

Emerging Evidence on COVID-19

Evidence Brief of vitamin D and zinc supplementation for therapeutic use on COVID-19 cases

Introduction

Is there evidence of the efficacy of therapeutic or prophylactic supplementation of vitamin D or zinc in the prevention or treatment of COVID-19?

Vitamin D and zinc are micronutrients that play various physiological roles, including a role in the immune system (1). Deficiencies of these micronutrients have been postulated to put individuals at higher risk of developing infection or more serious progression of disease, thus data on the association of deficiencies and COVID-19 disease outcomes are also summarized in this review. This evidence brief highlights the most recent systematic reviews on these micronutrients supplementation or status and COVID-19, where systematic reviews were not identified, primary research in published or prepublication format up to Jan 7, 2021 has been included. To date evidence in the Canadian context is pending.

Key Points

Vitamin D

- Vitamin D is a prohormone, a substance the body converts to a hormone, which is important for calcium homeostasis and bone health and is also implicated in other systems including immune function. The immunomodulating functions of vitamin D are complex and not fully understood. Research conducted prior to the pandemic suggests there is limited evidence of a potential benefit of vitamin D supplementation to lower risk of developing acute respiratory infections (2, 3).
- Nutrition standards in Canada include dietary recommendations for vitamin D for all age groups to help maintain 25-hydroxyvitamin D serum levels above 40 nmol/L in support of bone health (4). Vitamin D supplementation is advised for adults over 50 y of age (4). Other guidelines such as one from the United States and United Kingdom that have considered the evidence for COVID-19 continue to recommend supplementation for bone health, but not for treatment or prevention of COVID-19 (5, 6).
- Seven systematic reviews were identified in bibliographic databases, five of which included literature up to Fall 2020 and are summarized below along with three grey literature reports on the therapeutic efficacy of vitamin D for COVID-19 or acute respiratory tract infections.
- Five systematic reviews reported on observational studies that detailed associations between insufficient and/or deficient levels of vitamin D and increased risk of severe COVID-19 and mortality (Table 1). The associations across studies were not consistently significant, however vitamin D deficiency was shown to be high among COVID-19 cases, and mean vitamin D levels were lower with

increasing severity of COVID-19. For outcomes of severity, associations were reported in some studies for ICU admittance, mechanical ventilation or oxygen therapy as well as mortality. Most studies contributing to these outcomes were considered to have a high risk of bias. The groups at risk of vitamin D deficiency are the same groups at risk of severe COVID-19, this relationship is complex and although some studies have reported associations with low vitamin D and COVID-19 outcomes, these data cannot be extrapolated as a cause of the COVID-19 outcomes.

- Vitamin D as a treatment for patients with COVID-19 was assessed in three systematic reviews that collectively include two published and one prepublished randomized controlled trial (RCT) and 2 quasi-experiments conducted in adults (Table 1).
 - Evidence that vitamin D treatment in COVID-19 patients may reduce the risk of severe disease progression (RR 0.04, 95%CI 0.01 -0.29, 1RCT, 76 observations) (7).
 - Evidence that vitamin D treatment reduces mortality was not significant across 2 RCTs (RR 0.56; 95%CI 0.05 – 5.85, 2 RCT, 313 observations) (7), but was significant across two quasi-experimental studies and one RCT (OR 0.26; 95%CI 0.10-0.71) (8).
 - In one trial (n=237) a single adverse event was recorded (RR 2.98; 95%CI 0.12-72.30) (7).
- Several clinical trials were registered on clinicaltrials.gov. Of 45 on vitamin D, four indicated they were completed, but have not posted results. The objectives of these studies varied across treating COVID-19 with vitamin D (n=33) to exploring vitamin D levels (n=12) along with other micronutrients.

Zinc

- Zinc is an essential micronutrient that is required for adaptive and innate immune response (1). It has been used against other respiratory viruses and diarrhea in children with conflicting results across studies (9). Globally up to 20% of people are deficient in zinc, inadequate intake of zinc is more prevalent in low and middle income countries (9).
- Zinc has demonstrated antiviral properties *in vitro* studies have found that zinc inhibit viral RNA-dependent RNA polymerase against SARS-CoV-1 (1). Cellular uptake of zinc has been shown to increase when zinc is combined with a zinc ionophore such as hydroxychloroquine. Thus, many ongoing clinical trials are examining the addition of zinc to existing treatments (1).
- One guidance document from the United States addressed zinc supplementation and COVID-19, the recommendation is against supplementation above the current dietary allowances (10).
- Two systematic reviews were identified. One high quality systematic review includes non-SARS-CoV-2 research and indicates moderate evidence for the role of zinc as a therapeutic in the prevention and reduction of severe disease progression across respiratory tract infection literature. The other review identified one retrospective observational study, also summarized in Table 2.

- A high quality systematic review last updated in August did not identify any RCTs related to the therapeutic use of zinc for COVID-19.
- As a therapeutic, two retrospective cohort studies evaluated the impact of adding zinc sulphate to standard of care treatment for COVID-19 cases:
 - Multivariable analysis showed an increased frequency of being discharged home (OR 1.53, 95% CI 1.12–2.09) and reduction in mortality or transfer to hospice among patients who did not require ICU level of care remained significant (OR 0.449, 95% CI 0.271–0.744) (11).
 - Zinc sulfate was not significantly associated with a change in risk of in-hospital mortality (adjusted hazard ratio, 0.66; 95% CI, 0.41 to 1.07; P = .09) in one retrospective cohort (12).
- This is an area of active research, 21 registered trials were identified on clinicaltrials.gov, three were completed, but have not posted results. Most registered trials were looking at supplementing or treating with zinc as a monotherapy or in combination with other compounds, others were exploring zinc levels along with other micronutrients.

Overview of the Evidence

For vitamin D as a therapeutic for COVID-19, three systematic reviews of high to low quality based on AMSTAR 2 criteria (herein referred to as AMSTAR) included three RCTs and two quasi-experiments, each with some risk of bias concerns and missing information in the study protocols (13). There were also variations in the vitamin D treatment and standard of care across studies. Thus, the overall confidence in this evidence was low and the conclusions of this review are likely to change with future research.

Five systematic reviews with an AMSTAR quality rating from high to low examined associations between vitamin D levels and COVID-19 infection, severity or mortality (13). The studies included in these reviews were observational studies, frequently retrospective in design and considered at high risk of bias. The outcomes summarized in each review varied as did the inclusion of prepublications, which meant each review examined a different subset of studies. Thus, the overall confidence in these results is low and additional research is likely to change the conclusions of this review.

Limited evidence was identified on the use of zinc in treatment of COVID-19. Two systematic reviews on zinc were identified; the quality ranged from low to high AMSTAR ratings (13). Two retrospective cohorts at high risk of bias due to their retrospective study design were also included. Thus, the overall confidence in these results is very low and additional research is likely to change the conclusions of this review.

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VITAMIN D

Table 1. Vitamin D and COVID-19

STUDY	KEY OUTCOMES
Effect of Vitamin D supplementation or use as a therapeutic	
<p>National Institute for Health and Care Excellence (NICE), COVID-19 rapid guideline for practitioners on Vitamin D and evidence review (AMSTAR high quality) (5)</p> <p>UK</p> <p>Published December 17, 2020</p>	<ul style="list-style-type: none"> - Vitamin D supplementation <ul style="list-style-type: none"> • The guideline states vitamin D should not be recommended for the sole purpose of preventing COVID-19, as there was insufficient evidence to support this. • The recommendations for general population supplementation were related to maintenance of bone and muscle health. Insufficient exposure to sunlight has been linked to suboptimal vitamin D levels, and supplementation was recommended, particularly during the winter months. - Vitamin D for treating COVID-19 infection <ul style="list-style-type: none"> • One RCT (Castillo et al) added Calcifediol (0.532mg) on admission, day 3 and 7 and then weekly in addition to standard of care. This study had serious risk of bias and was considered very low evidence. Results: 1/50 calcifediol treatment group and 13/26 controls were admitted to the ICU (OR 0.03 (95%CI 0.003-0.25). Mortality occurred in 0/50 and 2/26 in the treatment and control arms (OR 0.097, 95%CI 0.004-2.099) - Vitamin D status associations with COVID-19 outcomes <ul style="list-style-type: none"> • 12 studies were included in their review (an additional 12 were not included because they were still in preprint). The association between COVID-19 status and vitamin D levels were conflicting (non-significant and negative association) and analyses were highly variable. Outcomes of severity were also conflicting for ICU, mechanical ventilation or oxygen therapy. One study reported a protective association with severe COVID-19 and supplementing with Vitamin-D.

<p>Nikniaz et al (prepublication MedRxiv) (8) Systematic Review and Meta-analysis (AMSTAR moderate quality) Jan 5, 2021 (search date Dec 16, 2020)</p>	<ul style="list-style-type: none"> - This review included 4 clinical trials (2 RCTs (Castillo and Rastogi) and 2 quasi-experiments (Annweiler x2)), of 259 COVID-19 cases, hospitalized and not-hospitalized. Oral vitamin D supplementation, including cholecalciferol and calcifediol (n=139). The therapeutic protocols ranged from 60,000 to 80,000 IU dosing for a duration range of 7 to 14 days. <i>(Note: Dosing in these studies is above upper limits of supplement safety for vitamin D.)</i> - Across 3 studies, a significantly lower odds of mortality among the intervention groups compared with the control groups (OR = 0.264, 95% CI = 0.099–0.708, p-value = 0.008) was reported. Both quasi-experiments on geriatric populations reported a significant impact on survival. - Castillo et al. reported lower ICU admissions, odds ratio (OR) of 0.03 (95% CI: 0.003 - 0.25) and two studies showed significant improvement in clinical status with vitamin D treatment.
<p>COVID-NMA Project (7) Living Synthesis (Not evaluated) France Jan 7, 2021 (Search date Dec 4, 2020)</p>	<ul style="list-style-type: none"> - Three RCTs (Castillo, Rastogi, and Murai) were summarized and the summary of findings table indicates the evidence was very low quality however, treatment with vitamin D may have a protective association with disease severity (very low certainty), but no association was identified for mortality (very low certainty) or adverse events at this time (low certainty).
<p>Association of vitamin D levels and clinical outcomes</p>	
<p>Liu et al. (IJID) (14) Systematic Review and Meta-analysis (AMSTAR rating high quality) Jan 2, 2021 (search date Sept 25, 2020)</p>	<ul style="list-style-type: none"> - Across 10 observational studies (rated as medium to high quality by review author) included 361 934 participants (4178 COVID-19 cases), vitamin D deficiency was associated with increased risk of COVID-19 (OR = 1.43, 95% CI 1.00 to 2.05) and people with COVID-19 were shown to have significantly lower vitamin D levels. There was significant heterogeneity.
<p>Pereira et al. (Crit Rev Food Sci Nutr) (15) Systematic Review and Meta-analysis (AMSTAR rating low quality)</p>	<ul style="list-style-type: none"> - Reports on the association between vitamin D deficiency and COVID-19 severity, via an analysis of the prevalence of vitamin D deficiency and insufficiency in people with the disease.

<p>Nov 2, 2020 (search date Oct 9, 2020)</p>	<ul style="list-style-type: none"> - 27 observational studies considered at low (n=4) and high (n=23) risk of bias were included. - A higher odds of vitamin D deficiency was found in severe COVID-19 cases, OR 1.65 95%CI 1.30–2.09, I² 35.7% and vitamin D levels were significantly lower among severe cases. - For severe deficiency, increased hospitalization OR 1.81 (95%CI 1.41–2.21, I² 0.0%) and mortality OR 1.82 (95%CI 1.06–2.58, I² 59.0%) were reported.
<p>Das et al. (prepublication MedRxiv) (16) Systematic Review (AMSTAR rating low quality) Dec 3, 2020 (search date Nov 3, 2020)</p>	<ul style="list-style-type: none"> - 11 published observational studies considered to be moderate to high quality by the review author were included. All studies examined the possible association between vitamin D deficiency and the incidence or severity of COVID-19 disease were included. Analysis is descriptive, no meta-analysis was planned. - Individual study results were presented in the tables. Consistently there were associations between vitamin D deficiency and more severe COVID-19 and/or mortality.
<p>Ghasemian et al (prepublication MedRxiv) (17) Systematic Review (AMSTAR rating low quality) Oct 26, 2020 (search date Oct 10, 2020)</p>	<ul style="list-style-type: none"> - 16 observational studies, rated by the author as fair quality, on possible associations between vitamin D deficiency and COVID-19 were included. - Across included COVID-19 cases the meta-analysis results indicated 48% (33-63) were vitamin D deficient and 29% (8-65) were insufficient and 25% (8-59) had normal levels of vitamin D. A similar analysis of a comparable control group was not presented in the review. - The other summaries reported in this review do not address the review question.
<p>Not on COVID</p>	
<p>The Scientific Advisory Committee on Nutrition (SACN), rapid review on vitamin D and acute respiratory tract infections (ARTI). (2) UK December 2020</p>	<ul style="list-style-type: none"> - This rapid review was updated from June to December to support the work of the NICE rapid guideline for practitioners on vitamin D. - This review reports a protective association with daily vitamin D supplementation and ARTIs for dosages >400IU and < 1000IU per day in 1-16 year olds (moderate quality evidence).

	<p><i>ARTI: refers to any infection of the sinuses, throat, airways or lungs. Upper RTIs (URTI) include tonsillitis, laryngitis and the common cold. Lower RTIs (LRTIs) include bronchitis and pneumonia. Influenza affects both upper and lower respiratory tracts.</i></p>
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ZINC

Table 2: Zinc and COVID-19

Study	Key Outcomes
<p>Hunter et al. (prepublication MedRxiv) (18) Systematic Review (AMSTAR rating high quality) Nov 4, 2020 (search date Aug 2020)</p>	<ul style="list-style-type: none"> - This living systematic review identified 128 RCTs on zinc as a therapeutic, no RCTs specific to SARS-CoV-2 or COVID-19 met the inclusion criteria. - Studies of respiratory tract infections indicate treatment with zinc may prevent infection, reduce severity, and decrease duration of illness (moderate, low, low quality of evidence for these outcomes respectively). Quantitative outcomes available in text. - Adverse events were not higher than active controls and none were serious (moderate quality evidence). - Overall confidence in the results was very low due to risk of bias and indirectness across studies within outcomes.
<p>James et al. (prepublication MedRxiv) (9) Systematic Review (AMSTAR rating low quality) Oct 19, 2020 (search conducted Aug 11, 2020)</p>	<ul style="list-style-type: none"> - A systematic review of COVID-19 papers on zinc netted 1 prepublication (Carlucci included below) from 79 potentially relevant citations.
<p>Yao et al (Chest, letter to the editor) (12) Retrospective cohort USA January 2021</p>	<ul style="list-style-type: none"> - Retrospective study that evaluated mortality in COVID-19 patients (n=242) treated with or without zinc sulphate. - Results: Multivariate Cox regression, zinc sulfate was not significantly associated with a change in risk of in-hospital mortality (adjusted hazard ratio, 0.66; 95% CI, 0.41 to 1.07; P = .09).
<p>Carlucci et al. (J Med Micro) (11)</p>	<ul style="list-style-type: none"> - Retrospective observational study to compare outcomes among hospitalized COVID-19 patients ordered to receive

<p>Retrospective cohort USA Sept 2020 (conducted Mar-Apr 2020)</p>	<p>hydroxychloroquine and azithromycin plus zinc sulphate (n=411) versus hydroxychloroquine and azithromycin alone (n=521).</p> <ul style="list-style-type: none"> - The addition of zinc sulphate did not impact the length of hospitalization, duration of ventilation or intensive care unit (ICU) duration. - In univariate analyses, zinc sulphate increased the frequency of patients being discharged home, and decreased the need for ventilation, admission to the ICU and mortality or transfer to hospice for patients who were never admitted to the ICU. - After adjusting for the time at which zinc sulphate was added to our protocol, an increased frequency of being discharged home (OR 1.53, 95% CI 1.12–2.09) and reduction in mortality or transfer to hospice among patients who did not require ICU level of care remained significant (OR 0.449, 95% CI 0.271–0.744).
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Methods:

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a refworks database and an excel list that can be searched. Targeted keyword searching was conducted within these databases to identify relevant citations on COVID-19 and SARS-COV-2. Search terms used included: (vitamin D, 25(OH)D, 25hydroxyvitaminD, calcitriol*) or (zinc), an additional filter for systematic reviews was used to identify reviews initially.

A grey literature search was conducted targeting key government websites and evidence synthesis organizations for current evidence syntheses on these topics.

This review contains research published up to January 7, 2021

Each potentially relevant reference was examined to confirm it addressed the review question and key findings were extracted into tables in the review.

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