therapy on Intensive Care Unit Admission and Mortality Among Patients Hospitalized for COVID-19: A Pilot Randomized Clinical study, J. Steroid Biochem. Mol. Biol. 203 (October) (2020), 105751, https://doi.org/10.1016/j.jsbmb.2020.105751. Published online 2020 Aug 29. PMCID: PMC7456194.