Research paper

Vitamins and immune system: Is there any role in the prevention and treatment of COVID-19?

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Abstract
WHO declared COVID-19 a pandemic caused by coronavirus associated with mild to severe respiratory symptoms. Individuals with compromised immune system are more prone to developing COVID-19. This review paper is aimed at examining the effect of vitamins A, C, D, E, K and B-complex (vitamins B1, B6, B9, B12) on the immune system and share some evidences whether their supplementation can be helpful in the prevention, treatment, and management of COVID-19 patients. Only a few studies have been done to investigate the effect of supplementation of these vitamins in reducing the risk of respiratory tract infections. In this review, attempt has been made to summarize the possible benefits of the above mentioned vitamins to enhance the human immune response and suggest that their suitable supplementation in COVID-19 patients could be useful in the management of this infection. Rigorous clinical trials need to be conducted to confirm the putative benefits of vitamin supplementation to contain the spread of this disease.

Keywords: Viral infection; coronavirus; COVID-19; immune system; vitamins supplementation

1. Introduction

The current pandemic of COVID-19 is a devastating event and unfortunately no effective drug is available so far. In this scenario, a healthy immune system is the only weapon to combat this disease [1]. Among all living creatures, human immune system is a very powerful defense system which consists of different types of cells and chemical mediators that protect body from foreign invaders [2]. A balanced diet and healthy nutrition are the two key elements that can enhance the immune system [3], while an unbalanced and low nutritional diet can lead to a weak response to any viral infection such as COVID-19 [2].

Adequate amounts of vitamins are essential for a well-functioning immune system [4]. Recent investigations have explained the importance of vitamins supplementation in reducing the risk of COVID-19 infection [5]. Keeping in view the high mortality rate in elderly patients with weak immune system, this review is aimed at investigating the latest findings whether supplementation of nutrients such as vitamins A, C, D, E, K, B_1, B_6, B_9 and B_{12} could have an effective role in reducing the viral load of COVID-19 and also the duration of hospitalization of the affected patients.

2. **Methodology**

Search Strategy and Selection Criteria

In this systematic review all the searches were carried out through 'Google Scholar', 'PubMed', 'Embase', Science Direct, 'Scopus' and 'Researchgate'. Searches keywords included "Vitamins and Coronaviruses", "Vitamins and COVID-19", and "Vitamins and Immune System" "Vitamin A", "Vitamin B", "Vitamin C", "Vitamin D", "Vitamin E", "Vitamin K", "Folate", "Influenza", and "Respiratory Tract Infection". Seventy-seven papers with non-duplicate record were retrieved including screening of relevant titles and abstracts. Out of which only 53 studies related to coronaviruses and COVID-19 and vitamins were identified in addition to 3 preprints published during the last few months as shown in the Figure 1.

3. **Vitamins Supplementation in COVID-19 Management**

3.1 Vitamin A

Vitamin A also known as "anti-infection vitamin" is responsible for the anti-inflammatory factors involved in enhancing the immune system [2], and also the mucosal integrity, such as those of the respiratory tract which is required for the secretion of mucin for preventing the body against external invaders [6].

Vitamin A regulates antibody production, innate and adaptive immune system [5]. Its deficiency can lead to respiratory tract infection and results in impaired regeneration of mucosal membrane barrier that increases pathogenesis [5]. Increased expression of IL-12 and TNF-α in vitamin A deficiency may lead to unnecessary inflammatory responses [5]. Vitamin A is known for its protective role against lung infections, leading to a conjecture about a potential role in the prevention and management of COVID-19 [5]. In a study which included children between ages 2 to 8 years (n=79) having vitamin A and vitamin D deficiency were vaccinated with influenza virus and supplemented with these vitamins for over three seasons. The result showed an increased immune response against influenza virus vaccination [7]. In another study, vitamin A supplementation was found to reduce clinical manifestations and mortality and morbidity rates in pneumonia by shortening the length of hospital stay [8]. It has been suggested that vitamin A appears to have the potential to prevent lung infections [9]. However, the authors did not mention any specific dose of vitamin A supplementation [10].

3.2 Vitamin D

Vitamin D is a steroid hormone precursor that is produced in the skin under the action of thermal radiation (UV) yielding 7-dehydroxycholesterol also known as vitamin D3 or calcitriol [11]. Vitamin D has been reported to have a very crucial role in both innate and adaptive immune system [5, 12]. Vitamin D stimulates anti-microbial peptides cathelicidin and defensin. These peptides enhance the innate cellular immunity. Defensin enhances the anti-oxidative genes expression [5], while cathelicidin (LL-37) which is synthesized by macrophages and epithelial cells is necessary for induction of anti-bacterial and antiviral activity [13]. Role of vitamin D in decreasing the disease severity in patients of COVID-19 has been well documented. In a review, it is indicated that following exposure to severe acute respiratory coronavirus-2 (SARS-CoV-2), the adequate endogenous vitamin D levels in young adults would increase intracellular-glutathione and suppress ROS production and NF-kB expression [14]. However, in elderly people, vitamin D deficiency could lead to serious COVID-19 disease as these patients had been found to be with lower vitamin D levels [14, 15]. Other studies have shown that adequate

vitamin D levels may help in protecting the epithelium of respiratory system from pathogenic attack and thereby minimizing the risk of infection [5].

Various clinical trials have shown that vitamin D supplementation for the prevention of severity of respiratory infection led to variable results due to different amounts of vitamin D doses and the length of duration of the treatment (1 week to 8 months) [10]. Overall, vitamin D supplementation showed a protective effect against acute respiratory distress syndrome (ARDS) in a meta-analysis of 25 randomized controlled trials which included a total of 10,933 individuals [10]. These authors further suggested that during the COVID-19 pandemic, vitamin D supplements should be taken by the patients and staff in the hospitals to elevate their 25(OH)D levels up to 100-125 nmol/L to better combat the disease. However, clinical trials need to be conducted to investigate the appropriate doses to acquire these concentrations. Furthermore, an amount of 10,000 IU/d should be taken for a month followed by 5,000 IU/d to maintain these levels [10].

The COVID-19 mortality rate varies from country to country. In general, it is lower in the southern hemisphere as compared to the northern hemisphere [16]. It has been suggested that the northern hemisphere residents are relatively more prone to vitamin D deficiency due to less exposure to sun in winters than the people in the southern hemisphere where there is summer at that time (January-May) [5]. Therefore, in countries with high vitamin D deficiency there would be high rates of morbidity and mortality related to COVID-19 [17]. Probably, due to the widespread intake of vitamin D supplements in Norway, the mortality rate of COVID-19 has been observed to be relatively lower [5]. Moreover, individuals with insufficient vitamin D levels were also found to be more prone to having coagulopathy and weak immune function [18], and were more likely to require ICU admission [5]. However, the high mortality rates among the people in Brazil and Peru during their summer season indicate that further studies based on the determination of actual levels of vitamin D in these people are required to investigate the association of vitamin D levels and severity of the disease. It is reported that elevated levels of proinflammatory cytokine IL-6 has been observed in patients with COVID-19 admitted in ICU [19]. This event of activation or secretion of cytokines/chemokines in COVID-19 patients has been termed as '*cytokine storm*' [19]. The cytokine storm has been found as an important indicator of the severity of the infection, organ failure and death [19]. Furthermore, the levels of C-reactive protein (CRP), which is a marker of inflammation, have been shown to be associated with severe COVID-19 symptoms and vitamin D deficiency in patients with this disease [20].

Vitamin D has a key role during cytokine storm, which has been a major pathophysiologic factor in COVID-19 patients [21]. In a meta-analysis based on various studies covering 20,966 case subjects, it was observed that individuals with low vitamin D levels had high risk of pneumonia [22]. This is in line with the observations in some of the previous studies which have shown that vitamin D supplementation could reduce the risk of viral infection [5]. While the protective role of vitamin D against COVID-19 has not yet been investigated thoroughly, supplementation of this vitamin could potentially reduce the synthesis of pro-inflammatory cytokines and afterwards limit ARDS mortality rates in patients with this infection. Many clinical investigations have been planned to elucidate the effect of vitamin D supplementation in COVID-19 patients [5].

3.3 Vitamin E

Vitamin E is a lipid-soluble antioxidant [5]. Its deficiency can lead to a poor immune system that ultimately results in reduced proliferation of lymphocytes and less antibody production during infection [5]. Vitamin E involvement in modulation of PGE2 production that suppresses the T cell response shows its influence on innate and adaptive immune responses [5].

Vitamin E also has immune boosting property and carries a strong anti-oxidative activity which enables it to fight against foreign invaders such as bacteria and viruses. It also helps T-cell membrane to maintain its integrity [23,24]. The association between vitamin E levels and COVID-19 has not yet been studied directly. However, some of the related studies have pointed out the role of vitamin E in reducing the duration of influenza virus infection [5]. Although, the beneficial effects of vitamin E on immune system are appreciable, yet few investigations have been done describing the role of vitamin E administration in patients with COVID-19 infection. However, a recent review highlighted the immune-boosting potential role of vitamin D, C, and E in the management of COVID-19 patients [5].

3.4 Vitamin K

Vitamin K comes under the family of lipid-soluble vitamins [25]. Vitamin K has a therapeutic potential against various disease agents. These investigators further reported that vitamin K_3 had the potential to reduce the lung injury in an ARDS mouse model by inhibiting the activation of NF-κB factor. The putative mechanism was that an inflammatory cytokine TNF-α would bind to the TNF-α receptor (TNFR) to activate NF-kB signaling pathway, thereby triggering inflammatory responses that would switch on various inflammatory infections. For example, high level of NF-kB signaling activation was reported in individuals with acute lung injury or sepsis. The increased level of NF-kB p65 has been observed in both alveolar macrophages and peripheral blood mononuclear cells (PBMCs) in patients with acute lung injury. Furthermore, it has been reported that NF-kB activation is more prolonged in patients who do not survive from sepsis. These findings indicate that NF-kB activation is the main cause for respiratory inflammation and sepsis. It has been shown that vitamin K_3 has the potential to inhibit the activation of NF-kB. This suppression of NF-kB signaling by vitamin K_3 supplementation can reduce the mortality in ARDS. These observations are suggestive that vitamin K_3 supplementation may also prove helpful in treatment of COVID-19 infection. However, clinical trials would be required to investigate the effects of vitamin K_3 supplementation on COVID-19 patients as well as the exact dosages or protocol for supplementation. Regarding deficiency of vitamin K, elevated levels of inflammatory cytokine, IL-6 and CRP have been observed in patients with vitamin K deficiency [19]. The association of reduced coronary calcification and cardiovascular disease (CVD) with high intake of vitamin K has also been reported in some other studies [19]. To investigate the diagnostic role of vitamin K deficiency, the serum levels of prothrombin induced by vitamin K absence-II (PIVKA-II) have been measured in a cohort of COVID-19 patients (62 patients including 45 males with 68.4 years mean age and 17 females with 69.8 mean age) admitted in ICU [19]. The PIVKA-II levels of these patients indicated vitamin K deficiency two times greater in male patients compared to female patients (72.3% vs. 36.8%, respectively) [19]. In the same study, the association of IL-6 with vitamin K deficiency in these patients was also investigated to find out the anti-inflammatory role of vitamin K. The IL-6 levels of male patients were greater than levels in female patients [19]. Surprisingly, the severity of symptoms of COVID-19 infection was also greater in men than

women, and it could be due to the lower vitamin K and greater IL-6 levels in the male gender [19].

The above mentioned results suggest that vitamin K deficiency leads to the activation of T helper type 2 (Th2) storm along with the production of IL-2 during the early phase of COVID-19 [3]. This study showed that vitamin K deficiency was observed in almost all COVID-19 patients, and is more frequent in men compared to women, and the increased IL-6 levels in male were associated with vitamin K deficiency [19]. These findings suggest that vitamin K deficiency could be a possible risk factor in COVID-19 patients, especially in males. However, further investigation in clinical settings are necessary to obtain a conclusive evidence [19].

3.5 Vitamin C

Vitamin C is a water soluble vitamin. It is a good antioxidant and has the ability to scavenge free radicals produced by immune cells [6]. High concentration of vitamin C in leucocytes determines their function in regulation of immune activity primarily in neutrophils and monocytes [26]. It is also involved in T cell proliferation and immunoglobulin synthesis [6]. Vitamin C favors inflammatory responses through deregulation of pro-inflammatory cytokines IL-6 and TNF-α [5]. TNF-α is under investigation in the current pandemic and it has been observed that it facilitates the entry of SARS-CoV-2 into host cells [5]. Vitamin C has the ability to decrease the levels of TNF-α and ultimately increase IL-10 levels [5]. A Number of clinical investigations have pointed out that a dose of 1 gram vitamin C per day can elevate IL-10 levels. IL-10 interacts with IL-6 to control inflammation by negative feedback in COVID-19 patients [5]. Another clinical trial showed that intravenous (IV) delivery of vitamin C had a positive influence on decreasing inflammation in respiratory tract infection [27]. Vitamin C can also decrease the risk of sepsis often seen in COVID-19. The effective role of high vitamin C dose has been reported in 50 COVID-19 Chinese patients with severe symptoms [28]. However, this observation needs to be supported by more clinical trials [28]. In this regard, vitamin C supplementation appears to be a prudent option in micronutrient deficient individuals that are at a risk of COVID-19 infection and could be helped in avoiding this disease through support to their immune system [5]. Therefore, several clinical trials are being conducted to evaluate the benefits of vitamin C supplementation in COVID-19 patients.

Furthermore, it has been shown that vitamin C through its anti-oxidant property plays a protective and beneficial role in other viral diseases. Vitamin C supplementation boosts respiratory defense mechanism. It not only protects against viral infections but also reduces the duration and severity of symptoms through its anti-histamine property. In a study on elderly patients with pneumonia and tuberculosis, low levels of vitamin C in their plasma have been reported [29]. Administration of this vitamin reduced both severity and duration of the infection in these patients [29]. This protective role against pulmonary infections makes it an important nutrient supplement to be useful in COVID-19. During COVID-19 infection, cytokine storm has been shown to shoot up with the progression of disease [22]. Vitamin C has been suggested to function as a defense against this storm [22]. In a case study, a patient with ARDS has been treated with high-dose of vitamin C administration [30]. It was shown that patient did not require the ventilator after 5 days which was considered quite a remarkable gain, however this patient had also received anti-viral medications [30], suggesting that further work would be needed.

3.6 Vitamin B

B-complex vitamins have also been implicated in boosting our immune system. Vitamin B_1 deficiency can lead to inflammation, infiltration of T-cells and overproduction of cytokines i.e., IL-1, TNF-α and IL-6 [5]. Deficiency of this vitamin can also increase the levels of eicosanoids. Cobalamin (vitamin B_{12}) has a vital role in the synthesis of white blood cells. Its immunomodulatory factor to increase the production of cytotoxic T cells against viral infections makes it an important player in the immune system [31]. Vitamin B_{12} deficiency can impair expression of immunoglobulins [32], and cause a decrease in number of lymphocytes along with suppression of NK cell activity and decrease in $CD4^+/CD8^+$ ratio [31].

Pyridoxine (vitamin B_6) plays an essential role in T-cell and interleukins production [32]. It functions as a cofactor in the synthesis of antibodies and cytokines. Therefore, its deficiency may result in impaired antibody production, lymphocyte growth and maturation, and T-cell activity [32]. It is reported that vitamin B_6 deficiency is associated with the depletion of thoracic duct lymphocytes and also with reduced lymphocyte proliferation [32]. Therefore, B_6 is important in body's defense system to fight infections [33]. However, its beneficial effects towards COVID-19 have not been investigated. Future studies are required to evaluate the possible role of vitamin B_6 supplementation in the prevention and control of COVID-19 [34].

Vitamin B9 (folate) deficiency, has been found to be associated with weak immune response which was manifested by altered proliferation of circulating T-lymphocytes during infection [13]. Moreover, $CD4^+$ and $CD8^+$ ratio was also altered by decreasing $CD8^+$ proliferation [13]. All the above mentioned observations point towards a very significant role of B-complex vitamins on human immune system. However, no clinical trials have been designed to obtain some concrete evidence regarding any beneficial role of B-complex vitamins (B1, B6, B9, B12) in the prevention and management of COVID-19. Most of the trials which have been conducted so far use a combination of all the major vitamins including B vitamins [35].

Conclusion and future prospects

Various research studies have demonstrated that lipid-soluble vitamins (A, D, E and K) and water soluble vitamins C and B have a profound influence on human immune system. Since immuno-compromised individuals, especially the elderly people are more vulnerable to viral infections such as COVID-19, there is a possible role of these vitamins in COVID-19 patients. Supplementation of higher doses of these vitamins is likely to have a beneficial effect during COVID-19 infection. Currently, a number of clinical investigations are being conducted to elucidate the effective and potential role of vitamins supplementation to prevent, manage and treat the COVID-19 infection. Hopefully, the outcomes of these trials will clarify the use of these vitamins in the prevention of viral diseases including COVID-19. So far, vitamin D appears to be most promising as indicated by a recent report by Alison Caldwell from the University of Chicago suggesting a protective role of this vitamin in Black people [36]. The Editor of Lancet Diabetes & Endocrinology opined that we should wait for the outcomes of a number of clinical trials which are underway in countries where pandemic situation continues to worsen to obtain some conclusive evidence about the protective role of vitamin D against COVID-19 [37]. It is important to note that supervised supplementation with vitamins would be associated with negligible risk to human health. However, the benefits could be enormous, especially when there is not sufficient availability of an effective vaccine against COVID-19.

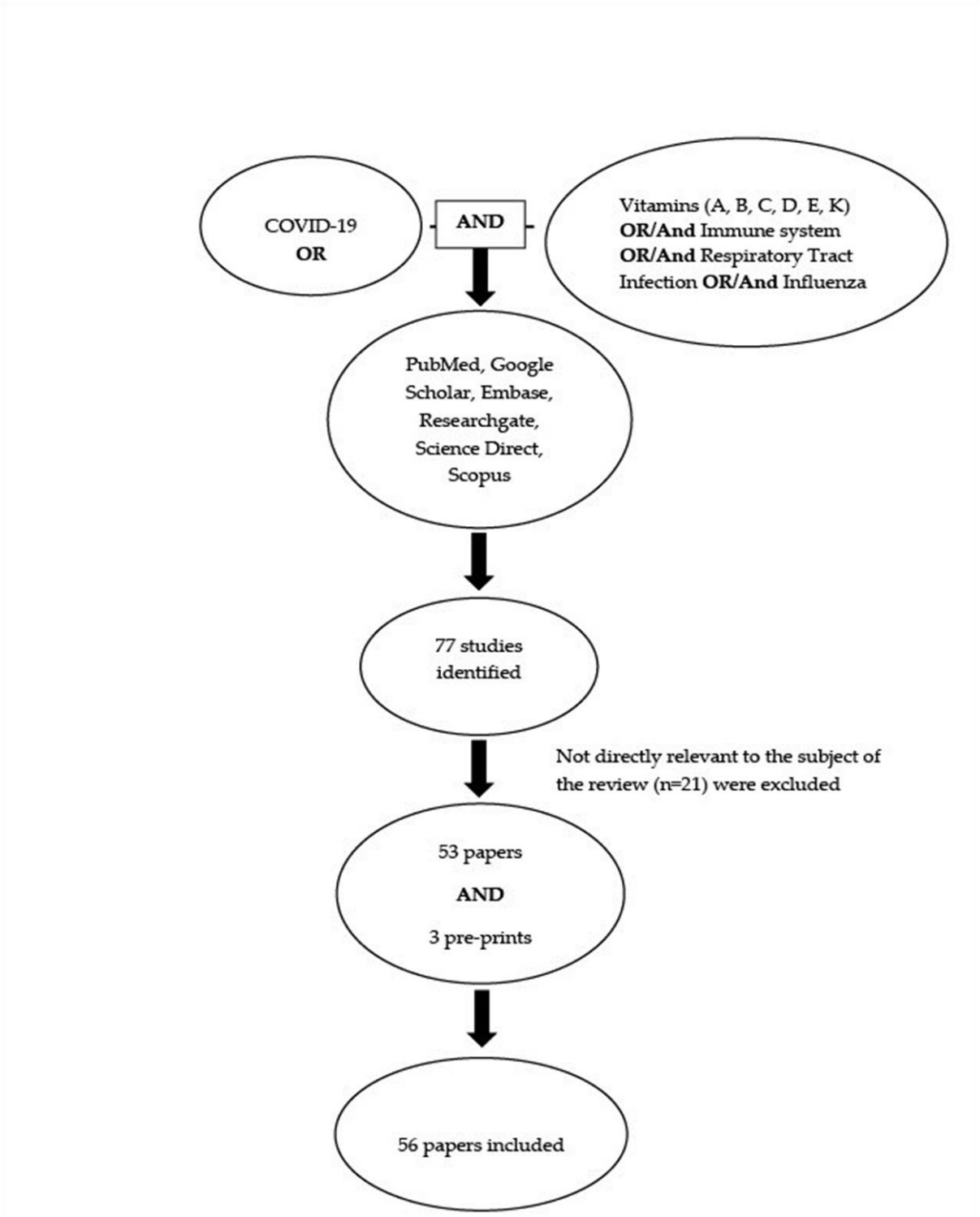

Figure 1: Procedure of articles selected for systematic analysis during this study.

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