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## ABCDE in COVID-19: How Vital are the Vital Amines

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**Abstract**

Dietary supplementation is considered for prevention and/or treatment of COVID-19. Present review was conducted to understand the role of vitamins in COVID-19. Review articles, in English language, published within past one year, were considered in this report. Electronic databases were searched, till 30th June 2020.

Of initially identified 90 publications, 13 review articles were selected for present qualitative synthesis. Out of the five vitamins considered here, vitamin D followed by vitamin C was most researched upon.

Vitamin D deficiency is associated with increased susceptibility to respiratory infections including occurrence and poor outcome of COVID-19, which is likely to depend on prior vitamin D status of the individual. Most authors have recommended vitamin D supplementation especially in vitamin D deficient and high risk individuals, in daily or weekly regimen, with higher doses for vulnerable individuals.

Some authors have opined that supplementation with vitamin C provides protection against respiratory infections and can even reduce duration, severity and impact of the disease, but it is not known whether a supplemental dose of vitamin C administered to patients without their deficiency would result in a benefit.

Very few articles were available on other vitamins. While Vitamin A supplement may be of a small benefit and hence has been recommended, vitamin E supplementation has been noted to be harmful for both prevention and treatment.

Evidence is lacking for all the vitamins under review here and hence impact of supplementation of vitamins is still unclear. Importance of maintaining optimal nutrient status to strengthen the immune system to ward off any disease cannot be over-ruled. However, nutrient supplement may also be a potential alternative for prevention and/or treatment of the disease, especially vitamin D in high risk individuals. Further intervention research is required to establish or refute the possibly effective role of vitamins in prevention/treatment of COVID-19.

**Keywords:** COVID-19; Vitamins; ABCDE; Nutrient supplement.

**Introduction**

The world is currently under the grip of a pandemic of COVID-19, the most severe in recent times. It began as a cluster of cases of pneumonia of unknown cause, detected in Wuhan, Hubei Province in China, at the end of the year 2019. It

was first reported to the World Health Organization (WHO) Country Office in China on 31st December 2019. Thailand was the first country to report a case from outside China, on 13th January 2020.<sup>1</sup> On 26th February 2020 the disease had spread to all regions of the WHO.<sup>2</sup>

Caused by a novel Coronavirus, there is no

established preventive or therapeutic remedy for this disease. Several interventions for prevention and treatment of the disease are currently under research, one of which is dietary supplementation with various nutrients including vitamins. Effectiveness of this relatively innocuous and harmless strategy needs to be explored and if found to be beneficial, this intervention might have a great role in containing the pandemic. Present review was conducted to understand the observation and opinion of researchers across the world, regarding the possible role of vitamins in prevention and/or treatment of COVID-19.

## Materials and Methods

A qualitative synthesis, which may be named as a narrative review of reviews, was done on review articles across the world, regarding the role of vitamins in COVID-19. Systematic review and meta-analysis was not attempted as these have already been done by some authors on the very few original studies available. Since vitamin K has complex involvement in pathophysiology of thrombolysis in the course of the disease and also because it cannot be used by the people as nutrient supplement and hence has no community beneficial implication, it was not considered in this review.

### Selection of studies

Review articles, which included systematic, scoping and narrative reviews, on vitamins and COVID-19 were considered in this report, based on pre-specified eligibility criteria. Filters used were English language, past one year, human subjects. Inclusion criteria were publication on vitamin and COVID-19 in the context of prevention and/or treatment. Exclusion criteria were publication on vitamin K, trial protocol, communication, blog, newspaper article. Outcome measure included occurrence, severity and outcome of respiratory illnesses including COVID-19. Role of vitamin in any other condition was not considered.

### Search strategy

Electronic databases PubMed, PubMed Central, BioMed Central and PLoS were searched, till 30th June 2020. Search terms used were vitamin/ vitamin A/ vitamin B/ vitamin C/ vitamin D/ vitamin E AND severe acute respiratory syndrome coronavirus 2/ SARS-CoV-2/ COVID-19, separately

for each vitamin. Search was also conducted with alternative terms for each vitamin, but no additional results were obtained. Publications quoted in articles identified for review was also considered. Data was extracted using a common format, noting the salient observations and recommendations given by the authors of each publication. Findings were presented in the context of role of the five vitamins A, B, C, D and E in prevention and/or treatment of respiratory disease conditions, with recommendations for use against COVID-19.

## Results

Total 90 documents were identified, of which titles of 31 were not relevant to the topic of present review. Of the remaining 59 studies, 12 were duplicates and 9 did not meet the inclusion criteria. Out of the 38 studies meeting the inclusion criteria, 25 were rejected on the basis of exclusion criteria. Finally 13 review articles were selected for the present qualitative synthesis.<sup>3-15</sup> (Figure 1)

Out of the five vitamins A, B, C, D and E considered here, vitamin D<sup>3-15</sup> followed by vitamin C<sup>3,5-7,9-11,14,15</sup> were most researched upon. Three articles for vitamin A,<sup>7,9,11</sup> one for vitamin B<sup>7</sup> and three for vitamin E<sup>9,11,15</sup> could be located.

Table 1 shows observation of various researchers on effect of vitamin D on respiratory illnesses and recommendation for COVID-19. More than half of the publications specifically reviewed research on COVID-19,<sup>4,7,8,9,13-15</sup> while the rest reported role of vitamins in respiratory illnesses in general.<sup>3,5,6,10,11,12</sup> Though one author has observed it has not been specifically evaluated for prevention of COVID-19 infection and should be further studied before it is recommended to patients,<sup>5</sup> most researchers have recommended vitamin D supplementation.<sup>3,4,6-8,10-12,15</sup> Benefit of supplementation may be more in already deficient<sup>5,10-12</sup> and high risk<sup>4,8</sup> individuals, with maximum benefit in individuals with both these attributes.<sup>7</sup> However, one author<sup>13</sup> has mentioned that it is unclear if results may vary according to baseline nutrient status. One author has suggested maintenance of optimal nutrient status through consumption of balanced diet<sup>9</sup> and another author has advised caution in supplementation so as to not exceed the recommended dose.<sup>13</sup>

Dosage recommendation in the studies included here specified weekly or daily regimen with more focus on the latter. Suggested recommendations are -continuing daily vitamin D consumption of 600 or

**Table 1:** Vitamin D and COVID-19.

Author	Observation	Recommendation
Adams <sup>3</sup>	Observational data consistently associate low vitamin D levels with acute respiratory tract infections and oral vitamin D supplementation reduces the risk of acute respiratory tract infections. Trial evidence is less consistent.	May continue to follow recommendations for daily vitamin D consumption For adults, this is within the range of 600 or 800 IU to 4000 IU.
Avolio <sup>4</sup>	Significantly lower 25(OH)D levels found in SARS-CoV-2 patients compared with negative patients, observation persisting on stratification of patients according to age.	Those at risk of COVID-19 may take 10,000 IU/day of vitamin D for a few weeks, followed by 5000 IU/day.
Bauer <sup>5</sup>	Vitamin D deficiency has been associated with a higher incidence of acute respiratory infections, with a link between the seasonality of influenza and vitamin D deficiency. Vitamin D supplementation decreased incidence of acute respiratory infection, protective effect being greater in patients with low baseline levels of vitamin D.	It has not been evaluated for prevention of COVID-19 and should be further studied before it is recommended.
Calder <sup>6</sup>	Daily supplementation of vitamin D reduces the risk of acute respiratory tract infections in both children and adults.	Daily intake of 2000 IU/day is recommended.
Chen <sup>7</sup>	COVID-19 was reported to mostly affect middle-aged to elderly people who might have insufficient vitamin D due to their lack of exposure to sunlight.	Vitamin D supplement might work as an adjuvant therapy for COVID-19
Grant <sup>8</sup>	Most of the beneficial effects of vitamin D in COVID-19 are from observational studies of disease incidence or prevalence with respect to serum 25 (OH) D concentrations. However, intervention studies have not reported that vitamin D supplementation reduced the risk of disease	People at high risk should take 10,000 IU/d of for a few weeks, followed by 5000 IU/d. Higher doses are needed for treatment of COVID-19.
Iddir <sup>9</sup>	Protective effects of vitamin D administration were reported regarding incidence, severity and mortality of respiratory tract infection including influenza and COVID-19. Protective effect is most with daily dosing. Older and male patients with pre-existing conditions and below normal vitamin D levels showed higher odds of death.	Optimal nutrient status should be maintained and nutritional deficiencies should be controlled.
Infusino <sup>10</sup>	Vitamin D deficiency has been associated with increased susceptibility to respiratory infections. Randomized controlled trials and their meta-analysis showed vitamin D administration reduces risk of acute respiratory tract infections, with benefits more evident in participants with low levels.	It is reasonable, even in the absence of specific data, to administer vitamin D to healthy individuals and COVID-19 patients
Jewardena <sup>11</sup>	Observational studies predominantly report statistically significant associations between low vitamin D status and increased risk of both upper and lower respiratory tract infections, but results from RCTs were conflicting.	Supplementation may be effective especially those who are deficient in a dose of 5000IU/d for prevention and 10000IU/d for treatment
Kakodkar <sup>12</sup>	Evidence showed there is protective effect of vitamin D supplementation against bacterial and viral acute respiratory tract infection and their outcome, with protective effects increasing in individuals on daily or weekly regimen compared to those on a monthly bolus of vitamin D. Protective effect is higher in individuals with vitamin D deficiency corrected with supplementation.	It may be beneficial to individuals with vitamin D deficiency
Lanham-New <sup>13</sup>	Association between seasonal URTIs and low vitamin D status. Supplementation effective but more so in developing countries. Studies investigating vitamin D and COVID-19 are currently underway	Vitamin D intake (total from both foods and dietary supplements) should be limited to 4000 IU/day (100 µg/day) for adults
Rozga <sup>14</sup>	Individuals infected with COVID-19 may have baseline nutrient deficiencies or increased nutrient needs due to COVID-19 pathology. Sparse evidence of interventions described some benefit of vitamin D supplementation.	It is unclear if results may vary according to baseline nutrient status.
Zabetakis <sup>15</sup>	Though some studies have not shown any effect, many researchers observed an overall protective effect of vitamin D supplementation against acute respiratory tract infections and COVID-19. Patients who are very vitamin D-deficient experience the most benefits. Vulnerable groups should maintain their vitamin D status to reduce the risk of respiratory infections, including COVID-19.	Doses of 10,000 IU/d of vitamin D for several weeks, followed by 5000 IU/d. Higher doses of vitamin D are advisable for vulnerable individuals.

**Table 2:** Vitamin C and COVID-19.

Author	Observation	Recommendation
Adams <sup>3</sup>	Despite theoretical benefits, evidence does not support the routine use of vitamin C for prevention of viral infections, including common cold. However, shortening in duration of common cold has been shown. Trials showed that giving intravenous vitamin C did not significantly alter disease severity scores.	Should not rely on dietary supplements to prevent or cure COVID-19
Bauer <sup>5</sup>	Vitamin C may decrease susceptibility to viral respiratory infections. High doses reduce severity and duration of symptoms from common cold. Studies on hospitalized and critically ill patients have shown mixed results on mortality, length of stay in the intensive care unit, and duration of mechanical ventilation.	The impact of vitamin C for the treatment of patients with COVID-19 is unclear
Calder <sup>6</sup>	Significant reductions seen in risk and impact of both upper and lower respiratory tract infections, including disease severity and risk of death in older patients. Requirement for vitamin C increases during infection.	Daily intake of at least 200 mg/day for healthy individuals and 1-2 g/day for sick individuals is recommended.
Chen <sup>7</sup>	Vitamin C supports the integrity of immune system and may be used against the coronavirus. Several trials showed that vitamin C supplement could significantly lower the incidence of pneumonia. IV vitamin C infusion may prevent undesirable effects.	Vitamin C can be an alternative adjuvant agent for the treatment of COVID-19.
Iddir <sup>9</sup>	Vitamin C was shown to reduce duration of infection and relieve symptoms of common cold, but did not prevent infection of upper respiratory tract diseases. In elderly population it improves respiratory condition.	Optimal nutrient status should be maintained, to strengthen the immune system during the COVID-19 crisis.
Infusino <sup>10</sup>	Vitamin C increases the resistance to coronavirus and may affect susceptibility to lower respiratory tract infections. Supplementation has positive effects on symptoms, duration and mortality due to pneumonia.	Beneficial effect of vitamin C supplementation in absence of deficiency is not known
Jeyawardena <sup>11</sup>	No conclusive evidence was found to indicate benefit of using vitamin C mega-dose prophylaxis in the community to reduce the incidence of common cold.	Supplementation may not be effective and is unlikely to be beneficial
Rozga <sup>14</sup>	Interventional and observational studies have reported no significant difference in outcome, compared with placebo group.	Evidence is lacking
Zabetakis <sup>15</sup>	Vitamin C supplementation has shown to reduce severity and duration of common cold, though not prevent its contraction. Healthy individuals with adequate dietary intake may not benefit from supplementation. Patients with infections have lower vitamin C levels due to alterations in the metabolism.	Supplementation with 1-2 g/day may be advised for those at a higher risk of respiratory infections and 200 mg/day for healthy individuals.

800 IU to 4000 IU for adults, which is consistent with the recommended daily allowance and tolerable upper intake level;<sup>3</sup> daily intake of 2000 IU/day;<sup>6</sup> 5000 IU/d for prevention and 10000 IU/d for treatment;<sup>11</sup> 10,000 IU/d for several weeks, followed by 5000 IU/d,<sup>4,8,15</sup> with higher doses for vulnerable individuals.<sup>8</sup> However, total dose from dietary sources and supplementation should preferably be limited to 4000 IU/d.<sup>13</sup>

Table 2 depicts observation and recommendation of various researchers regarding effect of vitamin C on respiratory infections and its possible benefit in COVID-19. All nine publications located reported role of vitamin C in respiratory infections and none were specifically on COVID-19. Some authors concluded that the evidence is lacking and impact is unclear<sup>5,14</sup> and is unlikely to be beneficial.<sup>11</sup> Other authors have recommended maintenance of

optimal nutrition status is important to strengthen the immune system,<sup>9</sup> and not rely on dietary supplements to prevent or cure the disease.<sup>3</sup> Some authors however, opined that Vitamin C can be an alternative adjuvant agent for treatment,<sup>7</sup> but it is not known whether a supplemental dose of vitamin C administered to patients without their deficiency would result in a benefit.<sup>10</sup> Hence, supplementation may be advised for those at a higher risk of respiratory infections.<sup>15</sup> Two authors have recommended specific dosage of vitamin C as intake of at least 200 mg/day for prevention of the disease in healthy individuals and 1-2 g/day for treatment of individuals suffering from COVID-19.<sup>6,15</sup>

Rest of the vitamins viz. vitamin A, B complex group of vitamins and vitamin E have been described in a composite Table 3. Observation of various

**Table 3:** Other vitamins and COVID-19.

Author	Observation	Recommendation
<b>Vitamin A</b>		
Chen <sup>7</sup>	Vitamin A supplements provide some protection against complications in lung disease.	Vitamin A supplement may be a potential alternative for the treatment of COVID-19
Iddir <sup>9</sup>	Vitamin A supplementation did not affect the risk of lower respiratory diseases and symptoms.	Optimal nutrient status should be maintained.
Jewardena <sup>11</sup>	An enhanced immune response to influenza virus vaccination has also been observed in children (2-8 years) who were vitamin A-insufficient at baseline, after supplementation with vitamin A	Supplementation may be effective in a dose of 5000 IU/d for prevention and 20000 IU/d for treatment
<b>Vitamin B</b>		
Chen <sup>7</sup>	Vitamin B2 and ultraviolet light effectively reduced the titre of MERS-CoV in human plasma products. Vitamin B deficiency weakens the host immune responses.	Vitamin B supplement can be a remedy for COVID-19
<b>Vitamin E</b>		
Iddir <sup>9</sup>	Vitamin E supplementation was shown to reduce risk of re-hospitalization after first episode of hospitalization in elderly with pneumonia. Vitamin E supplementation reduced pneumonia incidence in elderly male smokers.	Optimal nutrient status should be maintained.
Jewardena <sup>11</sup>	Few studies have shown that vitamin E supplementation might cause harmful effects on the incidence of infectious disease and even increase the risk of pneumonia.	Supplementation may be harmful for both prevention and treatment and is not recommended
Zabetakis <sup>15</sup>	There is little evidence on the utility of vitamin E as a prophylactic or therapeutic agent against COVID-19.	There may be beneficial effect but there are no estimates of a beneficial dosage.

researchers on effect of these vitamins and their and recommendations for COVID-19 are recorded in this table. Very few articles were available on these vitamins. Importance of maintaining optimal nutrient status to reduce inflammation and oxidative stress, thereby strengthening the immune system has been focused<sup>9</sup> and it has also been suggested that supplement may be a potential alternative for treatment of the disease.<sup>7</sup> While one author has recommended Vitamin A supplement in a dose of 5000 IU/d for prevention and 20000 IU/d for treatment, vitamin E supplementation has been noted to be harmful for both prevention and treatment and hence the author has not recommended it for prevention and/or treatment of COVID-19.<sup>11</sup>

## Discussion

Present qualitative synthesis was done on observations and recommendations of various researchers in their review articles. Out of the five vitamins A, B, C, D and E considered here, vitamin D followed by vitamin C has been most researched upon. However, evidence is lacking for all the vitamins under review in the context of COVID-19 prevention and/or treatment and hence impact of supplementation of vitamins is still unclear.

Vitamin D deficiency has been consistently associated with increased susceptibility to respiratory infections<sup>3,5,6,10-12,13</sup> including occurrence and poor outcome of COVID-19.<sup>4,7-9,13-15</sup> However, some authors noted that association is mostly reported by observational studies and intervention studies have not reported any benefit.<sup>8,11</sup> Association is more in older patients<sup>7</sup> and supplementation is also more effective in old, male individuals with pre-existing conditions.<sup>9</sup> The role of vitamin D supplementation on antiviral immunity against respiratory infections is likely to depend on the vitamin D status of the individual.<sup>5,10,12,15</sup> Most authors have recommended vitamin D supplementation<sup>3,4,6-8,10-12,15</sup> especially in vitamin D deficient<sup>11,12</sup> and high risk individuals,<sup>4,8,15</sup> in daily<sup>3,6</sup> or weekly<sup>4,8,15</sup> regimen, separate for prevention and treatment,<sup>11</sup> with higher doses for vulnerable individuals.<sup>8</sup>

Regarding vitamin C, some authors have observed that supplementation provides protection against respiratory infections and can even reduce duration, severity and impact of the disease and on this basis, they suggested that Vitamin C can be an alternative adjuvant agent for treatment, but it is not known whether a supplemental dose of vitamin C administered to patients without their deficiency would result in a benefit.<sup>5-7,9,10,15</sup> Other authors have found no effect.<sup>3,11,14</sup>



Very few articles were available on rest of the vitamins, which were without any conclusive recommendation. While Vitamin A supplement may be of a small benefit and hence has been recommended,<sup>7,11</sup> vitamin E supplementation has been noted to be harmful for both prevention and treatment.<sup>11</sup>

Rationale behind recommending nutrient supplements lies in the fact that overall nutritional deficiency has been observed to impair immune system. Calder et al., in their review, discussed the various mechanisms through which vitamins and minerals exhibit immune response. Up-regulation of the immune response of the body occurs by collective action of vitamins and minerals through developing and maintaining physical barriers that resist entry of pathogens; producing and activating antimicrobial proteins; promoting phagocytosis by neutrophils and macrophages; and generating memory cells. Cytokine production and antioxidant activity are initiated that aids in promotion of and recovery from inflammation. Of all vitamins, vitamins C and D play a major role.<sup>6</sup>

Evidence supporting the role of vitamin D in reducing risk of COVID-19 is that vitamin D deficiency is associated with occurrence and poor outcome of respiratory illnesses. Case fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower vitamin D concentration.<sup>8</sup> Link between vitamin D deficiency and poor outcome in COVID-19 patients has been indirectly observed by some authors. Rhodes et al found positive correlation between mortality per million population due to COVID-19 and latitude where the country is located. They observed that all countries that lie below 35°N have relatively low mortality. They linked this finding with the fact that countries located above this latitude do not receive sufficient sunlight during winter and suggested there is a possible role for vitamin D in determining outcomes from COVID-19.<sup>16</sup> Panarese and Shahini observed similarly that rate of deaths and hospitalisations are highest in patients from countries in Northern latitudes, followed by those close to the Equator and both rates are lowest in Southern latitudes. They suggested this decreasing North-South gradient has a link with vitamin D deficiency.<sup>17</sup> This theory is plausible as the outbreak has occurred at a time when it is winter and early spring in the Northern hemisphere when vitamin D concentrations are lowest. On the other hand, the number of cases in the Southern Hemisphere in summer and early autumn are low when population has the highest vitamin

D blood levels.<sup>8,9</sup> However, such data must be interpreted in the context of interplay of several other factors like health infrastructure, testing strategies, public health measures and the time of their implementation, population isolation, age of population, population density, urban connectivity and disease transmission, as well as mandatory vitamin D fortification and supplementation policies, across various countries.<sup>9,18</sup>

The urban population, especially the older ones, are often less exposed to sunlight which might be enhanced even more than earlier times, as a consequence of "shut-down" measures to control the spread of Covid-19.<sup>17,19</sup> Regular sunlight exposure is the best preventive measure against vitamin D deficiency and can prevent diseases associated with it. Sunlight exposure can be obtained from open windows or balconies for those who do not live in houses with gardens. Oral vitamin D supplement should be considered only if exposure to sunlight is not possible.<sup>13,19</sup>

Present review observed that while vitamin D supplementation has been recommended, there is not much evidence regarding other vitamins. However, for maintaining good health balanced nutrition providing optimum quantity of all nutrients is has been stressed upon by all researchers. Zabetakis et al discussed two types of diets which are contrary to each other. One of these is the 'Mediterranean' diet which is synonymous with anti-inflammatory properties and the other is the 'Western' dietary pattern, prevalent in developed countries, which is characterized by high consumption of high-calorie and processed foods. Mediterranean type of diet is characterised by high dietary intake of minimally processed fruits, vegetables, legumes, olive oil, whole grains, nuts, and monounsaturated fats; followed by low-to-moderate consumptions of fermented dairy products, fish, poultry, wine; and low consumption of processed and red meats. Authors suggested consumption of such type of diet for maintenance of adequate nutrition and overall health.<sup>15</sup>

Present study being a qualitative synthesis lacks objective assessment and hence observation of the author of the present review is likely to be biased. However, strength of this study lies in the fact that conclusion was drawn from several review articles which by themselves have incorporated findings of many more systematic reviews and original articles. In absence of good quality original research, this review has summed up observations and recommendations of many studies and has thus thrown light on a very relevant aspect of

prevention and control of a disease, regarding which evidence-based intervention measures have not yet been identified.

## Conclusion

The importance of maintaining optimal nutrient status to reduce inflammation and oxidative stress, thereby strengthening the immune system to ward off any disease cannot be over-ruled. Nutrient supplement may also be a potential alternative for prevention and/or treatment of COVID-19, especially in certain groups of high risk individuals. A common nutritional workup protocol should be designed for assessing all COVID-19 positive individuals at the outset, so as to initiate vitamin supplementation at the earliest if deficiency is identified.

Prophylactic supplementation should be considered for high risk and vitamin deficient non-infected individuals, to achieve optimal blood levels. For healthy individuals, regular exposure to sunlight and consumption of five portions of fruits and vegetables per day along with recommended intake of other groups of food items, while following all guidelines of the World Health Organization regarding nutrition and food safety, is the mainstay to remain healthy in the present COVID-19 crisis.<sup>20</sup>

Well-designed and meticulously conducted intervention research is the need of the hour to establish or refute the possibly effective role of such a simple yet harmless and cost-effective measure that can be implemented by the community, in fighting the battle that is currently prevailing across the world.

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