The link between corona vIruses and VItamin D (VIVID): an extensive and rigorous systematic review and meta-analysis

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Citation

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Review question

- What is the effect of vitamin D supplementation on health outcomes related to coronaviruses in general and COVID-19 in specific?

- Is serum 25-hydroxyvitamin D level associated with coronaviruses related health outcomes?

Searches

We searched four databases (MEDLINE (OVID), Embase.com, CINAHL (EBSCO), and Cochrane) with no limit on language. We used MeSH terms and keywords relevant to vitamin D and COVID-19. We expanded the search to include the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) viruses due to the scarcity of evidence relevant to COVID-19. We have limited the MeSH terms related to the Coronaviridae family to the period 2002-August 11, 2020 since the first outbreak was detected in 2002. We also screened ClinicalTrials.gov and WHO primary trial registries for ongoing trials on vitamin D and COVID-19, updated until August 11, 2020. Due to the continuous updates in the topic of COVID-19, we will also search the grey literature including MedRxiv, the Endocrine society, CDC and the WHO websites.

Types of study to be included

Due to the scarcity of data, we will include in our review all types of studies providing original data, to better answer our questions.

Inclusion:

We will include original data from:

Clinical trials

Observational studies

We will screen the references of the below types of studies:

Case series

Reviews

Commentaries and letters

Exclusion:

Case reports

Condition or domain being studied

COVID-19 is the third major outbreak due to coronaviruses following SARS and MERS epidemics in 2002

and 2012, respectively. The first case of COVID-19 was detected in Wuhan, China, in December 2019 (WHO, 2019). In March 2020, this novel outbreak was declared as a global pandemic by the World Health Organization (WHO, 2020). Recent studies have shown that severity and mortality rates due to COVID-19 infection are greater in elderly and chronically ill patients (Yancy CW, 2020; CDC COVID Response Team, 2020). Vitamin D deficiency, defined as serum 25(OH)D levels < 20 ng/ml (Ross, 2011), is more common in this population, as compared to healthy adults and is associated with an increased risk of respiratory infections (Arihiro, 2019). Conversely, Vitamin D plays an essential role in modulating immunity and decreasing the risk of infections via several mechanisms. In fact, immune and inflammatory cells possess 1-alpha hydroxylase activity and express nuclear vitamin D receptors that mediate their activation and proliferation (Yamamoto, 2019). In addition, vitamin D inhibits the production of pro-inflammatory cytokines (Zhang, 2012). This action may have significant clinical implications in preventing and delaying the progression of several diseases, including potentially COVID-19 infection and related health complications.

Participants/population
Adult patients (>18 years old)

Both men and women

COVID-19, SARS or MERS infections

Intervention(s), exposure(s)
For clinical trials: Intervention: Vitamin D supplementation including active vitamin D at any dose

For observational studies: Exposure: vitamin D deficiency, defined as a serum 25-hydroxyVitamin D level <20 ng/ml, or using any other cutoff as defined in individual studies

Comparator(s)/control
Inclusion:

For clinical trials: Placebo, control, or vitamin D, including active vitamin D at a different dose

For observational studies: Patients with serum 25-hydroxyVitamin D level ?20 ng/ml
Exclusion:

For clinical trials: Different co-interventions between arms

Main outcome(s)
Mortality

* Measures of effect
We will report the risk ratio and its 95% confidence interval if available

Additional outcome(s)
Complications (Acute Respiratory distress Syndrome (ARDS), acute respiratory failure, pneumonia, cytokine storm, organ failure, septic shock, Disseminated Intravascular Coagulation (DIC), neurological and rhabdomyolysis)

Severity of symptoms as defined by the National Health Commission & National Administration of Traditional Chinese Medicine, or based on any other definition used in individual papers.

Need for hospitalization

Hospital stay duration

Need for ICU admissions

ICU stay duration

Need for non-invasive and invasive ventilation

Time on respirators

Time to symptomatic recovery

Time to seronegative conversion

Risk of positive seroconversion of family members

* Measures of effect

For continuous data, we will report the weighted mean differences with their corresponding 95% confidence intervals. For dichotomous data, we will report the risk ratio or odds ratio and its 95% confidence interval.

Data extraction (selection and coding)

Two reviewers (AB, MB) will screen titles and abstracts of all identified records, independently and in duplicate, using a priori developed screening sheets. We will perform a calibration exercise to familiarize the reviewers with the screening process and limit discrepancies between them. We will then retrieve the full texts of potentially eligible records, and two reviewers (AB, MB) will screen them independently and in duplicate using the full-text screening sheet and will record the exclusion reasons. Using specific forms, two reviewers (AB, MB) will then extract data from all included records independently and in duplicate. Extracted data will include: the author's name, country and year of publication, the study population, sampling method and sample size, age, gender and comorbidities. For clinical trials we will abstract data on the intervention, co-intervention, comparator, outcomes, compliance and adverse events if available. For observational studies we will collect data on vitamin D levels, case definition and outcomes. Any disagreements during these stages will be resolved through discussion or the help of a third reviewer/expert in the field (MC, GEHF).

Risk of bias (quality) assessment

For clinical trials, two reviewers (AB, MB) will use the Cochrane Risk of bias tool, version 1 (Higgins, 2011) independently and in duplicate. We will assess the following domains: bias due to sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, and selective outcome reporting.

For observational studies, two reviewers (AB, MB) will use the New Castle-Ottawa quality assessment scale independently and in duplicate. We will assess the following categories: Selection, comparability, and outcome (Wells, 2000).

Two reviewers (AB, MB) will use the Grading of Recommendations Assessment, Development, and Evaluation working group methodology (GRADE) to assess the quality of evidence of all included studies for each outcome separately. The initial level of evidence will be established based on the study design. We will then assess the following domains: risk of bias, consistency, directness, precision, and publication bias.

Strategy for data synthesis

In case a quantitative analysis was appropriate, a separate meta-analysis for each outcome will be performed if at least two studies or trials were identified for a given comparison. For clinical trials our comparisons would include vitamin D supplementation vs placebo or control, or low vs high doses of vitamin D. For observational studies we will compare outcomes in participants with vitamin D deficiency or insufficiency vs those with normal levels of 25(OH)D. We will perform our analyses for each study design separately. We will use RevMan 5.3 to calculate and report the findings. If heterogeneity between studies is not significant, we will use the Mantel-Haenszel method for the fixed effect model. If heterogeneity is high, we will choose the random effects model instead. In case of high levels of heterogeneity between the trials (I^2 ?50%), we will perform sensitivity and subgroup analyses to identify and explain the source of heterogeneity. In particular, non-peer reviewed articles will be included in a sensitivity analysis. In case of small sample bias, we will use the random effect estimate rather than the fixed effect estimate. We will explore the possibility of publication bias using a funnel plot if at least 10 studies are available in the final meta-analysis. If the funnel plot shows asymmetry, we will consider publication bias. In case a quantitative synthesis is not appropriate, we will provide a qualitative summary of our findings. A systematic narrative

review will present and summarize the characteristics and results of all included studies.

Analysis of subgroups or subsets
If applicable, we will perform subgroup analysis by age groups (young adults 18-50 years vs older adults >50 years), by gender and BMI (normal BMI < 25 kg/m2, overweight 25-30 kg/m2, obese ?30 kg/m2)

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Type and method of review
Intervention, Meta-analysis, Prevention, Systematic review

Anticipated or actual start date
30 June 2020

Anticipated completion date
11 September 2020

Funding sources/sponsors
None

Conflicts of interest

Language
English

Country
Lebanon

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Cholestanes; Humans; Viruses; Vitamin D; Vitamins

Date of registration in PROSPERO
14 August 2020

Date of first submission
12 August 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

14 August 2020