Vitamin D

RECOMMENDATION

We recommend against the use of Vitamin D supplementation to prevent COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

It was pointed out that although the study by Jollife et al. found that Vitamin D supplementation reduced the risk of acute respiratory infection (ARI) overall, this systematic review was done prior to the COVID-19 pandemic, hence the population assessed did not include COVID-19 patients. In relation to the preventive effect of Vitamin D against ARI, it was noted that the duration of the trials in the systematic review ranged from 7 weeks to 12 months, and such a duration for effect to be seen is not deemed beneficial since vaccines will soon be available. Overall, the panel recognized that all the studies evaluated on its efficacy and safety were indirect evidence.

EVIDENCE SUMMARY

Should Vitamin D supplements be used in the prevention of COVID-19?

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Key Findings

One direct evidence of very low quality was found. A retrospective cohort study on frail, elderly nursing home residents (N=66) reported that fewer patients died among those who received 80,000 IU of Vitamin D during the week following the diagnosis of COVID-19, or within one month prior to diagnosis, when compared to patients who received other medications. There was no direct evidence on the safety of Vitamin D supplementation as prevention for COVID-19.

Introduction

Vitamin D plays a significant role in muscle, bone, and immune health and supports the induction of antimicrobial peptides in response to both viral and bacterial stimuli by inducing innate antimicrobial effector mechanisms. Vitamin D lowers the risk of COVID-19 infection through the maintenance of the integrity of cellular junctions, attenuation of cytokine storm, suppression of T

helper cell type 1 responses and promotion of T regulatory cell induction[1]. Vitamin D modulates the renin-angiotensin system in rat models with lipopolysaccharide-induced acute lung injury [2]. A meta-analysis of observational studies (16 studies, N = 4922) showed that 89% of COVID-19 patients had Vitamin D insufficiency (48%; 95% CI, 29%-67%) or deficiency (41%; 95% CI, 26.7%-50.1%) [3]. The meta-analysis of Jolliffe et al. (42 RCTs, N = 46,331) showed that Vitamin D supplementation reduced the risk of Acute Respiratory Infections overall (Odds Ratio [OR] 0.91, 95% CI 0.84 to 0.99; p for heterogeneity 0.01) compared to placebo [4]. In the same systematic review, a meta-analysis of adverse events reported that Vitamin D supplementation did not have a statistically significant effect on work/school absences due to ARI, hospitalizations or emergency department attendances for ARI, serious adverse events of any cause, mortality of any cause, hypercalcemia or renal stones [4]. Vitamin D supplementation has thus been investigated as a potential prevention of COVID-19.

Review Methods

We searched for existing traditional/ living systematic reviews and/or traditional/ living COVID-19 databases and CPGs, published studies (PubMed, Cochrane Library, Herdin), MedRxIV, and BioRxIV (search date up to December 15, 2020). Ongoing trials were searched in Clinicaltrials.gov Registry and EudraCT (search date up to December 15, 2020). We used the following keywords and MeSH terms: “Vitamin D,” “ergocalciferol,” “cholecalciferol,” "prevention," and COVID-19 related terms in the search strategy.

The following PICO criteria were used:

Population: people at risk for COVID-19

Intervention: Vitamin D supplements as a prophylaxis, as a single agent, any dose, any duration;

Comparator: placebo, any active control, no intervention;

Outcomes: incidence of COVID-19; Adverse events;

Study design: observational studies, quasi-experimental studies, randomized controlled trials (RCTs)

Results

We found one direct evidence on the efficacy of Vitamin D supplementation for the prevention of COVID-19. A retrospective cohort study by Annweiler et al. [5] on frail, elderly nursing home residents (N=66) reported that fewer patients died among those who received 80,000 IU of Vitamin D during the week following the diagnosis of COVID-19 or within one month prior to diagnosis (HR = 0.11, 95 % CI 0.03 to 0.48; P = 0.003) after adjustment for all potential confounders), when compared to patients who received other medications. The number of patients who received other medications was small (n = 9) compared to the Vitamin D group (n = 57). This study provided very low quality of evidence due to indirectness, i.e., the authors did not state how many patients received a Vitamin D bolus prior to the diagnosis of COVID-19 therefore we could not ascertain the preventive efficacy. Furthermore, it was an observational study, and the comparator group (no Vitamin D supplements) was small (n = 9).

We found no direct evidence on the safety of Vitamin D supplementation as a prevention of COVID-19. Indirect evidence on safety was found from two systematic reviews. High dose, long-term Vitamin D supplementation was not found to increase the risk of adverse events or deaths of any cause. Vitamin D supplementation may increase the risk for hypercalcemia and possible hypercalciuria (low quality evidence due to indirectness).

Recommendations from Other Groups

There are no recommendations for Vitamin D as a prophylaxis of COVID-19. In the UK Guideline with NICE Evidence Review (NG187), there are recommendations for Vitamin D supplementation for maintaining immune health [6].

Research gaps

There are nine registered clinical trials investigating Vitamin D supplementation for the prevention of COVID-19 [7-15] (Appendix 3).

References

[1] Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020;12(4).

[2] Xu J, Yang J, Chen J, Luo Q, Zhang Q, Zhang H. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. Mol Med Rep. 2017;16(5):7432-8.

[3] Ghasemian R, Shamshirian A, Heydari K, Malekan M, Alizadeh-Navaei R, Ebrahimzadeh MA, et al. The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis. medRxiv. 2020:2020.06.05.20123554.

[4] Jolliffe DA, Camargo CA, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. medRxiv. 2020:2020.07.14.20152728.

[5] Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier JM, Lafaie L, Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. J Steroid Biochem Mol Biol. 2020;204:105771.

[6] COVID-19 rapid guideline: vitamin D NICE guideline [NG187] Published date: 17 December 2020: National Institute for Health and Care Excellence; 2020 [Available from: https://www.nice.org.uk/guidance/ng187.

[7] Reducing Asymptomatic Infection With Vitamin D in Coronavirus Disease (RAID-CoV-2) [Internet]. US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT04476680.

[8] PRevention of COVID-19 With Oral Vitamin D Supplemental Therapy in Essential healthCare Teams (PROTECT). [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04483635.

[9] Vitamin D Supplementation in the Prevention and Mitigation of COVID-19 Infection (VitD-COVID19) [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04482673.
[10] Oral 25-hydroxyvitamin D3 and COVID-19 [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04386850
[11] Trial of Vitamin D to Reduce Risk and Severity of COVID-19 and Other Acute Respiratory Infections (CORONAVIT) [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04579640.
[12] Vitamin D and COVID-19 Trial (VIVID) [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04536298.
[13] The Effect of D3 on Selected Cytokines Involved in Cytokine Storm in the Covid-19 Uninfected Jordanian People [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04476745.
[14] Vitamin D3 Supplementation to Prevent Respiratory Tract Infections [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04596657.
[15] Reducing Asymptomatic Infection With Vitamin D in Coronavirus Disease (RAID-CoV-2) [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04476680.

Appendix 1. Characteristics of Included studies

No.	Author (year)	Country/ Setting	Study design	Population	Intervention	Comparator	Outcomes
1	Annweiler (2020)	France	retrospective cohort (record review)	N = 66 elderly nursing home residents (disabled, neurocognitive, psychiatric) with COVID-19 (clinical signs/ confirmed by rtPCR)	n = 57 Oral Vitamin D3 bolus (80,000 IU) in the week following suspicion or diagnosis of COVID-19 or the month prior to diagnosis	n = 9 Other medications (corticosteroids, HCQ, Antibiotics)	Mortality Ordinal Scale of Clinical Improvement (OSCI) for COVID-19

Appendix 2. GRADE Evidence Profile

Author(s): Dofitas, Belen & Eubanas, Gina
Question: Vitamin D supplements compared to placebo, other drugs, standard preventive measures for prevention of COVID-19
Setting:
Bibliography: Anweiller (2020)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin D supplements	placebo, other drugs, standard preventive measures	Relative (95% CI)	Absolute (95% CI)		
Mortality: Vit D for prevention of ARI (follow up: mean 36 days; assessed with: proportion of participants)												
1	observational studies	serious [a]	not serious	very serious [b]	serious [c]	none	10/57 (17.5%)	5/9 (55.6%)	**HR 0.11** (0.03 to 0.48)	**470 fewer per 1,000** (from 532 fewer to 233 fewer)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Retrospective review of records; Vitamin D bolus given within the week of diagnosis or one month prior to diagnosis of COVID-19; comparison group had small sample size: majority of patients were given Vit D (n = 57) versus other medications (n = 9)
b. No data on number of patients given Vitamin D prior to diagnosis of COVID-19 therefore we can not ascertain preventive efficacy
c. small sample size of comparator group: other medication (n = 9)

Appendix 3. Registered clinical trials

No.	Clinical Trial ID/Titile	Country /Setting	Study design	Population	intervention	Comparator	Outcomes
1	Efficacy of Vitamin D Supplementation to Prevent the Risk of Acquiring COVID-19 in Healthcare Workers NCT04535791	Mexico	Interventional RCT; parallel assignment	Adults,Health workers (doctors, residents, nurses, technicians, stretcher-bearers, cleaning crew)	Cholecalciferol 4000 IU daily for 30 days	placebo	Outcome Measures: 1) No. of participants with Covid-19; 2) No. of participants with hospitalization for Covid -19; and 3) Serum concentration of 25 (OH) vitamin D
2	PRevention of COVID-19 With Oral Vitamin D Supplemental Therapy in Essential healthCare Teams (PROTECT). NCT04483635	Canada	RCT parallel assignment, triple blind	2414 Health care workers 18 to 69 yrs old	Weekly bolus dose of Vitamin D 100 000 IU Vit D3 + weekly 10 000 IU	Placebo	Primary Outcome : 1) Change in incidence of laboratory-confirmed COVID-19 infection [Time Frame: 16 weeks]; COVID-19 suspected/confirmed infection ; 5) Number of workday absences for any reason; 6) adverse reactions
3	Vitamin D Supplementation in the Prevention and Mitigation of COVID-19 Infection (VitD-COVID19) NCT04482673	United States	Randomized parallel assignment; quadruple blind; phase 4 interventional	140 adults aged 50 yrs and older	COVID-19 Negative Active : vitamin D3 (6000 IU) per day for 12 months and daily 800 IU vitamin D3. Intervention: Daily Vitamin D3. COVID-19 Positive Active Treatment bolus (20,000 IU) per day for 3 days followed by high dose vitamin D (6000 IU) per dayfor 12 months. 800 IU vitamin D3/day. Interventions: Drug: Daily Vitamin D3 Drug: Bolus vitamin D3	Placebo Comparator: COVID-19 Negative Placebo placebo for 12 months. All will receive a multivitamin 800 IU vitamin D3/day. Intervention: Drug: Daily placebo. Placebo Comparator: COVID-19 Positive Placebo placebo as a bolus followed by daily placebo for 12 months. All participants will receive a multivitamin containing 800 IU vitamin D3/day. Interventions: Drug: Daily placebo Drug: Bolus placebo	Primary outcome : 1) Change in total circulating 25(OH)D concentration [Time Frame: monthly in COVID-19 negative participants through study completion for 1 year]; 2) Change in total circulating 25(OH)D concentration in COVID-19 positives [Time Frame: baseline, 2 and 4 weeks, then months 3, 6, 9 and 12 in COVID-19 positive participants]; 3) Change in SARS-CoV-2 antibody titers; intake; 5) perceived stress; 6) Charlson comorbidity index; 7) pandemic stress
4	Oral 25-hydroxyvitamin D3 and COVID-19 NCT04386850	Iran	multicenter randomized double-blinded placebo-controlled clinical trial with parallel groups	health care providers and hospital workers with a negative test for COVID-19 and a close patient relative with a negative test for COVID-19 who lives with the infected patients	25 mcg of 25(OH)D3 once daily at bedtime for 2 months	placebo daily for 2 months	COVID-19 (SARA-Cov-2) infection [Time Frame: 60 days]; Severity of COVID-19 (SARA-Cov-2) infection [Time Frame: 60 days]

5	Trial of Vitamin D to Reduce Risk and Severity of COVID-19 and Other Acute Respiratory Infections (CORONAVIT) NCT04579640	UK	open-label, phase 3, randomised clinical trial	UK resident ≥16 years old with sub-optimal vitamin D status	Capsules containing 800 IU (20 micrograms) or 3,200 IU (80 micrograms) cholecalciferol	standard of care (national recommendation of 400 IU/day vitamin D)	Proportion of participants experiencing at least one doctor-diagnosed or laboratory-confirmed acute respiratory infection of any cause. [Time Frame: Over 6 months]
6	Vitamin D and COVID-19 Trial (VIVID) NCT04536298	USA	Cluster-Randomized, Double-Blind, Placebo-Controlled	Household members of newly infected COVID-19 patients	Vitamin D softgel capsules; each capsule contains 3200 IU of vitamin D3. Three capsules per day (9600 IU/day) will be taken on days 1 and 2, and one capsule per day (3200 IU/day) will be taken on days 3 through 28	Placebo softgel capsules. Three capsules per day will be taken on days 1 and 2, and one capsule per day will be taken on days 3 through 28	SARS-CoV-2 infection in close household contacts [Time Frame: 4 weeks]; Self-reported disease severity in close household contacts [Time Frame: 4 weeks]
7	The Effect of D3 on Selected Cytokines Involved in Cytokine Storm in the Covid-19 Uninfected Jordanian People NCT04476745	Jordan	randomized parallel, open-label trial	Covid-19 uninfected adults with vitamin D deficiency	Vitamin D3 (50,000) IU / week for 8 weeks	No intervention	IL-1 beta, IL-6, TNF serum levels [Time Frame: 8 weeks]
8	Vitamin D3 Supplementation to Prevent Respiratory Tract Infections NCT04596657	USA	randomized parallel, open-label trial	Hospital worker 52 years old and above	vitamin D3 supplementation (5000 IU)	Control	Respiratory tract infection (including COVID-19) [Time Frame: 9 months]; Incidence of acute respiratory tract infection
9	Reducing Asymptomatic Infection With Vitamin D in Coronavirus Disease (RAID-CoV-2) NCT04476680	UK	randomized,double-blind, parallel group trial	18 - 30 years old w/o any previous or current COVID -19 infection	Vitamin D 1000 IU	Placebo	Seroconversion [Time Frame: 24 weeks]; asymptomatic seroconversion for SARS-CoV-2