



Fat-Soluble Vitamins and the Current Global Pandemic of COVID-19: Evidence-Based Efficacy from Literature Review

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ABSTRACT

AIM; Balanced nutrition which can help in maintaining immunity is essential for prevention and management of viral infections. While data regarding nutrition in coronavirus infection (COVID-19) are not available, in this review, we aimed to evaluate evidence from previous clinical trials that studied nutrition-based interventions for viral diseases (with special emphasis on respiratory infections) and summarise our observations. **Materials and Methods;** Even though the literature investigation is an obligatory segment for systematic review and meta-analysis several critical studies about narrative review encouraged integrating a section about search strategies. In that way, this manuscript comprises the section of materials and methods. The literature search was not systematic but was based on the four core bibliographic databases (Google Scholar, PubMed, Scopus, and China National Knowledge Infrastructure). **Conclusion;** The big data presented by various previous studies depict the efficacy of fat-soluble vitamins such as vitamin A, D, E, and K in immune-modulation and lowering the severity of disease in patients with COVID-19 infection. These vitamins are pivotal in the maintenance and modulation of innate and cell-mediated, and antibody-mediated immune responses. The fat-soluble vitamins are functional in various ways, including increasing the levels of cathelicidins and β -defensins, regulating RONS

production, and influencing the acquired immune system by reducing immunoglobulin secretion by plasma cells and pro-inflammatory cytokines production to modulate T cells function, etc. Vitamin A, D, E, and K boost the body's defense mechanism against COVID-19 infection and specifically prevent its complications such as cytokine storm and other inflammatory processes, leading to increased morbidity and mortality overemphasis. However, more detailed randomized double-blind clinical pieces of evidence are required to define the use of these supplements in preventing or reducing the severity of the COVID-19 infection.

Keywords: SARS-CoV-2, COVID-19, fat-soluble vitamins, micronutrients, immune response.

INTRODUCTION

A strong and well-built immune system is of absolute necessity for every individual. Immune physiology is strongly correlated with adequate intakes of vitamins and trace elements. Healthy dieting, including regular intake of vitamins and trace elements, is responsible for the immune system's proper function. Henceforth, a sufficient amount of vitamins should be present in our daily meals due to their capacity to influence and strengthen the immune system. A recent report demonstrated that the benefits of vitamins to the human body could not be overemphasized. Vitamin supplementation, especially vitamin D, is crucial, especially when vitamins are deficient or insufficient. It has been well established that high-quality nutrition is vital in modulating immune homeostasis. Any subclinical deficiency micronutrients or even protein-energy malnutrition may of impair one's immune responses.

Enhancement of body innate immunity using vitamin supplements in patients suffering from viral infections has shown positive impacts. A typical example is vitamin A and D supplementation, which increases pediatric patients' humoral immunity following influenza vaccination. A review by Calder et al suggested that one of the primary ways to protect a person against viral infections is to maintain a well-balanced nutritional status. Furthermore, balanced nutrition and a varied diet have been proven to complement vitamin deficit and minimize frequent and unnecessary consumption of marketed vitamin supplements. A recent study by Wu suggested nutritional protein-rich foods should be incorporated into daily meals. Unfortunately, during the lockdown period, the achievement of a well-balanced diet appeared tedious due to logistics, economic troubles, and movement restrictions, however taking a multivitamin–mineral (MVM) supplement for a limited time is very helpful, especially among the elderly populations who are more vulnerable to COVID-19 infection.

Currently, malnutrition increases the burden of morbidity and mortality due to infectious diseases, which significantly affects the health care systems from an economic standpoint and the nutrition care of any country. A higher predisposition to morbidity recommendations that could improve the body's immune system and significantly limit lung damage from COVID-19 and other lung infections. In addition to proper dietary intake, lifestyle modification is necessary to prevent and treat viral diseases like the current COVID-19. To complement such efforts, regular fundamental hygienic practices should be maintained, and every individual is urged to comply with rules laid down by the government and the health authorities. The typical healthy eating practice encourages everybody to take a minimum of five servings of different (at least 05) fruits since one fruit is not enough to meet and combat the current

global pandemic of COVID-19 situation and vegetables each day and the main meal that should contain more carbohydrates. Other components of a healthy diet include a few segments of meat or protein for vegetarians. A reasonable amount of and mortality caused by protein-energy malnutrition from inadequate dietary intake has been attributed to an increased rate of infections and delayed recovery, leading to a higher demand for several nutrients. Furthermore, malnourished patients or patients at risk of malnutrition are expected to take extra supplements to improve their energy, protein, and micronutrient levels. Notably, for a viral infection like COVID-19 with minimal therapeutic approaches available for prevention and treatment, nutritional strategies for enhancing immunity remain an avenue to be explored.

Furthermore, medical nutrition therapy (MNT) performs an essential responsibility in the averting and management of malnutrition. The COVID-19 pandemic is predictable to escalate the risk of all types of malnutrition. Moreover, movement control policy, popularly known as lockdowns, messed up the overall healthcare services that deterred maternal and child health, increasing mortality. Researchers anticipated child stunting, micronutrient malnutrition, and maternal nutrition to intensify because of the disruption of national and international economies and the food supply chain. Additionally, 3.9 million children of South Asia have a higher possibility of developing muscle-wasting. Thereafter, registered dietitian nutritionists (RDNs) should be motivated and energetically take the initiative to create and implement appropriate nutrition policy planning to evaluate, avert, and manage malnutrition through a multidisciplinary team-based approach for ongoing COVID-19-infected patients or patients at risk.

A most critical warning sign of the vitamin C deficiency ailment is known as scurvy. Scurvy has been frequently correlated with increased susceptibility to infections, predominantly of the respiratory tract, pneumonia, and pulmonary tuberculosis, and remains the primary cause of death. A classic example is the consumption of vitamin C, which plays a prophylactic role due to its ability to facilitate the favorable immune response required for the growth and repair of body tissues. It also reduces the susceptibility of the lower respiratory tract to infections. It has been reported that patients with acute respiratory infections when receiving intravenous vitamin C followed by serum level increase positively correlate to minimizing the respiratory symptoms. Multiple studies reported that vitamin C possesses significant anti-inflammatory, immunomodulation, antioxidant, antithrombotic, and antiviral activities. Vitamin C positively impacts both innate and adaptive immune systems and exhibits through virucidal activity. Additionally, vitamin C promotes T-lymphocytes' growth and maturation process and works shoulder to shoulder in improving leukocytes physiology performance regarding the phagocytic and chemotactic process. Moreover, vitamin C, with its antioxidant action, improves the phagocytic property; in this manner, it leads to increased formation of reduced vitamin C (ascorbic acid) from oxidized vitamin C (dehydroascorbic acid).

Furthermore, vitamin E is a potent antioxidant and can modulate the host's immune functions. On the other hand, several studies demonstrated the harmful effects of vitamin E intake on the immune response. The same view has also been backed up by researchers who discouraged vitamin E supplementation in cardiovascular disease and cancer prevention. It was also speculated that a high dosage of vitamin E supplementation might increase all-cause

mortality. Taken together, there is a need to investigate the prospects of these vitamins as an effective measure in the treatment of COVID-19.

Objectives of the Study

This review aims and scopes to highlight 1) role of vitamin A, D, E, and K in COVID-19 antiviral effects of vitamin E on COVID-19, immune-boosting effects of vitamin E relevant to combat COVID-19, and to conclude and give prescribers and policymakers direction.

Materials and Methods

Even though the literature investigation is an obligatory segment for systematic review and meta-analysis several critical studies about narrative review encouraged integrating a section about search strategies. In that way, this manuscript comprises the section of materials and methods. The literature search was not systematic but was based on the four core bibliographic databases (Google Scholar, PubMed, Scopus, and China National Knowledge Infrastructure).

Role of Vitamin A in COVID-19

Vitamin A plays a vital role in metabolism and immune response. Its pleiotropic influences have been established, ranging from a diverse physiological task in maintaining the required biological need of our system, including well-known fact in improving the eyesight. In recent reviews, vitamin A acts by boosting all-trans-retinoic acid (ATRA), and it is also pivotal in the maintenance of innate cell-mediated and antibody-mediated responses. In another study on vitamin A, Field et al ascertained vitamin A's capacity to resist infection. A report by Mora et al proposed a decline in vitamin A uptake has a critical influence on the immune response. This was also further testified in the work of Cunningham-Rundles et al, who stated that HIV-infected pregnant women should be encouraged to eat food rich in vitamin A. This is because the decrease in vitamin A could predispose her to an increased risk of congenital HIV and AIDs. Food substances rich in vitamin A are primarily vegetables such as carrots, spinach, and sweet potato. These vegetables also constitute a group of fat-soluble compounds such as retinol, retinoic acid, and β -carotene that play a vital role in regulating immune responses and reducing susceptibility to infections. The mechanism adopted by vitamin A to reduce infection is often through modifying epithelial cell integrity and function, improving specific and non-specific immunity of the host, and lymphoid mass use.

The three primary active forms of vitamin A include retinol, retinoic acid, and retinol. Hence, they are regarded as "anti-infectives as many of the body's defense mechanisms against infections depend on their constant supply. Semba et al believed that adequate vitamin A supplementation helped reduce morbidity and mortality resulting from different infectious diseases. Examples of such conditions include diarrhea, measles, HIV infections, measles-related pneumonia, and malaria. In furtherance to this, vitamin A remains of significant importance as it offers some protection against life-threatening complications and infections such as malaria, HIV, and lung diseases. Often, they are made refractory to infection during subsequent rounds of viral replication nevertheless Jee et al believed that diets low in vitamin A supplements are likely to reduce inactivated bovine coronavirus vaccines' effectiveness, increasing the calves' vulnerability to infectious diseases. Another significant link of vitamin A

to COVID-19 infection was more pronounced in its activity against the infectious bronchitis virus (IBV), a kind of coronavirus that was found more in chickens fed with a diet deficient vitamin A as opposed to those provided with adequate proportions of vitamin A. Lastly, vitamin A is envisaged to be a promising option in treating the COVID-19 pandemic by preventing lung infection. The method by which vitamin A and retinoids prevent measles replication is through the up-regulation of mineral elements and the innate immune response in bystander cells free of infections.⁶⁸

Multiple earlier studies have reported that type 1 interferons (IFN-I) possess antiviral effects in two closely related coronaviruses, SARS-CoV and MERS-CoV, either administered single-handedly or in mish-mash with other nevertheless Antiviral medication . Additionally, retinoids are closely interconnected molecules associated with vitamin A that have robust immune-modulating chattels, together with the capability to escalate and heighten the efficacy of IFN-I. Moreover, retinoids and their related compounds have been well documented as a safe therapeutic option for over 60 years. In that way, multiple studies have reported that retinoids possess potential possibilities in the management of COVID-19. Recently, seven core targets of vitamin A against COVID-19 were recognized. Those are MAPK1 (mitogen-activated protein kinase 1), IL-10 (interleukin 10), EGFR (epidermal growth factor receptor), ICAM1 (intercellular adhesion molecule MAPK14 (mitogen-activated protein kinase), CAT (catalase), and PRKCB (protein kinase C β). Thereby, several studies reported that vitamin A and related compounds have a potentially beneficial role in the management of COVID-19. Moreover, it has been reported that vitamin A can minimize COVID-19-induced adverse effects on the angiotensin system and minimize medication-related adverse effects. On top of these novel beneficial effects, vitamin A, is well known for the positive role in promoting innate and adaptive immunity. By this means, vitamin A prevents or diminishes primary and secondary infections. In consequence, it improves respiratory health by curtailing inflammation and fibrosis. Furthermore, COVID-19 has been found to persuade inflammatory response/cytokine storms, especially involving liver, lung, and kidney, which further increases the risk of depletion of vitamin A stores that demand supplementation and has the prospect to restore the acceptable status and combat the grave life-threatening disease.

Role of Vitamin D in COVID-19

Numerous physiological, hereditary, and environmental factors account for the emerging disparity and fluctuations in the number of confirmed COVID-19 cases, morbidity, and mortality across different nations. Movement restrictions (lockdown) to reduce the exposure to COVID-19-infective cases to ensure social distancing. This measure to control COVID-19 is probably one of the best instruments policymakers incorporated throughout the globe to save their countrymen. Thereafter, COVID-19 risk somewhat minimizes; nevertheless, people are less exposed to sunlight, which has enhanced vitamin D deficiency risk. Vitamin D functions in various ways, including interaction with the nonspecific defense mechanisms, activation of Toll-like receptors, and/or increment in the levels of cathelicidins and β -defensins. This influences the acquired immunity by lowering immunoglobulin released by

plasma cells and pro-inflammatory cytokines production to modulate T cell function. Promising results further described vitamin D nutrients as an essential supplement in treating respiratory tract infections, autoimmune diseases, and pulmonary fibrosis. An increase in serum 25(OH)D is associated with increased beneficial bacteria and lowered pathogenic bacteria in the body.

A classic example is that of three hospitals of Southern Asian origins that conducted a retrospective multicentre study of 212 cases with laboratory-confirmed infection of COVID-19, with a depicted data related to clinical features and serum 25(OH)D levels. The results suggested that an increased serum 25(OH)D level in the body could either improve clinical outcomes or mitigate severe to critical outcomes. However, a decreased serum 25(OH)D level in the body could lead to a detrimental consequence.

The defensive effect of vitamin D against SARS-CoV-2 infection can be linked to its previous effect on other respiratory infections. This notion was further supported by a meta-analysis that conclusively affirmed that vitamin D intake is beneficial in acute respiratory tract infections. After having millions of the confirmed COVID-19 cases, evidence continually depicts the older populace and malnourished individuals as the most vulnerable groups in this disease condition. Univariate analysis in an Indonesian retrospective cohort study consisting of 780 confirmed cases of COVID-19 depicted that older patients, males sufferers with a pre-existing medical condition, and those with lower vitamin D levels were associated with an increased odds ratio of mortality. When controlling independent variables during epidemiology such as age, sex, and comorbidity, low vitamin D status is strongly associated with increasing cases of COVID-19 mortality. Seneca et al demonstrated that older people have an average serum vitamin D level of 26 nmol/L in Spain, 28 nmol/L in Italy, and 45 nmol/L in the Nordic countries. In Switzerland, the intermediate vitamin D level is 23 nmol/L in nursing homes; and data from Italy indicated that 76% of women over 70 years of age have vitamin D levels below 30 nmol/L. These estimates of low vitamin D levels among the elderly across Europe showed that the aging population represents the group with the highest risk of morbidity and mortality with SARS-CoV-2 infection.

The recommended dietary allowances (RDA) for Vitamin D are 10 µg/day and 15–20 µg/day for infants and adults, respectively. Additionally, the sources to supply Vitamin D account for a limited number of nutritional sources such as cod liver oil, catfish, mushrooms, etc. The content of most of the milk supplies in the US is added with 400 IU vitamin D per quart, and the same applies to the vegetative alternatives (soy milk, almond milk, oat milk, etc.). Currently, the majority of breakfast, including bowls of cereal and some orange juice brands, yogurt, margarine, and soy beverages, are fortified with vitamin D. This vitamin is usually added in two different forms that are vitamin D₂ (ergocalciferol) and D₃ (cholecalciferol) that collectively increase vitamin D in the blood. Based on previous studies, patients with respiratory disease, to rapid and safe increase serum 25(OH)D levels, and patients with low circulating levels (below 50 nmol/L) can be offered vitamin D supplementation of 50,000 IU twice a week. During the COVID-19 pandemic, it is crucial that all people in the hospital, including the patients and staff, take vitamin D supplements to raise 25(OH)D concentrations as an essential step in preventing infection spread.

Role of Vitamin E

Vitamin E, a fat-soluble vitamin, is a potent antioxidant and has the ability to modulate host immune functions. Vitamin E deficiency is known to impair both humoral and cellular immunity. However, few studies have shown that vitamin E supplementation might cause harmful effects on the incidence of infectious disease. A study among 50–69 years old adult smokers showed that vitamin E supplementation increases the risk of pneumonia. Similarly, supplementation of vitamin E (200 IU/day) did not have a statistically significant effect on lower respiratory tract infections in elderly nursing home residents. However, positive effects of vitamin E have been observed in the treatment of chronic hepatitis B in a small pilot RCT, where a significantly higher normalization of liver enzymes and HBV-DNA negativization, was observed in the vitamin E group. Similar results have been observed in a RCT in the paediatric population, where vitamin E treatment resulted in a higher anti-HBe seroconversion and virological response.

Role of Vitamin K in COVID-19

VITAMIN K one of the fat-soluble vitamins, is essential for synthesizing several proteins – factor II (prothrombin), factors VII, IX, and X involved in regulating blood clotting (coagulation). Natural vitamin K is found in two different forms: K1 (phylloquinone), an effective form of dietary vitamin K and mainly found in green leafy vegetables, and K2 (menaquinones). They are primarily of microbial origin, and sources are especially from fermented foods like cheese, curds, and animal livers. It is noteworthy to understand that these menaquinones are synthesized by human intestinal microbiota. The third form of vitamin K is K3 (menadione), which is synthetically or artificially produced. The dietary reference intake of vitamin K recommended by Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies is 120 mcg for adult males and 90 mcg for adult females. Research has revealed the role of vitamin K beyond blood coagulation. Vitamin K's consumption, combined with anticoagulant drugs such as warfarin, can threaten individuals who take them. Vitamin K and vitamin K-dependent proteins are vital for calcification (maintaining bone and cardiovascular health), energy metabolism, and inflammation. To lower the risk of vascular deformation, an adequate intake of vitamin K2 is found to be effective. This is because it activates matrix Gla protein (MGP), inhibiting calcium deposition in the vessel walls. Another importance of this vitamin K is its ability to act as a potent antioxidant reducing the lipid peroxidation in the cell by producing vitamin K-hydroquinone, a robust radical scavenging species. Vitamin K has been found to have an anti-inflammatory activity, which would probably modulate through NF- κ B signaling.

Typically, the risks for vitamin K deficiency in adults include high consumption of vitamin K antagonists like warfarin (which blocks the vitamin K-dependent pathway, reducing the body's ability to produce blood-clotting proteins) and individuals with liver diseases and disorders. Mothers who are on anticonvulsant medications (to prevent seizure) could act as a

risk factor for infants and can lead to a bleeding disorder known as vitamin K deficiency bleeding (VKDB) of the newborn. Excessive intakes of K1 and K2 forms of vitamin K are not related to abnormal coagulation, and no known associated toxicity has been reported yet. Nevertheless, in Menadione's case, it can interfere with glutathione activity (antioxidant), resulting in oxidative damage to the cell membrane. Menadione has also been reported to induce hepatic toxicity, jaundice, and hemolytic anemia.

Consequently, menadione is no longer suggested for vitamin K deficiency treatment. Vitamin K deficiency can contribute to excessive bleeding, poor bone development, increased risk of osteoporosis and fractures, as well as several cardiovascular diseases involving vascular calcification and atherosclerotic plaques. Reduced vitamin K levels have also been reported in COVID-19 patients. Several factors may contribute decreased dietary intake, high alcohol consumption, and excessive use of medications containing anticoagulants like warfarin during the lockdown.

Recently researchers observed the link between individuals with vitamin K status and COVID-19 outcomes. Coagulopathy is one of the primary features of poor outcomes in patients who develop sepsis from an infection. Similarly, coagulopathy has been observed in severe COVID-19 patients and is associated with poor prognosis, as observed by Tang et al in consecutive patients. One of the most common laboratory findings in COVID-19 patients is the elevation of D-dimers. Coagulopathy and disseminated intravascular coagulation (DIC) appear to be associated with high mortality rates. Among the parameters, the D-dimer peak was a strong predictor of COVID-19 mortality. The other laboratory markers recommended by the International Society of Thrombosis and Hemostasis (ISTH) for monitoring DIC formation are fibrinogen, prothrombin time, and platelet count.

Patients in the Intensive Care Unit (ICU) are at risk of vitamin K deficiency with elevated D-dimer protein levels. This deficiency reduces the functional levels of coagulation factors II, VII, IX, and X, predisposing them to develop coagulopathy, increasing hemorrhage risk, and DIC formation. DIC is well recognized for its function in contributing to multi-organ system failure due to the accumulation of thrombus in the microvasculature. Also, low vitamin K level appears to be associated with increased elastin degradation, preferably degrading the lung tissue, resulting in breathing difficulty in COVID-19 patients. Since COVID-19 patients with severe disease are associated with co-morbidities such as cardiovascular diseases, type II diabetes, or hypertension, which are linked to reduced vitamin K level it is hypothesized that low vitamin K levels might be associated with severity in COVID-19. Furthermore, a study conducted by Dofferhoff et al measuring the level of desphospho-uncarboxylated matrix Gla protein (DP-ucMGP, inversely related to vitamin K status) and comparing between COVID-19 patients and controls concluded that reduction of vitamin K levels in COVID-19 patients than the controls and is related to poor prognosis.

For the treatment of COVID-19 induced coagulopathy, the use of an anticoagulant is recommended. A study concluded that the use of unfractionated heparin (UFH) might be a better choice of anticoagulant for treating coagulopathy in COVID-19 patients when compared to low molecular weight heparin (LMWH).¹⁹⁸ However, the correct dose needs to be established. Simultaneously, the use of recombinant activated factor VIIa (rVIIa) is not recommended for COVID-19 patients. Likewise, Thachil et al suggested the need to switch the

patient receiving vitamin K antagonist (VKA) to direct oral anticoagulants (DOAC) for coagulation therapy to reduce laboratory testing frequency monitoring during this pandemic. Nevertheless, it is not applicable for patients with mechanical heart valves or anti-phospholipid syndrome. Since there is a risk of vitamin K deficiency in patients admitted to ICU, administering vitamin K supplements to patients during admission to ICU might help reduce the risk of vitamin K deficiency and further complications. However, other studies are still needed to verify the results. Notably, the prescription of anti-vitamin K anticoagulants is not recommended for pregnant or lactating women. It may place the newborn at an increased risk of vitamin K deficiency.

Furthermore, prolonged use of broad-spectrum antibiotics like cephalosporins can interfere with vitamin K synthesis by intestinal flora and lower vitamin K absorption level by altering gastrointestinal functioning, which should be considered during the infection. These studies illustrate that poor vitamin K status is linked to poor prognosis and worse outcomes. Thus, maintained vitamin K2 level is essential for better health, including cardiovascular, bone, and lung health. However, further studies are required to assess whether vitamin K administration improves the severity of COVID-19 patients

Conclusion; The big data presented by various previous studies depict the efficacy of fat-soluble vitamins such as vitamin A, D, E, and K in immune-modulation and lowering the severity of disease in patients with COVID-19 infection. These vitamins are pivotal in the maintenance and modulation of innate and cell-mediated, and antibody-mediated immune responses. The fat-soluble vitamins are functional in various ways, including increasing the levels of cathelicidins and β -defensins, regulating RONS production, and influencing the acquired immune system by reducing immunoglobulin secretion by plasma cells and pro-inflammatory cytokines production to modulate T cells function, etc. Vitamin A, D, E, and K boost the body's defense mechanism against COVID-19 infection and specifically prevent its complications such as cytokine storm and other inflammatory processes, leading to increased morbidity and mortality overemphasis. However, more detailed randomized double-blind clinical pieces of evidence are required to define the use of these supplements in preventing or reducing the severity of the COVID-19 infection.

Recommendations;

Based on the supportive evidence, it is crucial to take vitamins like vitamin A, D, E, and K in recommended portion to maintain a healthy immune system and physiology. Future studies are highly advocated to determine pharmacokinetics and pharmacodynamics with adverse drug reaction profile and cost. Apart from these fat-soluble vitamins, other micronutrients and minerals are also essential in maintaining adequate immunity. Eating vegetables and fruit containing the above vitamins daily is recommended to maintain a balanced diet. Supplementation of vitamin D can prove a crucial step to help prevent a worse prognosis in COVID-19.

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