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(REVIEW ARTICLE)

Vitamin supplements in the Era of SARS-Cov2 pandemic

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Abstract

Recently, the rapid and extensive spread of a novel human RNA betacoronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing a worldwide public health emergency, originated in Wuhan, China. The disease caused by this new coronavirus, called "COVID-19", is very contagious. Although most of infected subjects are asymptomatic or present with mild flu-like symptoms, the rapid spread of the virus has resulted in a significant amount of serious interstitial pneumonia that may quickly develop into severe acute respiratory distress syndrome (ARDS), septic shock, sepsis-induced coagulopathy and fatal multiorgan dysfunction. Hence, the unabated spread of the disease demands an immediate need to explore all the plausible therapeutic and prophylactic strategies for reducing the high morbidity and mortality of this infection. At present, there is no vaccine or certainly effective antiviral treatment for human SARS-Cov-2 and the mainstay of clinical management is prevalently symptomatic treatment combined with a panel of drugs having variable and uncertain efficacy. Unfortunately, no many drugs have yet been approved to treat human SARS-Cov-2 infection and many agents are administered in off label route; several options are being studied to control or prevent clinical manifestations of this infection, including monoclonal antibodies, antiviral and anti-cytokine agents, antibiotics, and other drugs. Given that several vitamins are known to have antimicrobial properties and immunomodulatory activity, a potential role of vitamins in the COVID-19 treatment was investigated.

Keywords: SARS-CoV-2 infection; COVID-19; Vitamin supplements

1. Introduction

In these months, the diffusion of a novel human RNA betacoronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is causing a worldwide public health emergency, originated in Wuhan, China. The disease caused by this new coronavirus is commonly called "COVID-19", which is the acronym of "coronavirus disease 2019" [1].

Although most of infected subjects by SARS-Cov-2 are asymptomatic or present with mild flu-like symptoms, such as fever, cough, arthromyalgias and fatigue [2], but also diarrhea, ageusia and anosmia [3,4] , the rapid spread of the virus has resulted in a significant amount of serious interstitial pneumonia that may quickly develop into severe acute respiratory distress syndrome (ARDS), septic shock and fatal multiorgan dysfunction that are the most severe clinical manifestations of SARS-Cov-2 infection. The severe progression of COVID-19 seems to result from the so called "cytokine storm", due to massive SARS-Cov-2-induced release of pro-inflammatory mediators and cytokines,

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particularly interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα), linked to viral replication and leading to cytokine release syndrome-like [5]. "Sepsis-induced coagulopathy" [6,7] may be a potential serious complication of SARS-Cov-2 pneumonia and this event is associated with poor prognosis [8,9]. Acute pulmonary embolism [10,11], microthrombotic occlusion of small pulmonary vessels [12,13] and disseminated intravascular coagulation [14] have been reported in critical patient with COVID-19.

Hence, the unabated spread of COVID-19 demands an immediate need to explore all the plausible therapeutic and prophylactic strategies for reducing the high morbidity and mortality of this infection. At present, there is no vaccine or certainly effective antiviral treatment for human SARS-Cov-2 and the mainstay of clinical management is prevalently symptomatic treatment combined with a panel of drugs having variable and uncertain efficacy [15].

Originally, the therapeutic approach was to repurpose some drugs already used to treat two previous infections caused by other human coronaviruses as severe acute respiratory syndrome (SARS) [16] and Middle East respiratory syndrome (MERS), taking advantage also from chinese experience data [17]. At the moment, a multitude of compounds are under investigation for the treatment of this emerging disease, including vaccines, monoclonal antibodies, antiviral and anti-cytokine agents, antibiotics and other drugs. Unfortunately, no many drugs have yet been approved to treat human SARS-Cov-2 infection and many agents are administered in off label route. Several options are being studied to control or prevent clinical manifestations of the infection and many studies and clinical trials have been started and are currently ongoing in all Countries affected by this severe pandemic.

Despite some vitamins are known to have antimicrobial properties and immunomodulatory activity, at the moment poor relevance regarding a potential role of vitamins supplementation in the therapeutic armamentarium against Sars-Cov-2 we have found. In this narrative review any benefits from vitamins in the COVID-19 treatment was investigated.

2. Discussion

We following provide and discuss data from our research in evaluating evidence regarding a potential role of vitamins and their supplementation in patients with SARS-Cov-2 infection.

2.1. Vitamin C

There is evidence that patients with acute infections, in particular critically ill patients [18], have low circulating levels of Vitamin C, due prevalently to metabolic consumption [19,20] and several experimental and clinical studies have proved antimicrobial properties and antiviral effects of Vitamin C [21-24].

It has been shown, in vitro and in vivo studies that Vitamin C might reduce the risk of infections and exerts immunomodulatory functions, particularly in high concentrations and in form of dehydroascorbic acid [22, 23, 25-29]. Vitamin C may have beneficial effects in patients with viral infections by increasing α/β interferon production and downregulating pro-inflammatory cytokines production [30,31]. Additionally, Vitamin C is a powerful antioxidant compound against free radicals and reactive oxygen species [32,33]. There is evidence that Vitamin C infusion may improve sepsis and sepsis-induced multiorgan dysfunction and reduce mortality in patients with sepsis and severe acute respiratory failure [18,21,22]; improvement of lung inflammation, induced by influenza A virus/H1N1, was also reported in patients taking Vitamin C [34]. Past controlled trials have reported significantly lower incidence of pneumonia in vitamin C-supplemented individuals, suggesting that Vitamin C might prevent the susceptibility to lower respiratory tract infections under certain conditions [35]. Results from other new larger trials are awaited and further data on severe respiratory viral infection are needed.

Fruit and vegetables as citrus fruits, kiwi, mango, strawberries, papaya, tomatoes, green leafy vegetables, and broccoli are natural sources of Vitamin C [33] and recommended daily allowance (RDA) of Vitamin C is 75 and 90 mg for women and men respectively [33,36,37]; additional supplement of 35 mg daily is suggested in smokers, given that these subjects have lower Vitamin C status than nonsmokers [33]. Other evidence indicates that the RDA for Vitamin C could be too low and suggests that 200 mg daily is the optimum intake of Vitamin C for adult population, particularly during stress conditions [38].

Vitamin C is generally safe and well tolerated, even in large doses; gastrointestinal disorders were observed in some individuals taking Vitamin C at dosage higher than 2 g daily and increased risk of kidney stones was also reported, due to high amounts of Vitamin C intake [33]. Despite there is no sure evidence on benefit of Vitamin C in patients with SARS-Cov-2 infection, waiting for the results of further studies recently initiated [39], we believe that nutritional Vitamin C supplementation is advisable and Vitamin C infusion should be evaluated in hospitalized patients.

2.2. Vitamin D

In addition to its role in maintaining bone integrity, Vitamin D also stimulates the maturation of many cells, including immune cells. It is well known that Vitamin D receptors are expressed on immune cells, as B cells, T cells, and antigen-presenting cells and it has been proved as Vitamin D has the capability to modulate innate and adaptive immune responses; moreover, there is evidence that Vitamin D deficiency is associated with increased susceptibility to common infections, like sepsis, pneumonia, influenza and other infectious diseases [40,41]. Data from a recent systematic review and meta-analysis [42] regarding the effect of Vitamin D-calcium co-supplementation on inflammatory biomarkers confirm beneficial effect on plasma levels of C-reactive protein while such a beneficial effect was not observed for IL-6 and TNF-α concentrations.

Vitamin D is a fat-soluble vitamin naturally contained in very few foods (fatty fish, fish liver oils, beef liver, cheese and eggs) and available as a dietary supplement; it is also endogenously produced when ultraviolet rays from sunlight strike the skin. In nutritional supplements and fortified foods, Vitamin D is available in two forms, D2 (Ergocalciferol) and D3 (Cholecalciferol) and current RDA for Vitamin D is 600 IU (15 μg) daily for adults up to 70 years of age and 800 IU (20 μg) daily for those over 70 years [43,44]. A high number of healthy adults have been reported to have low levels of Vitamin D, mostly at the end of the winter season [45]; in addition, housebound or institutionalized people may have Vitamin D deficiency as well as many elderly people, which have limited exposure to sunlight [46].

Since the hallmark of Vitamin D intoxication is hypercalcemia and its sequelae, which are associated with a rise in serum 25-hydroxyvitamin D levels, calcemia and 25-hydroxyvitamin D plasma levels monitoring is recommendable particularly in long-term Calciferol-treated patients. Vitamin D intoxication generally presents with non-specific symptoms that may vary and often include anorexia, weight loss, polyuria, and heart arrhythmias. The condition eventually leads to vascular and tissue calcification with subsequent renal and cardiovascular damage [47,48].

We have not found strong evidence regarding Vitamin D efficacy in COVID-19 patients, however, given that adult individuals are at increased risk to develop Vitamin D deficiency (serum levels <30 nmol/L), oral supplementation with prophylactic dosage of Vitamin D would not be inadvisable.

2.3. Vitamin E

Vitamin E is a group of eight lipidsoluble compounds, known as chromanols that are widely distributed in the plant kingdom and alpha-tocopherol has the highest bioavailability in the human body [49].

The antioxidant/radical scavenging activity of Vitamin E is well recognized as well as other non-antioxidant functions such as its role in cardiovascular diseases and cancer prevention and its protective functions against neurodegenerative diseases, as Parkinson's and Alzheimer's [50-53]. Apart from the antioxidant function, necessary to maintain membrane cells integrity and bioactivity, anti-inflammatory effects and immunomodulatory function of Vitamin E were also described [50,54]. In particular, animal and human studies have shown that Vitamin E deficiency causes impairment of humoral and T cell-mediated immune functions that may be restored by vitamin E repletion [54-61]. There is also evidence that Vitamin E supplementation may reduce inflammatory cytokines production and improve T cells proliferation through directly impacting membrane integrity, signal transduction and T cells differentiation [59,62-65]; moreover, Vitamin E supplementation improves leukocyte phagocytic capacity [60,66-69] and neutrophils and NK cells functions. Data from other studies show that Vitamin E supplementation was associated with 63% lower rate of re-hospitalization among older adults previously hospitalized with pneumonia [70] and lower incidence and shorter duration of upper respiratory infection in elderly nursing home residents (>65 years) [71].

Yet, other studies have not confirmed a strong efficacy of Vitamin E supplementation on immunological and infectious state of participants [72-74]. The discordant results on effectiveness of Vitamin E interventions may be attributed to differences in studies population and in Vitamin E administration; moreover, polymorphisms in Vitamin E-metabolism related genes, including apolipoprotein E, lipoprotein lipase, scavenger receptors and alpha-tocopherol transfer protein may influence the effect of Vitamin E supplementation. Genetic background has been identified as an important non-modifiable factor in both the bioavailability and cellular activity of Vitamin E [75].

The human diet contains different Vitamin E-related molecules and, fortunately, Vitamin E is widespread in nearly all foods and as a result most people are not at risk of deficiency, unless nutrient absorption is impaired. The cause of Vitamin E deficiency, characterized by peripheral neuropathy and ataxia, is usually fat malabsorption or genetic abnormalities in lipoprotein metabolism [76].

Seeds (wheat germ, sunflower seeds) and nuts (almonds, hazelnuts, pine nuts, peanuts and others) are among the best sources of Vitamin E, but also many animal-based foods (seashell, salmon, trout) are good sources of Vitamin E as well as vegetables (extra-virgin olive oil, red sweet pepper, beet greens, broccoli) and fruit (avocado, mango, kiwifruit) [77-79].

In healthy individuals, the RDA of Vitamin E is 15 mg daily of alpha-tocopherol; this is equivalent to 22 IU of natural source Vitamin E per day, or 33 IU from synthetic sources. Although deficiency is rare, Vitamin E supplementation above current dietary recommendations has been shown to enhance the function of the immune system and affects host susceptibility to infectious diseases, such as respiratory infections, reducing risk of infection or mitigating several viral and bacteria, particularly in older individuals. Vitamin E may enhance digitalis and insulin effects, then caution is recommended in patients on digitalis and insulin treatment. Moreover, prolonged use of high doses of Vitamin E (> 560 mg/800 IU daily) may be associated with increased bleeding tendency in patients with Vitamin K deficiency; increased risk of bleeding must be evaluate in patients treated with anticoagulant drugs. In patients taking high doses of Vitamin E gastrointestinal disorders, as nausea, diarrhea, flatulence, abdominal pain, and other side effects as asthenia, headache, blurred vision and dermatitis were reported [80,81]. Despite antioxidant and anti-inflammatory properties of Vitamin E are well demonstrated, as well as its immunomodulatory and antimicrobial activity, at the moment there are no significant evidence regarding the efficacy of Vitamin E supplements in patients with SARS-Cov-2 infections.

2.4. Vitamin A

Vitamin A is an unsaturated 20 carbon cyclic alcohol, also known as Retinol [82,83], that is part of a broad group of substances called Retinoids [84] including Retinaldehyde and Retinoic acid [85-87].

Vitamin A exerts many functions and metabolic effects via its interrelationship with hormones such as thyroid, insulin, and corticosteroids, and it is essential in a lot of physiologic processes, including epithelial differentiation, bone development and growth, reproduction, embryogenesis, antioxidant, hematopoiesis, brain development and vision [88-93]. Vitamin A is also essential for modulating and proper functioning of the immune system [94-96], particularly by regulating T cell–dependent responses [97-99]. Moreover, it has been observed as Vitamin A regulates cytokine expression in respiratory epithelial and macrophage cell lines by modulating IL-6 expression, so an essential role of Vitamin A in healthy immune response to respiratory pathogens it has been hypothesized. [100,101]. There is evidence that Vitamin A deficiency is more common during infection [98] and, especially in childhood, increases the morbidity and mortality risk from gastrointestinal and pulmonary tracts infections [102-104]. In addition, it has been reported that Vitamin A supplementation may reduce severe morbidity and mortality from infectious diseases such as measles, measles-related pneumonia, human immunodeficiency virus infection, diarrheal disease and malaria [105-108].

Vitamin A supplements are indicated for prevention or treatment of Vitamin A deficiency states. Vitamin A deficiency may occur as a result of inadequate nutrition or intestinal malabsorption but does not occur in healthy individual receiving an adequate balanced diet. For prophylaxis of Vitamin A deficiency, dietary improvement, rather than supplementation, is advisable [109,110]. The RDA for Vitamin A (Retinol Activity Equivalents) is 300 to 700 μg for children and approximately 700 to 900 μg for adults, amounts that may be provided by a normal diet [36, 111]. Some foods of animal origin (liver, fish liver oil, eggs, milk and butter) mainly contain Retinol [112]; vegetables and fruit (carrots, spinach, broccoli, peas, tomato, sweet potato, extra-virgin olive oil, apricots, peach) mainly contain carotenoids [113], in particular β-carotene [83], which are converted into Retinol in the liver.

Vitamin A at doses not exceeding the physiologic requirement is usually nontoxic; headache, nausea, vomiting, and irritability have been observed after excessive intake of Vitamin A. Moreover, high doses of Vitamin A can be toxic, leading to more serious symptoms as well as liver injury, jaundice, enlargement of the liver and spleen, portal hypertension and cirrhosis; excess of Vitamin A during pregnancy has been linked to birth defects. Too much Vitamin A can be harmful and Vitamin A toxicity can be critical and even result in death [114,115].

When considering Vitamin A supplementation, the potential benefits must be weighed against the risk of harm; the evidence for supplementation with Vitamin A is currently limited to expert opinion and is not backed up by rigorous trials. Further studies and clinical trials are needed to establish effective and safety of Vitamin A supplementation [110].

Apart from poor animal studies [116,117], searching for Vitamin A and SARS-Cov-2 and COVID-19 we have not found significant items, then, at the moment, we do not recommend Vitamin A supplementation in these patients. However, Vitamin A could be a promising option for the treatment of this novel coronavirus and the prevention of lung infection.

2.5. Group B Vitamins

B Vitamins have various functions but they act predominantly as coenzymes involved in cell energy metabolism and organic molecules synthesis [118-120]. In addition to these functions, they also play an essential role for the immune system that is composed of high turnover cells [121]; in particular Folic acid, Vitamin B12 (Cobalamin) and Vitamin B6 (Pyridoxine) exert direct regulatory effects on the immune response [122].

For instance, in animal and human studies Vitamin B6 and B12 have been shown to play an important role in the cytotoxic immune response mediated by Natural Killer and CD8+ T cells [123-125] and their deficiency was correlated to impairment of Natural Killer cell activity and B lymphocytes reduction due to their inhibited proliferation [124,126,127]. In addition, deficiency in Vitamin B6 leads to a lower activity of thymus in rats [127,128] while in the elderly it was associated with impaired T helper cell functions and IL-2 production [129]. An inverse relationship between Vitamin B6 and some inflammatory markers as C-reactive protein and IL-6 receptor was also observed [130,131].

Folate deficiency also causes negative effects on some immune functions [132,133]; moreover, since the metabolism of Folate and Vitamin B12 is closely related [134], the balance between these vitamins is also essential for the immune response so much that Natural Killer cell activity was found impaired by excessive levels of unmetabolized free Folic acid [135].

Suboptimal status of one or several B Vitamins might be found particularly in elderly individuals; in the case of Vitamin B12, the high prevalence of atrophic gastritis in this population results in disturbed absorption of Cobalamin and also of Vitamin B6 [136-140]. Although insufficient supply of Folate is common in many population groups and causes many health problems [138,140], the reported potentially negative effects of high Folate intake due to excessive supplementation or consumption of fortified foods should be considered. This is especially relevant in light of the balance between Vitamin B12 and Folate.

As foods of animal origin are the only natural source of Vitamin B12, deficiency may occur in subjects avoiding these foods or consuming low amounts like vegetarians or vegans or low-income populations especially in developing countries [141,142].

Although there are some evidence also regarding potential antimicrobial of Vitamin B2 (Riboflavin) [143] and B3 (Nicotinamide) [144] as well as weakening host immune response by B Vitamins shortage, we have not found strongly significant data to advise group B Vitamins supplementation in SARS-Cov-2 infected patients to enhance their immune response.

2.6. Vitamin K

Vitamin K is essential for the synthesis of hepatic blood coagulation factors, as factors II (prothrombin), VII, IX, and X [145,146] and it is well known that some anticoagulant drugs [147], employed in anti-thrombotic prophylaxis and treatment, act by inhibiting Vitamin K [148,149].

Green leafy vegetables and others as Brussels sprouts, broccoli, cauliflower and cabbage are rich dietary sources of Vitamin K; instead fish, liver, meat, eggs and cereals contain smaller amounts [150] and currently adequate intakes of Vitamin K are 90 and 120 μg daily for women and men, respectively [150,151].

Given that acute pulmonary embolism [10,11] and microthrombotic occlusion of small pulmonary vessels [12,13] may complicate the SARS-Cov-2 infection and were reported in critical patient with COVID-19, Vitamin K supplementation seems irrational and is not indicate in these patients. Moreover we have not found sufficient evidence proving the opposite.

3. Conclusion

SARS-CoV-2 infection is causing a worldwide public health emergency and several options are being studied to control and prevent clinical manifestations of this infection; many studies and clinical trials have been started and are currently ongoing in all Countries involved in this severe pandemic.

At the moment, several compounds are under investigation for the treatment of this emerging disease, but it seems that poor relevance has been devoted to the nutritional aspects in these patients. We have evaluated the evidence regarding a potential role of vitamins in the therapeutic armamentarium for patients with SARS-Cov-2 infection: the most

significant data concern Vitamin C and Vitamin D so we suggest the patients to modify their nutritional choices by preferring foods richer in these vitamins; however Vitamin C and Vitamin D supplementation should be consider at least in selected patients. About Vitamins A and Vitamin E we found weaker evidence as well as poor data regarding group B Vitamins, while we consider Vitamin K supplements harmful and not rational. We hope scientific community will quickly conduct further studies to provide more certainties and indications in this field.

Compliance with ethical standards

Disclosure of conflict of interest

The Authors declare no conflict of interest.

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