Annotated bibliography of studies on vitamin D in treatment of COVID19
as of Dec 31, 2021
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Reviews and Meta-Analyses

1. Tentolouris, N, (Dec, 29, 2021) The effect of vitamin D supplementation on mortality and Intensive Care Unit admission of COVID-19 patients. A systematic review, meta-analysis and meta-regression. Diabetes Metab Res Rev. 2021 Dec 29;e3517. https://pubmed.ncbi.nlm.nih.gov/34965318/

Aims: The aim of this systematic review and meta-analysis was to investigate the effect of vitamin D supplementation on mortality and admission to intensive care unit (ICU) of COVID-19 patients.

Methods: A systematic search of PubMed, Google Scholar, Embase, Web of Science and medRxiv with terms relative to vitamin D supplementation and COVID-19 was conducted on March, 26th , 2021. Comprehensive Meta-Analysis software was used for the quantitative assessment of data and random-effects model was applied. To investigate the association between the dose of vitamin D and the outcomes of interest, meta-regression analysis was performed.

Results: 2,078 patients from 9 studies with data on mortality were included (583 received vitamin D supplementation, while 1,495 did not). 61 (10.46%) individuals in the treated group died, compared to 386 (25.81%) in the non-treated group [odds ratio (OR): 0.597; 95% CI: 0.318-1.121; p=0.109]. 860 patients from 6 studies with data on ICU admission were included (369 received vitamin D supplementation, while 491 did not). 45 (12.19%) individuals in the treated group were admitted to ICU, compared to 129 (26.27%) in the non-treated group (OR: 0.326; 95%CI: 0.149-0.712; p=0.005). No significant linear relationship between vitamin D dose and log OR of mortality or log OR of ICU admission was observed.

Conclusion: This meta-analysis indicates a beneficial role of vitamin D supplementation on ICU admission, but not on mortality, of COVID-19 patients. Further research is urgently needed to understand the benefit of vitamin D in Covid-19.

2. Pal, June 2021, Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis, *Journal of Endocrinological Investigation* (2021) https://link.springer.com/article/10.1007/s40618-021-01614-4

Purpose: To provide a precise summary and collate the hitherto available clinical evidence on the effect of vitamin D supplementation on clinical outcomes in COVID-19 patients.

Methods: PubMed/MEDLINE, Scopus, and Web of Science databases were systematically searched using appropriate keywords till June 8, 2021, to identify observational studies and randomized controlled trials (RCTs) reporting adverse clinical outcomes (ICU admission and/or mortality) in COVID-19 patients receiving vitamin D supplementation vs. those not receiving the same. Both prior use and use of vitamin D after COVID-19 diagnosis were considered. Unadjusted/adjusted pooled odds ratio (OR) with 95% confidence intervals (CI) were calculated (PROSPERO registration number CRD42021248488).

Results: We identified 13 studies (10 observational, 3 RCTs) pooling data retrieved from 2933 COVID-19 patients. Pooled analysis of unadjusted data showed that vitamin D use in COVID-19 was significantly associated with reduced ICU admission/mortality (OR 0.41, 95% CI: 0.20, 0.81, $p = 0.01$, $I^2 = 66\%$, random-effects model). Similarly, on pooling adjusted risk estimates, vitamin D was also found to reduce the risk of adverse outcomes (pooled OR 0.27, 95% CI: 0.08, 0.91, $p = 0.03$, $I^2 = 80\%$, random-effects model). Subgroup analysis showed that vitamin D supplementation was associated with improved clinical outcomes only in patients receiving the drug post-COVID-19 diagnosis and not in those who had received vitamin D before diagnosis.

Conclusions: Vitamin D supplementation might be associated with improved clinical outcomes, especially when administered after the diagnosis of COVID-19. However, issues regarding the appropriate dose, duration, and mode of administration of vitamin D remain unanswered and need further research.

3. **Bui** L, Zhu Z, Hawkins S, Cortez-Resendiz A, Bellon A. (May, 2021) Vitamin D regulation of the immune system and its implications for COVID-19: A mini review. SAGE Open Med.9:20503121211014073. https://pubmed.ncbi.nlm.nih.gov/34046177

The novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is at the origin of the current pandemic, predominantly manifests with severe respiratory symptoms and a heightened immune response. One characteristic of SARS-CoV-2 is its capacity to induce cytokine storm leading to acute respiratory distress syndrome. Consequently, agents with the ability to regulate the immune response, such as vitamin D, could become tools either for the prevention or the attenuation of the most severe consequences of the coronavirus disease 2019 (COVID-19). Vitamin D has shown antimicrobial as well as anti-inflammatory properties. While SARS-CoV-2 promotes the release of proinflammatory cytokines, vitamin D attenuates the release of at least some of these same molecules. Inflammatory cytokines have been associated with the clinical phenomena of COVID-19 and in particular with its most dangerous complications. Therefore, the goals of this article are as follows: first, present the numerous roles vitamin D plays in modulating the immune response; second, gather data currently available on COVID-19 clinical presentation and its relation to cytokines and similar molecules; third, expose what it is known about how coronaviruses elicit an inflammatory reaction; and fourth, discuss the potential contribution of vitamin D in reducing the risk and severity of COVID-19.

Observational Studies

1. Bychinin MV, Klypa TV, Mandel IA, et al. (Aug, 2021) Low Circulating Vitamin D in Intensive Care Unit-Admitted COVID-19 Patients as a Predictor of Negative Outcomes. J Nutr 2021 May 12;107. https://pubmed.ncbi.nlm.nih.gov/33982128

Objectives: The study aimed to evaluate the serum 25-hydroxyvitamin D [25(OH)D] concentration in patients admitted to the intensive care unit (ICU) as a predictor of coronavirus disease 2019 (COVID-19) mortality.

Methods: A single-center retrospective observational study was conducted. Forty adult patients (50% men) with confirmed COVID-19 who were admitted to the ICU were enrolled. The primary endpoint was mortality at day 60. Serum 25(OH)D concentration was measured on the day of admission to the ICU. We used the Mann-Whitney test, Fisher's exact test, Kaplan-Meier analysis, and receiver operator characteristic (ROC) analysis to assess serum 25(OH)D concentration as a predictor of COVID-19 mortality.

Results: All 40 patients had a low median (IQR) serum 25(OH)D concentration at admission [12 (9-15) ng/mL]. The median (IQR) serum 25(OH)D concentration was greater in survivors [13.3 (10.0-17.1) ng/mL, n = 22] than in nonsurvivors [9.6 (7.9-14.2) ng/mL; n = 18], P = 0.044. The area under the ROC curve was 0.69 (95% CI: 0.52, 0.86; P = 0.044). The 60-d mortality rate of those with serum 25(OH)D concentrations ≤9.9 ng/mL (n = 14, 71%) tended to be greater than that of those with concentrations >9.9 ng/mL (n = 26, 31%) (P = 0.065), and they had a 5.6-fold higher risk of death (OR: 5.63; 95% CI: 1.35, 23.45; P = 0.018).

Conclusions: The ICU patients had a low serum 25(OH)D concentration. Serum 25(OH)D concentrations ≤9.9 ng/mL on admission can be used to predict in-hospital mortality in patients with COVID-19.

2. Mazziotti G, et al. (April, 2021) Vitamin D deficiency, secondary hyperparathyroidism and respiratory insufficiency in hospitalized patients with COVID-19. J Endocrinol Invest 2021 Mar 5;1-9. https://pubmed.ncbi.nlm.nih.gov/33666876

Purpose: Hypovitaminosis D has emerged as potential risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the general population with variable effects on the outcome of the coronavirus disease-19 (COVID-19). The aim of this retrospective single-center study was to investigate the impact of hypovitaminosis D and secondary hyperparathyroidism on respiratory outcomes of COVID-19.

Methods: Three-hundred-forty-eight consecutive patients hospitalized for COVID-19 at the IRCCS Humanitas Research Hospital, Rozzano, Milan (Italy) were evaluated for arterial partial pressure oxygen (PaO2)/fraction of inspired oxygen (FiO2) ratio, serum 25hydroxy-vitamin D [25(OH)D], parathyroid hormone (PTH) and inflammatory parameters at study entry and need of ventilation during the hospital stay.

Results: In the entire population, vitamin D deficiency (i.e., 25(OH)D values < 12 ng/mL) was significantly associated with acute hypoxemic respiratory failure at the study entry [adjusted odds ratio (OR) 2.48, 95% confidence interval 1.29-4.74; P = 0.006], independently of age and sex of subjects, serum calcium and inflammatory parameters. In patients evaluated for serum PTH (97 cases), secondary hyperparathyroidism combined with vitamin D deficiency was significantly associated with acute hypoxemic respiratory failure at study entry (P = 0.001) and need of ventilation during the hospital stay (P = 0.031).

Conclusion: This study provides evidence that vitamin D deficiency, when associated with secondary hyperparathyroidism, may negatively impact the clinical outcome of SARS-CoV-2-related pneumonia.

3. Charoenngam N, Shirvani A, Reddy N, et al. (April, 2021) Association of Vitamin D Status With Hospital Morbidity and Mortality in Adult Hospitalized Patients With COVID-19. Endocr Pract. 27:271-278. https://pubmed.ncbi.nlm.nih.gov/33705975

Objective: To determine the association between vitamin D status and morbidity and mortality in adult hospitalized coronavirus disease 2019 (COVID-19) patients

METHODS: We performed a retrospective chart review study in COVID-19 patients aged ≥18 year hospitalized at Boston University Medical Center between March 1 and August 4, 2020. All studied patients tested positive for COVID-19 and had serum levels of 25-hydroxyvitamin D (25[OH]D) results measured within 1 year prior to the date of positive tests. Medical information

was retrieved from the electronic medical record and was analyzed to determine the association between vitamin D status and hospital morbidity and mortality.

Results: Among the 287 patients, 100 (36%) were vitamin D sufficient (25[OH]D >30 ng/mL) and 41 (14%) died during hospitalization. Multivariate analysis in patients aged ≥65 years revealed that vitamin D sufficiency (25[OH]D ≥30 ng/mL) was statistically significantly associated with decreased odds of death (adjusted OR 0.33, 95% CI, 0.12-0.94), acute respiratory distress syndrome (adjusted OR 0.22, 95% CI, 0.05-0.96), and severe sepsis/septic shock (adjusted OR 0.26, 95% CI, 0.08-0.88), after adjustment for potential confounders. Among patients with body mass index <30 kg/m^2, vitamin D sufficiency was statistically significantly associated with a decreased odds of death (adjusted OR 0.18, 95% CI, 0.04-0.84). No significant association was found in the subgroups of patients aged <65 years or with body mass index ≥30 kg/m^2.

Conclusion: We revealed an independent association between vitamin D sufficiency defined by serum 25(OH)D ≥30 ng/mL and decreased risk of mortality from COVID-19 in elderly patients and patients without obesity.

4. Basaran N, Adas M, Gokden Y, et al. (March, 2021) The relationship between vitamin D and the severity of COVID-19. Bratisl Lek Listy 122:200-205. https://pubmed.ncbi.nlm.nih.gov/33618529

Aim: Vitamin D, which has immunomodulatory effect, can reduce risk of infections and concentrations of pro-inflammatory cytokines. The aim of this study was to investigate the relationship between the levels of vitamin D and severity of COVID-19.

Methods: A total of 204 patients with COVID-19 disease were enrolled in the study. All patients had viral pneumonia, which was confirmed with chest computer tomography. All cases were divided in two groups- mild (outpatients); and serious (inpatients)- according to their clinical and laboratory data. Serum vitamin D levels were measured by chemiluminescence method.

Results: Vitamin D deficiency was found in 41.7 % (n = 85) of cases and insufficiency was found in 46.0 % (n = 94), while in 12.3 % (n = 25) of cases normal vitamin D levels were found. The odds of having a serious clinical outcome were increased for vitamin D insufficiency patients 5.604 times (%95 CI:0.633-49.584) and for vitamin D deficiency patients 38.095 times (%95 CI:2.965-489.50) for each standard deviation decrease in serum 25(OH)D.

Conclusion: Adequate levels of vitamin D could suppress inflammation and reduce the severity of COVID-19. Vitamin D supplementation may have an important role in decreasing the impact of the pandemic (Tab. 5, Fig. 2, Ref. 27).

5. Gavioli EM, (Feb, 2021) An Evaluation of Serum 25-Hydroxy Vitamin D Levels in Patients with COVID-19 in New York City. J Am Coll Nutr. 2021 Feb 19;1-6. https://pubmed.ncbi.nlm.nih.gov/33605826

Aim: Deterioration of patients from COVID-19 is associated with cytokine release syndrome attributed to an elevation in pro-inflammatory cytokines. Vitamin D reduces proinflammatory cytokines, and has the possibility of reducing complications from respiratory tract illnesses.

Method: This was a retrospective, observational, cohort study of patients with COVID-19 disease within a New York City Health System. Adult patients were included if they tested

positive for SARS-CoV-2, and had a serum 25-hydroxy vitamin D level (25(OH)D) within the three previous months prior to their detected SARS-CoV-2 test. Patients were compared and evaluated based upon their 25(OH)D levels. The primary endpoints were hospitalization, need for oxygen support, and 90-day mortality.

Results: 437 COVID-19 patients were included [67 (IQR: 56-79) years] within this cohort. Deficient plasma 25(OH)D levels (<20 ng/ml) were associated with an increased likelihood of oxygen support [OR:2.23 (95% CI: 1.46-3.44, p = 0.0002)] from COVID-19. Deficient plasma 25(OH)D levels were not independently associated with 90-day mortality or risk of hospitalization. Hospitalization rates (98%), oxygen support (93%), and mortality rates (49%) were highest in patients who had 25(OH)D levels less than 10 ng/ml when compared to other 25(OH)D levels.

Conclusion: Serum 25-hydroxy vitamin D levels may affect the need for oxygen support therapy in patients with COVID-19.

6. **Ling** SF, et al. (Dec. 2020) 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. Nutrients. 12:3799. https://pubmed.ncbi.nlm.nih.gov/33322317

Aim: to determine whether COVID-19 mortality was affected by serum 25-hydroxyvitamin D (25(OH)D) levels, vitamin D status, or cholecalciferol therapy, and to elucidate any other predictors of COVID-19 mortality.

Methods: Patients hospitalised with COVID-19 were opportunistically recruited from three UK hospitals, and their data were collected retrospectively. Logistic regression was used to determine any relationships between COVID-19 mortality and potential predictors, including 25(OH)D levels and cholecalciferol booster therapy. A total of 986 participants with COVID-19 were studied, of whom 151 (16.0%) received cholecalciferol booster therapy.

Results: In the primary cohort of 444 patients, cholecalciferol booster therapy was associated with a reduced risk of COVID-19 mortality, following adjustment for potential confounders (OR_{adj} 0.13, 95% CI 0.05-0.35, p < 0.001). This finding was replicated in a validation cohort of 541 patients (OR_{adj} 0.38, 95% CI 0.17-0.84, p = 0.018).

Conclusion: In this observational study, treatment with cholecalciferol booster therapy, regardless of baseline serum 25(OH)D levels, appears to be associated with a reduced risk of mortality in acute in-patients admitted with COVID-19.

7. Radujkovic,A, (Sept. 2020), Vitamin D Deficiency and Outcome of COVID-19 Patients Department of Internal Medicine V, University of Heidelberg, 69121 Heidelberg, Germany, *Nutrients 12*(9), 2757; **https://doi.org/10.3390/nu12092757**

Aim: To explore possible associations of vitamin D (VitD) status with disease severity and survival, we studied 185 patients diagnosed with coronavirus disease 2019 (COVID-19) and treated at our center.

Methods: VitD status at first presentation was assessed retrospectively using accredited laboratory methods. VitD deficiency was defined as serum total 25-hydroxyvitamin D level < 12

ng/mL (<30 nM). Primary endpoint was severe course of disease (i.e., need for invasive mechanical ventilation and/or death, IMV/D).

Results: Within a median observation period of 66 days (range 2–92), 23 patients required IMV. A total of 28 patients had IMV/D, including 16 deaths. Ninety-three (50%) patients required hospitalization (inpatient subgroup). A total of 41 (22%) patients were VitD deficient. When adjusted for age, gender, and comorbidities, VitD deficiency was associated with higher risk of IMV/D and death (HR 6.12, 95% CI 2.79–13.42, $p < 0.001$ and HR 14.73, 95% CI 4.16–52.19, $p < 0.001$, respectively). Similar correlations were observed in the inpatient subgroup.

Conclusion: Our study demonstrates an association between VitD deficiency and severity/mortality of COVID-19, highlighting the need for interventional studies on VitD supplementation in SARS-CoV-2 infected individuals.

8. **Ohaegbulam**, K, (2020 Aug) Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. Am J Ther. 2020 Aug 13 : e485–e490. doi: 10.1097/MJT.0000000000001222

Methods: Vitamin D supplementation in patients after diagnosis of COVID-19. We report 4 vitamin D deficient patients diagnosed with COVID-19 in April 2020 who were provided with either cholecalciferol of 1000 IU daily (standard dose) or ergocalciferol 50,000 IU daily for 5 days (high dose) as part of supplementation.

Clinical Outcomes: Patients that received a high dose of vitamin D supplementation achieved normalization of vitamin D levels and improved clinical recovery evidenced by shorter lengths of stay, lower oxygen requirements, and a reduction in inflammatory marker status.

Conclusions: Vitamin D supplementation may serve as a viable alternative for curtailing acute respiratory distress syndrome in patients in underserved communities where resources to expensive and sought-after medications may be scarce. Randomized clinical trials will serve as an appropriate vessel to validate the efficacy of the therapeutic regimen and dissection of the pathway.

Intervention Studies

1. Alcala-Diaz JF, et.al. (May, 2021) Calcifediol Treatment and Hospital Mortality Due to COVID-19: A Cohort Study. Nutrients. 13:1760. https://pubmed.ncbi.nlm.nih.gov/34064175

Objective: To compare the administration or not of oral calcifediol on mortality risk of patients hospitalized because of COVID-19.

Design: Retrospective, multicenter, open, non-randomized cohort study, in hospitalized care.

Patients: Patients with laboratory-confirmed COVID-19 between 5 February and 5 May 2020 in five hospitals in the South of Spain.

Intervention: Patients received calcifediol (25-hydroxyvitamin D_3) treatment (0.266 mg/capsule, 2 capsules on entry and then one capsule on day 3, 7, 14, 21, and 28) or not.

Main outcome measure: In-hospital mortality during the first 30 days after admission.

Results: A total of 537 patients were hospitalized with COVID-19 (317 males (59%), median age, 70 years), and 79 (14.7%) received calcifediol treatment. Overall, in-hospital mortality during the first 30 days was 17.5%. The OR of death for patients receiving calcifediol (mortality rate of 5%) was 0.22 (95% CI, 0.08 to 0.61) compared to patients not receiving such treatment (mortality rate of 20%; $p < 0.01$). Patients who received calcifediol after admission were more likely than those not receiving treatment to have comorbidity and a lower rate of CURB-65 score for pneumonia severity ≥ 3 (one point for each of confusion, urea > 7 mmol/L, respiratory rate ≥ 30/min, systolic blood pressure < 90 mm Hg or diastolic blood pressure ≤ 60 mm Hg, and age ≥ 65 years), acute respiratory distress syndrome (moderate or severe), c-reactive protein, chronic kidney disease, and blood urea nitrogen. In a multivariable logistic regression model, adjusting for confounders, there were significant differences in mortality for patients receiving calcifediol compared with patients not receiving it (OR = 0.16 (95% CI 0.03 to 0.80).

Conclusion: Among patients hospitalized with COVID-19, treatment with calcifediol, compared with those not receiving calcifediol, was significantly associated with lower in-hospital mortality during the first 30 days.

2. **Sánchez-Zuno GA**, González-Estevez G, Matuz-Flores MG, et al. (May, 2021) Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. J Clin Med. 10:2378. https://pubmed.ncbi.nlm.nih.gov/34071293

Background: The immunomodulatory effects of vitamin D are known to be beneficial in viral infections; it is also known that its deficiency is associated with a prognosis more critical of Coronavirus Disease 2019. This study aimed to determine baseline vitamin D serum concentrations and the effects of its supplementation in asymptomatic or mildly symptomatic Coronavirus Disease 2019 outpatients.

Methods: 42 outpatients were included, 22 of which received a supplement of 10,000 IU of vitamin D3 for 14 days; the remaining 20 outpatients were designated as a control group. Serum levels of transferrin, ferritin, vitamin D, and D-dimer were measured at baseline in both groups. After 14 days, serum levels of total vitamin D were determined in the supplemented group.

Results: At baseline, only 19% of infected outpatients had vitamin D levels corresponding to sufficiency. All outpatients with vitamin D insufficiency had at least one symptom associated with the disease, while only 75% of patients with symptoms presented sufficiency. On the seventh and fourteenth day of follow-up, the supplemented group presented fewer symptoms with respect to those non-supplemented. A vitamin D3 dose of 10,000 IU/daily for 14 days was sufficient to raise vitamin D serum concentrations.

Conclusions: Immunomodulatory effects of vitamin D appear to be linked to the development of symptoms in positive outpatients. Vitamin D supplementation could have significant benefits in the Western Mexican population.

3. Annweiler C., et al. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. J. Steroid Biochem. Mol. Biol. 2020;204:105771. PMC7553119

Objective: Vitamin D may be a central biological determinant of COVID-19 outcomes.

Methods: The of this quasi-experimental study was to determine whether bolus vitamin D3 supplementation taken during or just before COVID-19 was effective in improving survival among frail elderly nursing-home residents with COVID-19. Sixty-six residents with COVID-19 from a French nursing-home were included in this quasi-experimental study. The “Intervention group” was defined as those having received bolus vitamin D3 supplementation during COVID-19 or in the preceding month, and the “Comparator group” corresponded to all other participants. The primary and secondary outcomes were COVID-19 mortality and Ordinal Scale for Clinical Improvement (OSCI) score in acute phase, respectively.

Results: The mean follow-up time was 36 ± 17 days. 82.5 % of participants in the Intervention group survived COVID-19, compared to only 44.4 % in the Comparator group (P = 0.023). The full-adjusted hazard ratio for mortality according to vitamin D3 supplementation was HR = 0.11 [95 %CI:0.03;0.48], P = 0.003. Kaplan-Meier distributions showed that Intervention group had longer survival time than Comparator group (log-rank P = 0.002). Finally, vitamin D3 supplementation was inversely associated with OSCI score for COVID-19 (β=-3.84 [95 %CI:-6.07;-1.62], P = 0.001).

Conclusion: bolus vitamin D3 supplementation during or just before COVID-19 was associated in frail elderly with less severe COVID-19 and better survival rate.

4. Annweiler G., et al Vitamin D Supplementation Associated to Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study. Nutrients. 2020;12:3377. doi: 10.3390/nu12113377. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

Background: The objective of this quasi-experimental study was to determine whether bolus vitamin D supplementation taken either regularly over the preceding year or after the diagnosis of COVID-19 was effective in improving survival among hospitalized frail elderly COVID-19 patients.

Methods: Seventy-seven patients consecutively hospitalized for COVID-19 in a geriatric unit were included. Intervention groups were participants regularly supplemented with vitamin D over the preceding year (Group 1), and those supplemented with vitamin D after COVID-19 diagnosis (Group 2). The comparator group involved participants having received no vitamin D supplements (Group 3). Outcomes were 14-day mortality and highest (worst) score on the ordinal scale for clinical improvement (OSCI) measured during COVID-19 acute phase.

Results: The three groups (n = 77; mean ± SD, 88 ± 5years; 49% women) were similar at baseline (except for woman proportion, p = 0.02), as were the treatments used for COVID-19. In Group 1 (n = 29), 93.1% of COVID-19 participants survived at day 14, compared to 81.2% survivors in Group 2 (n = 16) (p = 0.33) and 68.7% survivors in Group 3 (n = 32) (p = 0.02). While considering Group 3 as reference (hazard ratio (HR) = 1), the fully-adjusted HR for 14-day mortality was HR = 0.07 (p = 0.017) for Group 1 and HR = 0.37 (p = 0.28) for Group 2. Group 1 had longer survival time than Group 3 (log-rank p = 0.015), although there was no difference between Groups 2 and 3 (log-rank p = 0.32). Group 1, but not Group 2 (p = 0.40),

was associated with lower risk of OSCI score ≥5 compared to Group 3 (odds ratio = 0.08, *p*= 0.03).

Conclusions: Regular bolus vitamin D supplementation was associated with less severe COVID-19 and better survival in frail elderly.

5. **Ohaegbulam**, K, (2020 Aug) Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. Am J Ther. 2020 Aug 13 : e485–e490. doi: 10.1097/MJT.0000000000001222

Methods: Vitamin D supplementation in patients after diagnosis of COVID-19. We report 4 vitamin D deficient patients diagnosed with COVID-19 in April 2020 who were provided with either cholecalciferol of 1000 IU daily (standard dose) or ergocalciferol 50,000 IU daily for 5 days (high dose) as part of supplementation.

Clinical Outcomes: Patients that received a high dose of vitamin D supplementation achieved normalization of vitamin D levels and improved clinical recovery evidenced by shorter lengths of stay, lower oxygen requirements, and a reduction in inflammatory marker status.

Conclusions: Vitamin D supplementation may serve as a viable alternative for curtailing acute respiratory distress syndrome in patients in underserved communities where resources to expensive and sought-after medications may be scarce. Randomized clinical trials will serve as an appropriate vessel to validate the efficacy of the therapeutic regimen and dissection of the pathway.

Clinical Trials

1. Nogues, X. (2021, Sep) Calcifediol Treatment and COVID-19-Related Outcomes, Internal Medicine Department, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona 08003, Spain, J Clin Endocrinol Metab, 27;106(10):e4017-e4027, DOI: 10.1210/clinem/dgab405

Context: COVID-19 is a major health problem because of saturation of intensive care units (ICU) and mortality. Vitamin D has emerged as a potential treatment able to reduce the disease severity.

Objective: This work aims to elucidate the effect of 25(OH)D3 (calcifediol) treatment on COVID-19-related outcomes.

Methods: This observational cohort study was conducted from March to May 2020, among patients admitted to COVID-19 wards of Hospital del Mar, Barcelona, Spain. A total of 930 patients with COVID-19 were included; 92 were excluded because of previous calcifediol intake. Of the remaining 838, a total of 447 received calcifediol (532 µg on day 1 plus 266 µg on days 3, 7, 15, and 30), whereas 391 were not treated at the time of hospital admission (intention-to-treat). Of the latter, 53 patients were treated later during ICU admission and were allocated in the treated group in a second analysis. In healthy individuals, calcifediol is about 3.2-fold more potent on a weight basis than cholecalciferol. Main outcome measures were ICU admission and mortality.

Results: ICU assistance was required by 102 (12.2%) participants. Out of 447 patients treated with calcifediol at admission, 20 (4.5%) required the ICU, compared to 82 (21%) out of 391 nontreated (P < .001). Logistic regression of calcifediol treatment on ICU admission, adjusted by age, sex, linearized 25-hydroxyvitamin D levels at baseline, and comorbidities showed that treated patients had a reduced risk of requiring the ICU (odds ratio [OR] 0.13; 95% CI 0.07-0.23). Overall mortality was 10%. In the intention-to-treat analysis, 21 (4.7%) out of 447 patients treated with calcifediol at admission died compared to 62 patients (15.9%) out of 391 nontreated (P = .001). Adjusted results showed a reduced mortality risk with an OR of 0.21 (95% CI, 0.10-0.43). In the second analysis, the obtained OR was 0.52 (95% CI, 0.27-0.99).

Conclusion: In patients hospitalized with COVID-19, calcifediol treatment significantly reduced ICU admission and mortality.

2. Sabico, S, (june 2021) Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with Mild to Moderate Covid-19: A Randomized Clinical Trial. *Nutrients* 2021, *13*(7), 2170; https://doi.org/10.3390/nu13072170

Objective: This multi-center randomized clinical trial aims to determine the effects of 5000 IU versus 1000 IU daily oral vitamin D3 supplementation in the recovery of symptoms and other clinical parameters among mild to moderate COVID-19 patients with sub-optimal vitamin D status.
Study Design and Setting: A total of 69 reverse transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 positive adults who were hospitalized for mild to moderate COVID-19 disease were allocated to receive once daily for 2 weeks either 5000 IU oral vitamin D3 (n = 36, 21 males; 15 females) or 1000 IU oral vitamin D3 (standard control) (n = 33, 13 males; 20 females). Anthropometrics were measured and blood samples were taken pre- and post-supplementation. Fasting blood glucose, lipids, serum 25(OH)D, and inflammatory markers were measured. COVID-19 symptoms were noted on admission and monitored until full recovery.
Results: Vitamin D supplementation for 2 weeks caused a significant increase in serum 25(OH)D levels in the 5000 IU group only (adjusted p = 0.003). Within-group comparisons also showed a significant decrease in BMI and IL-6 levels overtime in both groups (p-values < 0.05) but was not clinically significant in between-group comparisons. Kaplan–Meier survival analysis revealed that the 5000 IU group had a significantly shorter time to recovery (days) than the 1000 IU group in resolving cough, even after adjusting for age, sex, baseline BMI, and D-dimer (6.2 ± 0.8 versus 9.1 ± 0.8; p = 0.039), and ageusia (loss of taste) (11.4 ± 1.0 versus 16.9 ± 1.7; p = 0.035).
Conclusion: A 5000 IU daily oral vitamin D3 supplementation for 2 weeks reduces the time to recovery for cough and gustatory sensory loss among patients with sub-optimal vitamin D status and mild to moderate COVID-19 symptoms. The use of 5000 IU vitamin D3 as an adjuvant therapy for COVID-19 patients with suboptimal vitamin D status, even for a short duration, is recommended

3. **Lakkireddy** M, et al. (May, 2021) Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. Sci Rep. 11:10641. https://pubmed.ncbi.nlm.nih.gov/34017029

COVID 19 is known to cause immune dysregulation and vitamin D is a known immunomodulator.

Aims to objectively investigate the impact of Pulse D therapy in reducing the inflammatory markers of COVID-19.

Methods: Consented COVID-19 patients with hypovitaminosis D were evaluated for inflammatory markers (N/L ratio, CRP, LDH, IL6, Ferritin) along with vitamin D on 0th day and 9th/11th day as per their respective BMI category. Subjects were randomised into VD and NVD groups. VD group received Pulse D therapy (targeted daily supplementation of 60,000 IUs of vitamin D for 8 or 10 days depending upon their BMI) in addition to the standard treatment. NVD group received standard treatment alone. Differences in the variables between the two groups were analysed for statistical significance. Eighty seven out of one hundred and thirty subjects have completed the study (VD:44, NVD:43).

Results: Vitamin D level has increased from 16 ± 6 ng/ml to 89 ± 32 ng/ml after Pulse D therapy in VD group and highly significant ($p < 0.01$) reduction of all the measured inflammatory markers was noted. Reduction of markers in NVD group was insignificant ($p > 0.05$). The difference in the reduction of markers between the groups (NVD vs VD) was highly significant ($p < 0.01$). Therapeutic improvement in vitamin D to 80-100 ng/ml has significantly reduced the inflammatory markers associated with COVID-19 without any side effects. Hence, adjunctive Pulse D therapy can be added safely to the existing treatment protocols of COVID-19 for improved outcomes.

4. Muri, I, (March 2021) Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial, JAMA 2021 Mar 16;325(11):1053-1060. **PMCID:** PMC7890452

Results: Of 240 randomized patients, 237 were included in the primary analysis (mean [SD] age, 56.2 [14.4] years; 104 [43.9%] women; mean [SD] baseline 25-hydroxyvitamin D level, 20.9 [9.2] ng/mL). Median (interquartile range) length of stay was not significantly different between the vitamin D_3 (7.0 [4.0-10.0] days) and placebo groups (7.0 [5.0-13.0] days) (log-rank $P = .59$; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82-1.39]; $P = .62$). The difference between the vitamin D_3 group and the placebo group was not significant for in-hospital mortality (7.6% vs 5.1%; difference, 2.5% [95% CI, –4.1% to 9.2%]; $P = .43$), admission to the intensive care unit (16.0% vs 21.2%; difference, –5.2% [95% CI, –15.1% to 4.7%]; $P = .30$), or need for mechanical ventilation (7.6% vs 14.4%; difference, –6.8% [95% CI, –15.1% to 1.2%]; $P = .09$). Mean serum levels of 25-hydroxyvitamin D significantly increased after a single dose of vitamin D_3 vs placebo (44.4 ng/mL vs 19.8 ng/mL; difference, 24.1 ng/mL [95% CI, 19.5-28.7]; $P < .001$). There were no adverse events, but an episode of vomiting was associated with the intervention.

Conclusions: Among hospitalized patients with COVID-19, a single high dose of vitamin D_3, compared with placebo, did not significantly reduce hospital length of stay. The findings do not support the use of a high dose of vitamin D_3 for treatment of moderate to severe COVID-19.

5. **Castillo** ME, (Oct, 2020). "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". The Journal of Steroid Biochemistry and Molecular Biology, 105751. https://doi.org/10.1016/j.jsbmb.2020.105751

Design: Parallel pilot randomized open label, double-masked clinical trial.

Setting: University hospital setting (Reina Sofia University Hospital, Córdoba Spain.)

Participants: 76 consecutive patients hospitalized with COVID-19 infection, clinical picture of acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1).

Procedures: All hospitalized patients received as best available therapy the same standard care, (per hospital protocol), of a combination of hydroxychloroquine (400 mg every 12 h on the first day, and 200 mg every 12 h for the following 5 days), azithromycin (500 mg orally for 5 days. Eligible patients were allocated at a 2 calcifediol:1 no calcifediol ratio through electronic randomization on the day of admission to take oral calcifediol (0.532 mg) (21,280 iu), or not. Patients in the calcifediol treatment group continued with oral calcifediol (0.266 mg) on day 3 and 7, and then weekly until discharge or ICU admission. Outcomes of effectiveness included rate of ICU admission and deaths.

Results: of 50 patients treated with calcifediol, one required admission to the ICU (2%) of 26 untreated patients, 13 required admission (50 %) p value X2 Fischer test $p < 0.001$. Univariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment versus without Calcifediol treatment: 0.02 (95 %CI 0.002−0.17). Multivariate Risk Estimate Odds Ratio for ICU in patients with Calcifediol treatment vs Without Calcifediol treatment ICU (adjusting by Hypertension and T2DM): 0.03 (95 %CI: 0.003-0.25).
Of the patients treated with calcifediol, none died, and all were discharged, without complications. The 13 patients not treated with calcifediol, who were not admitted to the ICU, were discharged. Of the 13 patients admitted to the ICU, two died and the remaining 11 were discharged.

Conclusion: Our pilot study demonstrated that administration of a high dose of Calcifediol or 25-hydroxyvitamin D, a main metabolite of vitamin D endocrine system, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19. Calcifediol seems to be able to reduce severity of the disease, but larger trials with groups properly matched will be required to show a definitive answer.

6. **Rastogi,** A (2020). Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomized, placebo-controlled, study (SHADE study). Postgrad Med J 2020;0:1–4. http://dx.doi.org/10.1136/postgradmedj-2020-139065

Aim Effect of high dose, oral cholecalciferol supplementation on SARS-CoV-2 viral clearance.
Design Randomised, placebo-controlled.
Participants Asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH)D<20 ng/ml) individuals.
Intervention Participants were randomised to receive daily 60 000 IU of cholecalciferol (oral nano-liquid droplets) for 7 days with therapeutic target 25(OH)D>50 ng/ml (intervention group) or placebo (control group). Patients requiring invasive ventilation or with significant comorbidities were excluded. 25(OH)D levels were assessed at day 7, and cholecalciferol supplementation was continued for those with 25(OH)D <50 ng/ml in the intervention arm.

SARS-CoV-2 RNA and inflammatory markers fibrinogen, D-dimer, procalcitonin and (CRP), ferritin were measured periodically.
Outcome measure Proportion of patients with SARS-CoV-2 RNA negative before day-21 and change in inflammatory markers.
Results Forty SARS-CoV-2 RNA positive individuals were randomised to intervention (n=16) or control (n=24) group. Baseline serum 25(OH)D was 8.6 (7.1 to 13.1) and 9.54 (8.1 to 12.5) ng/ml (p=0.730), in the intervention and control group, respectively. 10 out of 16 patients could achieve 25(OH)D>50 ng/ml by day-7 and another two by day-14 [day-14 25(OH)D levels 51.7 (48.9 to 59.5) ng/ml and 15.2 (12.7 to 19.5) ng/ml (p<0.001) in intervention and control group, respectively]. 10 (62.5%) participants in the intervention group and 5 (20.8%) participants in the control arm (p<0.018) became SARS-CoV-2 RNA negative. Fibrinogen levels significantly decreased with cholecalciferol supplementation (intergroup difference 0.70 ng/ml; P=0.007) unlike other inflammatory biomarkers.
Conclusion Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation.

Other materials

Brenner, H, (2020) Vitamin D insufficiency may account for almost nine of ten COVID-19 deaths: Time to act. comment on:“vitamin d deficiency and outcome of COVID-19 patients”*Nutrients* **2020.** https://www.mdpi.com/2072-6643/12/12/3642/htm

Radujkovic, (2020) Reply to: “Vitamin D Insufficiency May Account for Almost Nine of Ten COVID-19 Deaths: Time to Act. Comment on: Vitamin D Deficiency and Outcome of COVID-19 Patients. Nutrients 2020, 12, 2757” **https://www.mdpi.com/2072-6643/12/12/3643/htm**