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REVIEW

Vitamins, supplements and COVID-19: a review of currently available evidence

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Abstract

Background: In the midst of the COVID-19 pandemic, there has been an information overload of health data (both accurate and inaccurate) available to the public. With vitamins and supplements being readily accessible, many have turned to using them in an effort to combat the virus. The purpose of this review was to analyse clinical trials regarding vitamins and supplements for the treatment of COVID-19 infections.

Methods: Articles were identified through a literature search utilizing online databases and bibliographic review.

Results: A total of seven articles were identified for review. All articles evaluated the use of vitamins and supplements for the treatment of COVID-19. Drug therapies included oral vitamin D, intravenous and oral vitamin C, oral vitamin D/magnesium/vitamin B12, oral zinc, oral combination zinc/ascorbic acid, and intravenous alpha-lipoic acid. The end points of each study varied, including the Sequential Organ Failure Assessment score, mortality, rate of intensive care unit (ICU) admissions, negativity of COVID-19 tests, oxygen requirements, and symptom burden.

Conclusion: Of the vitamins and supplements that were studied, vitamin D presented the most promising data demonstrating significant decreases in oxygen requirements, need for ICU treatment, SARS-CoV-2 RNA test positivity, and mortality. All of these benefits were exhibited in hospitalized patients. Other vitamins and supplements that were evaluated in studies did not demonstrate any statistically significant benefits. Common shortcomings of the articles included generally small sample sizes, varying sites of study (which could determine the virus variant), a lack of standard of care as background therapy, and utilization of doses that were higher than standard.

Keywords: coronavirus, COVID-19, SARS-COV-2, severe acute respiratory syndrome coronavirus, supplement, vitamin.

Citation

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Introduction

SARS-CoV-2, the virus causing COVID-19, was first reported to the WHO on 31 December 2019 and was declared a global pandemic on 11 March 2020.[1–3] To date, there have been more than 229 million reported cases and 4.7 million deaths globally.[4]

Whilst the fight against the COVID-19 pandemic has persisted for more than 18 months at the time of writing, few therapies have proven effective in the management or prevention of COVID-19 infections, with the exception of vaccines.[5–7] Throughout the course of this pandemic, many therapies have been proposed as having utility, with many, but not all of them, falling short of providing meaningful results in clinical trials.[8–16] Some proposed therapies have never undergone clinical trials, and medical claims are being made based on theoretical or anecdotal evidence.[17] Since the publication of the preceding article that reviewed in-progress studies on vitamins and supplements in COVID-19,[18] various vaccines have been developed and used globally, with others in the pipeline.[5–7,19–24]

The National Institutes of Health (NIH) released and regularly updates a set of guideline recommendations based on evolving evidence. As of this writing, remdesivir is the only formally FDA-approved drug for the treatment of COVID-19 in patients meeting certain criteria,[25] including hospitalized patients requiring supplemental oxygen but who do not require high-flow oxygen, ventilatory support or extracorporeal membrane oxygenation.[25] Additionally, the NIH recommended against any medication, pre-exposure or post-exposure prophylaxis, for COVID-19.[26] The NIH guidelines also stated that there are insufficient data regarding the use of supplements for the treatment of COVID-19.[27]

For COVID-19 management in the outpatient setting, the NIH recommended bamlanivimab plus etesevimab[28] or casirivimab

plus imdevimab[29] in certain populations as defined by the Emergency Use Authorization (EUA) criteria.[30] Previously, bamlanivimab alone had received an EUA in the outpatient setting.[31] For COVID-19 management in the inpatient setting, the NIH recommended remdesivir, dexamethasone, and/or tocilizumab, depending on oxygen requirements and risk of disease progression.[32] Several other immunomodulators are currently in the pipeline.[33] The Infectious Diseases Society of America,[34] the Society for Critical Care Medicine[35] and the WHO[36] have each published their own set of fluid guideline recommendations that are generally in accordance with the NIH recommendations. The CDC did not recommend specific therapies but instead deferred to the NIH guidance.[37] Whilst there is no universal standard of care at the time of this publication, most institutions have protocolized COVID-19 management, with recommendations evolving with changing evidence.

With an abundance of news outlets and means of communication, there has been ample misinformation circulating amongst the public regarding the dos and don'ts of combatting this novel virus.[17] With vitamins and supplements being readily accessible to the general public without provider oversight, it is important to address their role in this pandemic as there has been much discussion surrounding their use. The purpose of this review was to analyse completed and published clinical trials regarding vitamins and supplements for the treatment and/or prevention of COVID-19 infections.

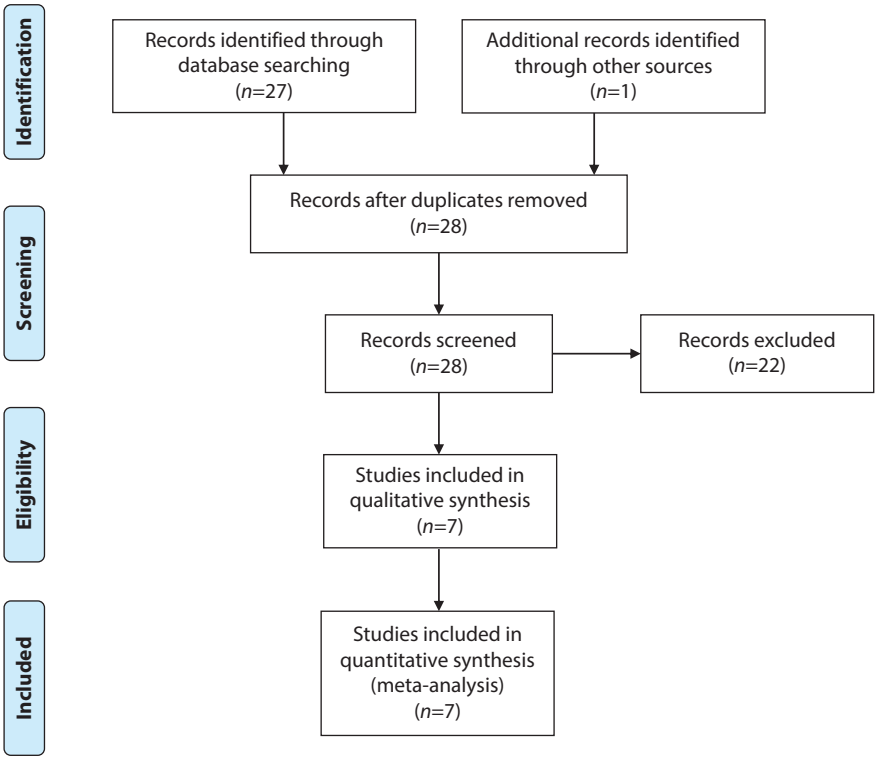
Methods

We performed a literature search using PubMed, Google Scholar and bibliography review using the National Clinical Trials (NCT) numbers from previous manuscripts and the following search terms: coronavirus/COVID-19/SARS-CoV-2/COVID and vitamins/supplements. The results were filtered to "clinical trial" and "randomized controlled trial". Both prospective and retrospective studies evaluating the use of vitamins and/or supplements for the prevention or treatment of COVID-19 and published on or before 26 February 2021were included. Studies were excluded if they did not report on an intervention or if complete/final results were not available. This manuscript was exempt from ethics review and Institutional Review Board approval as it did not involve human subject research.

Results

Twenty-seven manuscripts were identified from an initial database search, with six of which qualified for inclusion in this analysis (Figure 1). Reasons for study exclusion were non-interventional study (*n*=2), erroneous search result (*n*=11), inability to obtain access to paper (*n*=1) and study in progress (*n*=7). An additional China-based study that was not available through online databases was identified through a bibliography review and included in this review, making a total of seven qualifying trials for this paper.

Figure 1. Clinical studies included in review.[100]



All identified studies involved the treatment of COVID-19 and did not address prophylaxis therapies for COVID-19. The interventions in the studies were oral vitamin D, intravenous (IV) and oral vitamin C, oral combination vitamin D/magnesium/vitamin B12, oral zinc, oral combination zinc/ascorbic acid, and IV alpha-lipoic acid (ALA), with the majority of the studies investigating the use of vitamin D (n=4). Of the identified trials, two were retrospective, and five were prospective with randomization. Of the randomized trials, three were open-label, one was single-blind, and the other was unspecified. The proposed utility of each of the vitamins and supplements and available data are summarized below and in Table 1.

Vitamin D (cholecalciferol, calcifediol)

Vitamin D has previously been proposed to have antiviral effects, which led to a theoretical benefit of its use as an adjuvant in treating COVID-19 infections.[38–43] Several retrospective studies have addressed an observed correlation between low serum vitamin D levels and severity of the course of COVID-19 disease symptoms, which is evaluated later in this paper.[44–50] Amongst the vitamin D interventional trials assessed in this review, calcifediol use showed significant decreases in intensive care unit (ICU) admission rates, from 50% without therapy to 2% with therapy (p<0.001).[51] Additionally, patients receiving high-dose cholecalciferol showed significantly more negative SARS-CoV-2 tests prior to week 3 (p=0.018).[52] A retrospective study involving various dosing strategies of cholecalciferol was associated with decreased risk of COVID-19-related mortality (p<0.001).[53] With regard to vitamin D levels, in the SHADE study, the cholecalciferol group had achieved significantly higher vitamin D levels (>50 ng/mL) compared to the placebo group (p<0.001)[52] by day 14.[52]

Vitamin C (ascorbic acid)

Vitamin C, a water-soluble vitamin, plays various roles, including supporting connective tissues through collagen synthesis, wound healing, and enhancing the immune system through its bactericidal properties and antibody boosting.[54] It has previously been proposed as having a theoretical benefit in immune defence against COVID-19 infection, based on its known properties and hypothetical, inconsistent evidence supporting its role in symptom mitigation in the common cold.[55–57] Additionally, various studies have demonstrated the positive effects of vitamin C against Epstein–Barr virus, enterovirus/rhinovirus-induced acute respiratory distress syndrome, and severe sepsis and in mechanically ventilated patients with acute respiratory distress syndrome in the ICU.[58–66] IV vitamin C was investigated based on variable evidence of its use in critically ill patients and showed no mortality benefit but some symptom management benefit.[67] One study involving high-dose vitamin C in the setting of COVID-19 demonstrated a significantly longer hospital stay than the non-vitamin C arm. Additionally, there were no significant differences in mortality or ICU length of stay.[68] Vitamin C, alone and in combination with zinc, showed no significant decreases in COVID-19-related symptoms compared to no study intervention.[69]

Magnesium

Magnesium has previously been shown to increase 25-hydroxyvitamin D levels when they are <30 ng/mL at baseline;[70] thus, if vitamin D helps protect against COVID-19, magnesium could in turn also be beneficial. So far, magnesium has only been studied in combination with vitamins B and D. The combination therapy showed significant decreases in oxygen support (including ICU support) (p=0.006); however, there were no significant differences in the outcome of oxygen support, excluding any ICU support.[71]

Vitamin B12

Vitamin B12 has been observed to play a fundamental role in gut microbiome,[72] which can affect the innate immune response.[73] Some data report that SARS-CoV-2 RNA was found in the stool of patients testing positive for COVID-19, implying that there could be involvement of the gut–lung axis in COVID-19 infections.[74] Additionally, one study demonstrated that the faecal microbiome of patients testing positive for COVID-19 was significantly altered compared to a control group.[75] Similar to magnesium, vitamin B has only been studied in combination with vitamin D and magnesium. As stated above, this combination therapy showed significant decreases in oxygen support (including ICU support) (p=0.006); however, there were no significant differences in the outcome of oxygen support, excluding any ICU support.[71]

Zinc

The proposed immune-related mechanism of action of zinc is through enhancement of the innate anti-infective properties of basophils, eosinophils, and neutrophils.[76] Some weak evidence supports the use of zinc in mitigating symptoms of the common cold.[77–80] Additionally, zinc has demonstrated inhibition of RNA polymerase in vitro but this has not been studied in SARS-CoV-2.[81,82] Zinc supplementation has been minimally studied in COVID-19; however, one trial demonstrates that zinc, both alone and in combination with vitamin C, showed no significant decreases in COVID-19-related symptoms compared to no study intervention.[69]

Alpha-lipoic acid

ALA is an anti-inflammatory and antioxidant. It has previously been shown to decrease the levels of serum inflammatory cytokines and inflammatory-related symptoms in patients with acute coronary syndrome, liver transplantation, and kidney–pancreas combined transplantation.[83–86] Only one study investigated the use of ALA in COVID-19, and this study demonstrated no significant differences in the Sequential Organ Failure Assessment (SOFA) score by day 7 of therapy or

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Table 1. Summary of clinical trial evidence for vitamins and supplements.

Trial title	Location, study period (publication date)	Study design	Treatment arms	Background therapies	Inclusion/exclusion	End points	Main patient characteristics	Results	Conclusion
Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial[68]	• Iran • April–May 2020 (published 11 February 2021)	Open-label, randomized, controlled trial	1. Study group (*n*=30): 1.5 g vitamin C IV every 6 hours for 5 days 2. Control group (*n*=30): no additional therapy on top of background therapy	All participants received oral lopinavir/ritonavir 400/100 mg twice daily and a single stat dose of oral hydroxychloroquine (400 mg) on the first day of hospitalization according to the Iranian COVID-19 treatment protocol at time of study	**Inclusion:** • >18 y/o • Positive COVID-19 PCR test or COVID-19 suspicion based on clinical findings (mainly fever, dyspnoea, dry cough) • Imaging findings of COVID-19 on spiral chest CT or high-resolution CT • Clinical manifestations of ARDS or myocarditis • Oxygen saturation lower than 93% from admission or after 48 hours from the first COVID-19 treatment **Exclusion:** • Receiving antiretroviral therapy or immune system booster medications in the last 3 months • No proven or confirmed COVID-19 disease based on the inclusion criteria • Glucose-6-phosphate dehydrogenase deficiency • ESRD • Pregnancy	**Primary:** Duration of hospitalization • Mortality • Need for ICU admission **Secondary:** • Improvements in SpO_2 and vital signs • General well-being of the patient (undefined means of measurement)	• Average age: ~59 y/o • Male: 50% • Significantly more patients in the control group had fever (p=0.002) and myalgia (p<0.001) at baseline	**Primary:** • Median hospital stay was 8.5 days in the study arm *versus* 6.5 in the control arm (p=0.028) • No significant difference in mortality • No significant difference in ICU length of stay **Secondary:** • Body temperature on the 3rd day of admission was significantly higher in the control group (p=0.001), but there was no difference at discharge (p=0.454) • SpO_2 on the 3rd day of admission was higher in intervention group than in control (p=0.014), but there was no difference at discharge (p=0.406) • No significant differences in severity score (p=0.651)	There were improvements in peripheral oxygen saturation and body temperature in both groups during the time of admission, but there were no significantly better outcomes in the group that was treated with high-dose vitamin C at discharge

(Continued)

Table 1. (*Continued*)

Trial title	Location, study period (publication date)	Study design	Treatment arms	Background therapies	Inclusion/exclusion	End points	Main patient characteristics	Results	Conclusion
A randomized, single-blind, group sequential, active-controlled study to evaluate the clinical efficacy and safety of α-lipoic acid for critically ill patients with coronavirus disease 2019 (COVID-19)[87]*	• Wuhan, China • February–March 2020 (published 21 April 2020)	Randomized, single-blind, group sequential, active-controlled trial	1. ALA (1200 mg/d, IV infusion) once daily plus standard care for 7 days (*n*=8) 2. Standard care (unspecified) plus equal volume saline infusion for 7 days (*n*=9)	Not specified	**Inclusion:** • Patients diagnosed with critically ill COVID-19 complying with the COVID-19 Critical and Critical Diagnostic Standards **Exclusion:** • Patients who are participating in other clinical trials • Pregnant or breastfeeding patients • Other life-threatening diseases, such as cancer • Expected survival time <24 hours • Allergy to ALA or similar drugs (B vitamins) and intolerant to the recommended dosage of ALA in the past • History of immune system diseases or diseases closely related to the immune system	**Primary:** • SOFA score **Secondary:** • All-cause mortality in 30 days	• 76.5% male • Median age: 51–91 y/o • 52.9% on invasive ventilation • Median SOFA score at baseline: 4.06	**Primary:** SOFA score at day 7: • ALA group: score increased from 3.8 to 4 • Placebo group: score increased from 4.3 to 6 (*p*=0.36) **Secondary:** 30-day all-cause mortality: • ALA group: 37.5% • Placebo group: 77.8% (*p*=0.09)	ALA treatment did not significantly improve 30-day survival rate of patients with critically ill COVID-19, nor did it significantly slow down the increase in SOFA score

(Continued)

Table 1. (*Continued*)

Trial title	Location, study period (publication date)	Study design	Treatment arms	Background therapies	Inclusion/exclusion	End points	Main patient characteristics	Results	Conclusion
Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19)[71]	• Singapore • 15 January–15 April 2020 (published 1 September 2020)	Retrospective, cohort observational study	1. Daily oral combo tablet of 1000-IU dose of vitamin D3, 150 mg of magnesium oxide, and 500 mg of vitamin B12 for 14 days; DMB could be discontinued if a patient subsequently deteriorated or was deemed to have recovered based on symptom resolution and two consecutive negative SARS CoV-2 PCR tests (*n*=17) 2. No intervention (*n*=26)	Treatment with oral lopinavir/ritonavir or IV remdesivir or oral hydroxychloroquine (unspecified doses) • DMB: 17.6% • Control: 61.5%	**Inclusion:** • Hospitalized patients ≥50 y/o with COVID-19 in a tertiary academic hospital **Exclusion:** none stated	**Primary:** • The requirement of oxygen therapy when oxygen saturation fell <95% detected by pulse oximetry, ICU support, or both • Rate of ICU admissions • Death	• Mean age: ~61 y/o • Male: ~60% • Presence of comorbidities ■ Control: 76.9% ■ DMB: 47% • Median duration of DMB therapy: 5 days	**Primary end point:** • Oxygen requirements (including ICU support): 3 of 17 patients (17.6%) for DMB *versus* 16 of 26 patients (61.5%) for control group (p=0.006) • There were no significant differences in oxygen requirements without ICU support, ICU support alone, or mortality	DMB-treated patients were significantly less likely to require oxygen therapy than controls; however, comorbidities and background therapies were not equally matched at baseline
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[51]	• Spain • Unstated study period (published 29 August 2020)	Randomized open-label, double-blind clinical trial	1. Oral calcifediol 0.532 mg on days 1, 3, and 7 then weekly until discharge or ICU admission (*n*=50) 2. No intervention (*n*=26)	All patients received background therapy of combination of oral hydroxychloroquine (400 mg every 12 hours on the first day and 200 mg every 12 hours for the following 5 days), oral azithromycin (500 mg for 5 days, unspecified frequency) ± broad-spectrum antibiotic	**Inclusion:** • Patients hospitalized with COVID-19, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB65 severity scale (a validated tool that estimates mortality of community-acquired pneumonia to help determine inpatient *versus* outpatient treatment) **Exclusion:** • ≤18 y/o • Pregnancy	• Rate of ICU admissions • Death	• Mean age: 53 y/o • Male: 62%	• ICU admission: 50% in control group *versus* 2% in calcifediol group (p<0.001) • Death: 7.7% in the control group *versus* 0% in calcifediol group (no p value provided)	Administration of a high dose of calcifediol or 25(OH)D significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19

(Continued)

Table 1. *(Continued)*

Trial title	Location, study period (publication date)	Study design	Treatment arms	Background therapies	Inclusion/exclusion	End points	Main patient characteristics	Results	Conclusion
Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)[52]	• North India • Unstated study period (published 12 November 2020)	Randomized, placebo controlled study (unspecified whether blinded or not)	1. Patients with vitamin D (25(OH) D) deficiency (<20 ng/ml) were randomized to receive daily 60,000 IU of oral cholecalciferol for 7 days with the aim to achieve 25(OH) D levels >50 ng/ml or placebo for 7 days; subsequently, 25(OH)D levels were assessed at day 7 and a weekly supplementation of 60,000 IU oral provided to those with 25(OH) D >50 ng/ml or else continued on daily 60,000 IU vitamin D oral supplementation for another 7 days up until day 14 in participants with 25(OH)D <50 ng/ml in the intervention arm (*n*=16) 2. Daily placebo for 7 days (*n*=24)	All the participants received standard care for the SARS-CoV-2 infection as per institute protocol (unspecified)	**Inclusion:** • Individuals with SARS-CoV-2 infection who were mildly symptomatic (undefined) or asymptomatic with or without comorbidities admitted to a tertiary care hospital in north India **Exclusion:** • Patients unable to take oral supplementation (i.e. requiring invasive ventilation) • Significant comorbidities like uncontrolled hyperglycaemia or hypertension	**Primary:** • Proportion of participants who turn SARS-CoV-2 negative (confirmed twice at 24-hour interval) before week 3 in the two groups **Secondary:** • The change in level of inflammatory markers with treatment	• Median age: ~49 y/o • Male: 50% • Median 25(OH) D level: ~9.2 ng/mL	**Primary:** • 62.5% patients in the intervention group achieved SARS-CoV-2 negativity compared to 20.8% of patients (*p*=0.018) in the control arm **Secondary:** • Greater decrease in fibrinogen in the intervention arm (–0.9 ng/ml) *versus* the control arm (–0.04 ng/ml); *p*=0.001 • No significant differences in the change in D-dimer, CRP, ferritin or procalcitonin	A greater proportion of patients could attain SARS CoV-2 RNA negativity on high-dose vitamin D supplementation at 25(OH)D >50 ng/ml compared to vitamin D-deficient individuals

(Continued)

Table 1. (*Continued*)

Trial title	Location, study period (publication date)	Study design	Treatment arms	Background therapies	Inclusion/exclusion	End points	Main patient characteristics	Results	Conclusion
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[53]	• United Kingdom • 26 June–7 August 2020 (published 11 December 2020)	Retrospective, multi-centre, cross-sectional observational study	Patients received cholecalciferol booster therapy if they were vitamin D insufficient (serum 25(OH)D 25–50 nmol/L) or deficient (<25 nmol/L) as part of routine clinical care; dosing regimens varied from 40,000 IU daily to 20,000 IU every 2 weeks (*n*=984)	Not specified	**Inclusion:** • Inpatients with a clinical diagnosis of COVID-19 identified by clinical coding **Exclusion:** • <18 y/o • A final clinical diagnosis that was not COVID-19	• Predictors of COVID-19 mortality	• Median age: 73.3 y/o • Female: 48.2% • *n*=755 for available vitamin D levels: median at baseline 39.6 nmol/l	The following were significantly associated with reduced risk of COVID-19 mortality: • Age >74 (*p*=0.04) • Treatment with cholecalciferol booster therapy (*p*<0.001) • Diagnosis of asthma (*p*=0.006)	Treatment with cholecalciferol appeared to be protective against mortality, regardless of baseline serum 25(OH)D levels
Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial[69]	• Ohio and Florida, United States • 27 April–14 October 2020 (published 21 February 2021)	Prospective, randomized, clinical open-label trial	Each of the following was for a duration of 10 days: 1. 8000 mg of oral ascorbic acid (to be divided over two to three times per day with meals) (*n*=48) 2. 50 mg of oral zinc gluconate at bedtime (*n*=58) 3. Both therapies (*n*=58) 4. Usual care without any study medications (*n*=50)	Overall: • Antipyretics: 27.6% • NSAIDs: 15.4% • Bronchodilators: 14.5% • GI medications: 10.3% • Corticosteroids: 8.4% • Decongestants: 6.5% No statistically significant differences stated between groups	**Inclusion:** • New diagnosis of COVID-19 in an outpatient setting • Age ≥18 y/o • Women of childbearing potential had to confirm a menstrual period within the past 30 days or previous sterilization, and those who were perimenopausal required a negative pregnancy test; women of childbearing potential were required to have a confirmed negative pregnancy test to be enrolled	**Primary:** • The number of days required to reach a 50% reduction in symptom severity score from peak symptom score	• Average age: 45.2 y/o • Male: 38.3%	**Primary:** • Usual care: 6.7 days • Ascorbic acid: 5.5 days • Zinc: 5.9 days • Ascorbic acid and zinc: 5.5 days No significant difference between any groups	A significantly faster reduction in symptoms was not observed in any of the active treatment groups *versus* usual care

(Continued)

Table 1. (*Continued*)

Trial title	Location, study period (publication date)	Study design	Treatment arms	Background therapies	Inclusion/exclusion	End points	Main patient characteristics	Results	Conclusion
Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial[69] (*Cont*)					**Exclusion:** • Hospitalized patients • Residence outside of Ohio or Florida • Pregnant patients or actively lactating • Presence of advanced chronic kidney disease, liver disease awaiting transplantation, or a history of calcium oxalate kidney stones	**Secondary:** • The number of days required to reach a total symptom severity score of 0 • Cumulative severity score at day 5 • Hospitalizations • Deaths • Adjunctive prescribed medications • Adverse effects of the study supplements		**Secondary:** • No significant differences in any of the secondary outcomes between any groups	

*This article is pre-print and has not yet been peer-reviewed.
25(OH)D, 25-hydroxyvitamin D_3 ALA, alpha-lipoic acid; ARDS, acute respiratory distress syndrome; CRP, c-reactive protein; CT, computed tomography; DMB, vitamin D, magnesium, vitamin B; ESRD, end-stage renal disease; GI, gastrointestinal; ICU, intensive care unit; IU, international units; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; PCR, polymerase chain reaction; SOFA, Sequential Organ Failure Assessment; SpO_2, saturation of peripheral oxygen; y/o, years old.

mortality.[87] SOFA is a validated scoring system used to predict mortality in ICU patients.[88]

Vitamin, mineral and nutrient deficiency in COVID-19

Aside from interventional trials involving vitamins and supplements in COVID-19, data have also been published regarding serum levels of vitamins, minerals, and nutrients and their role in COVID-19.[89,90] Most of the data involve vitamin D levels. A full review of deficiencies in COVID-19 is beyond the scope of this article, but representative studies are discussed below to better contextualize supplementation in COVID-19. Interested readers can find a more in-depth analysis on this topic in the cited review articles.[91–94]

Several retrospective studies found a relationship between vitamin D levels and COVID-19 positivity rate. Amongst patients aged >70 years old, one study showed that patients positive for COVID-19 had significantly lower median vitamin D levels compared to those negative for COVID-19 (9.3 ng/mL *versus* 23.1 ng/mL, respectively; p=0.037).[48] Similarly, another study found positive COVID-19 tests were associated with deficient vitamin D status (defined as <20 ng/mL) at the time of testing (relative risk 1.77, 95% CI 1.12–2.81; p=0.02).[49] Moreover, a third study demonstrated an association between low vitamin D levels (defined as <30 ng/mL) and an increased likelihood of COVID-19 infection (p<0.001).[50]

Additional retrospective studies found vitamin D was also related to the severity and outcomes of COVID-19. Amongst patients who were positive for COVID-19, in both inpatient and outpatient settings and equally treated at a single site in Germany, those who had vitamin D deficiency (<12 ng/mL) had significantly higher hospitalization rates (p=0.004), required intensive oxygen therapy (p<0.001), and had significantly higher rates of invasive mechanical ventilation and/or death (p<0.001) or death alone (p<0.001). Insufficient levels of vitamin D (<20 ng/mL) were also associated with higher rates of invasive mechanical ventilation and/or death (p=0.004) or death alone (p=0.2).[95] In contrast, another study did not show a difference in mortality between vitamin D deficiency (≤30 nmol/L) and replete inpatient adults ≥65 years old in the United Kingdom. However, vitamin D deficiency was associated with significantly higher ventilation requirements (p=0.042).[96] In an Italian study, patients with severe vitamin D deficiency (<10 ng/mL) had higher median respiratory intermediate care unit stays compared to those with vitamin D levels ≥10 ng/mL (8 *versus* 12.5 days). Additionally, those with severe vitamin D deficiency had higher mortality rates (50% *versus* 5%; p=0.019).[97]

Minimal data exist regarding supplements or vitamins, besides vitamin D; however, there are some data on selenium and potassium. In one study, 64.7% of COVID-19 non-survivors had selenium levels <45.7 µg/L, whereas 39.3% of COVID-19 survivors had these levels. Additionally, the COVID-19 non-survivors had significantly lower selenium serum levels than the survivors (p<0.001).[98] In another study of 197 inpatients with COVID-19, those who were normokalaemic (K >3.5 mmol/L) had significantly fewer complications (including respiratory failure, sepsis, liver damage, respiratory distress and cardiac damage) than those with severe hypokalaemia (K <3 mmol/L) (p=0.006). Additionally, normokalaemic patients were less likely to be critically ill compared to severely hypokalaemic patients (p=0.03).[99]

Discussion

Of the vitamins and supplements that were studied, vitamin D presents the most promising data demonstrating significant decreases in oxygen requirements (p=0.006),[71] need for ICU treatment (p<0.001),[51] SARS-CoV-2 RNA test positivity (p=0.018)[52] and mortality (p<0.001).[53] All of these benefits were exhibited in hospitalized patients; no studies were conducted in the outpatient setting to demonstrate similar results. A shortcoming of most of the identified trials is the small sample size, with the exception of a large, retrospective trial evaluating various dosing strategies of cholecalciferol and its impact on COVID-19 mortality.[53] The end points of each study varied, including SOFA score, mortality, rate of ICU admissions, negativity of COVID-19 tests, oxygen requirements and symptom burden. Additionally, with each study taking place in different parts of the world, the study populations were likely affected by different virus variants. The lack of a global standard of care meant that background therapy varied from trial to trial. In many instances, the dose of the vitamin or supplement utilized in these trials was higher than standard over-the-counter doses,[89,90] making it unlikely that patients would take the doses that were studied in these trials without the supervision of a clinician.

Conclusion

With the lack of large randomized controlled trials, results from the studies to date must be interpreted cautiously. At this time, studies involving vitamins and supplements do not provide enough evidence to justify their use over other established pharmacological therapies and prevention techniques that have been proven for use in COVID-19 management and prevention.

Additionally, current data regarding vitamin D levels and COVID-19 suggest that low vitamin D levels are associated with increased risk of COVID-19 infection as well as with more complications during infection and higher rates of death. However, from these data alone, it cannot be deducted that vitamin D supplementation is beneficial in the setting of COVID-19 infections. More data are needed regarding other vitamins and minerals to deduct further effects of serum levels on COVID-19. Finally, with regard to selenium levels, the challenge for most institutions would be limited access to selenium testing.

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