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Review Article

Toxicity of Food Supplements as An Adjuvant for COVID-19 Treatment or Prevention

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ABSTRACT

Commercially available food supplements, especially vitamins and minerals, are becoming increasingly popular in the era of COVID-19 pandemic. Sales of food supplements increased dynamically because of the belief that they could be more effective than conventional antiviral or corticosteroid drugs as well as missing the specific medical therapy for preventing or treating this disease. The greatest interest is associated with immune-related nutrients and antioxidant agents, including vitamin C, vitamin D, vitamin E, selenium (Se), and zinc (Zn). These are currently under clinical investigation for possible application in the prevention and management of COVID-19. This review summarizes postulated mechanisms of commonly used supplements suggested reducing the duration and severity of viral infections by improving immune response. Their toxicity in the context of potential adverse effects is also discussed. Whether these molecules and the amount could hurt patients with COVID-19 are research questions worth evaluating. Considering both efficacy and safety, evidence supporting larger intakes of specific nutrients with immune-boosting and/or antioxidant properties needs further research. Until relevant responses are provided, age and gender related tolerable upper intake levels for vitamins and minerals should be considered to avoid weight gaining as an additional risk factor of developing complications during the disease course, besides the risk of inappropriate doses associated with toxicity. Herein, high-quality information respecting specific nutrients proposed to have positive effect against COVID-19 is disseminated and certain research gaps are addressed, requiring the research on the health effects of supplements to be tightly correlated to age, nutritional status, wellbeing and particular to existing co-morbidities.

Keywords: Coronavirus, Mineral, Nutrient, Supplementation, Vitamin

Introduction

During the COVID-19 pandemic, numerous pharmacological agents and an array of antivirals, corticosteroids, or combinations have been attempted to treat patients worldwide, but no efficacious intervention is available. The pathogenesis of this disease is complex involving suppression of host antiviral and innate immune response, induction of oxidative stress, and hyper-inflammation defined as the "cytokine storm", most often associated with acute lung injury, tissue fibrosis, and pneumonia [1, 2]. In a lack of a novel or alternative coronavirus intervention, some essential micronutrients ranging from treating deficiencies to preventing myriad diseases have been proposed to provide protection from serious outcomes of COVID-19. Hereupon, vitamins C, D, and E and zinc and selenium are the key nutrients that possess well-established immunomodulatory effects, with benefits in infectious disease. A more detailed description of the possible invert relationship of antiviral properties of the vitamins C, D and E, and minerals selenium (Se) and zinc (Zn) and pathophysiology of COVID-19 is given below in the specified section for each micronutrient. The most relevant activities of these micronutrients and probable clinical outcomes that might withstand COVID-19 during the SARS-CoV-2 life cycle are presented in Figure 1. Whether these

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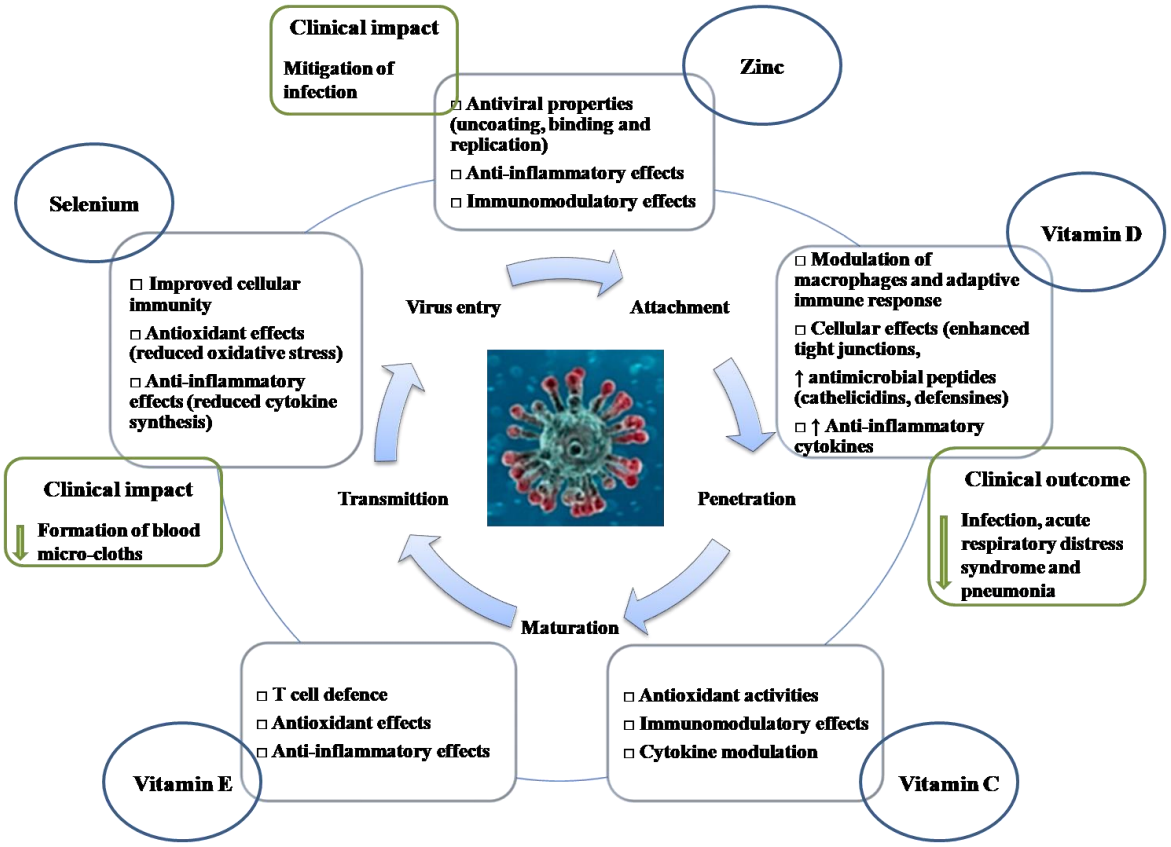

Figure 1. Protective activities of vitamin C, D and E, and Se and Zn against COVID-19

nutrients can help patients with COVID-19 is a question worth to be researched. However, commonly available supplements, such as vitamins and minerals, reduce the severity and duration of viral infections by improving immune response. Food supplements, in particular antioxidants, are currently under clinical investigation of potential application in prophylaxis and adjuvant therapy for COVID-19, but no randomized controlled trials confirm a direct link between nutritional supplementation and COVID-19 manifestations [3, 4]. According to Hamulka *et al.* [4], who analyzed the results of PLifeCOVID-19 Online Studies conducted during the first and second pandemic wave, convincing evidence is missing to support the increased intake of some nutrients or nutritional supplementation in COVID-19 prevention and treatment in healthy and well-nourished individuals. Anyway, partially based on the experience with other viral infections as well as seeking an effective alternative, sales of multivitamins and vitamin C supplements in UK have significantly increased by 93% and 110%, respectively, while Zn supplements sales in USA have increased by 415% [3, 5]. Namely, in an application-based community survey, data of a self-reported three months regular dietary supplement usage in the first waves of the pandemic up to 31st July 2020, by subscribers in the UK (372 720), the USA (45 757), and Sweden (27 373), have shown a lower risk of testing positive for SARS-CoV-2 in women taking probiotics, omega-3 fatty acids, multivitamin or vitamin D supplements, with no clear benefits for men nor any effect of vitamin C, garlic or Zn supplementation [3]. One of the survey disadvantages is missing information on neither exact intake of the supplements used nor the dosage regimens to establish a relationship of supplements dosage or intakes with disease outcomes. However, in a case of massive and risky, but popular overuse of food supplements, and in addition insufficient convincing evidence for increased use, people should be appropriately advised to their rationale use, especially those who are more likely to search medical information from online sources rather than to consult healthcare professionals. Irresponsible individuals who choose to self-diagnose, self-treat, or use the information without consulting with healthcare practitioners or pharmacists are at greater risk because food supplements, unlike

food, are not generally recognized as safe, nor can be assumed that they are all safe [6]. Without appropriate knowledge on side effects, biotransformation or bioavailability of the supplements, relatively high doses are generally recommended in COVID-19 pandemic and administered to large populations. Although, in some cases, alternatives are missing, patients should be warned against the delusive safety of food supplements and inappropriate administration of huge doses.

One recent study has addressed the significance of personalized or population-based strategies, which are canalized to reduce the burden of COVID-19. Analysis of the genetic variants associated with altered vitamin D levels, Zn and Se have shown that *DHCR7/NADSYN1* rs12785878 and *CYP2R1* rs10741657 are involved vitamin D synthesis as potential risk factors of severe COVID-19. Although few patients participated in the study, according to the authors, the obtained results combined with other factors such as nutrigenetics, micronutrient, status, lifestyle, and clinical parameters may be helpful to improve the antiviral response, especially in those people suffering from micronutrient deficiency [7]. In a study of Nedjimi [8], micronutrient deficiencies are claimed to be the main reason for the increase of the individual susceptibility to immune dysfunction, thus based on antiviral and anti-inflammatory effects, Zn, Cu, and Se were highlighted as a promising immune-enhancing agent against COVID-19 and its new strains. To guarantee the population is better prepared for new COVID-19 variants, high-quality clinical trials have to provide an answer whether sufficient amounts of vitamins D, C and E, and minerals zinc and selenium as an essential component of normal immune function can be dietary supplied or supplementation with these micronutrients is necessary as well as to define their relevant intakes, if supplementation is appropriate. Moreover, studies of individual micronutrient requirements are urgently needed, especially with the emergence of new variants of SARS-CoV-2.

Vitamin C

Biological function and potential application in COVID-19 management

A plethora of naturally found food products is rich in vitamin C. Among the fresh fruits, blackcurrants, green kiwi fruits, papayas, oranges, lemons, strawberries, pineapples, mangos, elderberries, grapefruits, limes, tangerines,and raspberries are considered to be the best natural source of vitamin C. Vegetable species rich in vitamin C included red and green peppers, parsley, kale, broccoli, Brussel sprouts, cauliflower, cabbage, zucchini, green peas, etc. [9]. Balanced nutrition can easily provide the updated recommended dietary intake for vitamin C, e.g., in healthy adults 95 mg/day [10]. When vitamin C supplementation is necessary, such as in common cold and other infections, it is important to know that oral vitamin C in smaller doses, 500 mg to 3 g daily, provides anti-inflammatory and antioxidant effects. Improvement of various immune cell functions is a principal mechanism of vitamin C's preventive and treating role during infections. According to Carr and Maggini [11], dietary vitamin C prophylactic intakes should be in a range of 100-200 mg/day (adequate to avoid saturating plasma levels above 200 mg/day).

In contrast, due to the increased inflammation and metabolic demand in existing infections, vitamin C doses need to be significantly higher up to several grams. Supportive treatment with vitamin C in the management of COVID-19 is based on its immunomodulatory effect, taking into account the massive host immune response initiated by SARS-CoV-2 and able to provoke the excessive release of proinflammatory cytokines and reactive oxygen species leading to oxidative stress [12]. The capacity of the body to use vitamin C during infection is increased because of scavenging oxygen free radicals and decreasing the gene expression of proinflammatory cytokines, and vitamin C levels can become depleted. Thus, patients may need higher doses with the severity of the infection [13]. To better understand the potential and safety of vitamin C as a part of COVID-19 treatment, often administered intravenously in a range of 15 to 24 g daily, an increasing number of clinical trials is planned or in a process already [14]. One recent pilot trial has shown that the addition of a high dose of vitamin C infusion (24 g per day for seven days) to the standard care treatment for severe COVID-19 did not affect ventilation-free days but may provide a potential benefit in oxygenation and IL-6 level, without adverse events observed [15]. There are also clinical trials that investigated vitamin C use as a therapeutic adjuvant for acute respiratory distress syndrome (ARDS) and septic shock as characteristic features of a more severe COVID-19 infection. Fowler *et al.* [16] reported a

Table 1. Age and gender related tolerable upper intake levels for vitamin C, D and E [21, 24, 44]

	Vitamin C (mg/day)		Vitamin D (IU/day)		Vitamin E (mg/day)	
Age (years)	Male	Female	Male	Female	Male	Female
0-0.5	NE[1]	NE[1]	1000	1000		
0.5-1	NE[1]	NE[1]	1500	1500		
1-3	400	400	2500	2500	200	200
4-8	650	650	3000	3000	300	300
9-13	1200	1200	4000	4000	600	600
14-18	1800	1800	4000	4000	800	800
Pregnancy		1800		4000		800
Lactation		1800		4000		800
19+	2000	2000	4000	4000	1000	1000
Pregnancy		2000		4000		1000
Lactation		2000		4000		1000

[1]NE (not established) - only recommended vitamin C sources are food and infant formula

significant reduction of 28-day all-cause mortality and intensive care unit days with parenteral vitamin C 50 mg/kg every six hours for 96 h, but without significant improvement in disease severity scores, C-reactive protein levels, or thrombomodulin levels compared with placebo in patients with sepsis and ARDS. Giving a combination of intravenous vitamin C, hydrocortisone, and thiamine did not improve longevity or exclude the need of vasopressor administration compared to hydrocortisone alone in patients with septic shock [17]. The analysis of clinical trials and/or research papers found under the search using terms such as virus diseases, respiratory insufficiency, coronavirus and sepsis, revealed that parenteral application of vitamin C in high doses seems to be a safe approach, especially in critically ill patients [18]. However, they concluded that more evidence for vitamin C effectiveness is needed at leastwise.

Safety concern

Although the body's storage capacity for the water-soluble vitamins is low and vitamin C has a generally safe profile, certain concerns regarding potential health risks of high vitamin C doses. Adverse effects which vitamin C at high intakes may induce include diarrhoea, nausea, heartburn, abdominal cramps, and other gastrointestinal disturbances due to the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract [19]. Moreover, high doses of vitamin C, even if effective to prevent certain complications of COVID-19 infection, may be difficult to be reached when using orally available forms of vitamin C, e.g., food supplements. High vitamin C intakes have also been reported to increase urinary oxalate and uric acid excretion, which may further stimulate the formation of kidney stones, especially in patients with pre-existing hyperoxaluria [20, 21]. In addition, vitamin C can act as a pro-oxidant contributing to oxidative damage [21], so considering the main pathological damage in COVID-19 infection, vitamin C supplementation should be carefully applied to avoid further damage complication of patient's oxidative status. Conflicting results can be found in the literature regarding the risk of oxidative damage associated with high vitamin C intakes to induce chromosomal and/or DNA damage and possibly contribute to cancer development [22, 23]. In Table 1 are given upper intakes for vitamin C from food and supplements. According to US Institute of Medicine [21, 24], long-term intakes of vitamin C above the upper limit may increase the risk of adverse health effects, but given levels defined as tolerable upper intake levels exclude medical conditions when vitamin C doses are recommended and supervised by health care practitioners. However, wide range of dosing of vitamin C (oral daily dose of 500 mg to parenterally administered dose of 24 g) in clinical trials aiming to examine this micronutrient as a part of acute COVID-19 treatment, in combination with standard therapy i.e., hydroxychloroquine, or with other supplements for prevention, shows lack of strong evidence for vitamin C can prevent or treat COVID-19 seeking unique purposed administration.

Vitamin D

Biological function and potential application in COVID-19 management

Vitamin D has hormone-like activities being

an important factor in regulating calcium metabolism and possesses immunomodulatory activities enrolling the innate and adaptive immune system. Vitamin D can improve innate immunity through macrophages and monocytes and shift the response of dendritic and T-cells toward a more tolerable and anti-inflammatory behavior [25]. Two forms of naturally occurring vitamin D are ergocalciferol (vitamin D_2), found in yeasts and cholecalciferol (vitamin D_3) which is endogenously synthesized from 7-dehydrocholesterol in skin exposed to sunlight. Both forms are further metabolized first in the liver to 25-hydroxyvitamin D (25(OH)D) and then in the kidneys into active metabolite calcitriol (1,25-dihydroxyvitamin D or $1,25(OH)_2D$), which exerts its endocrine and immune effects by binding to the vitamin D receptor in the cell nucleus. To maintain the physiological blood levels of vitamin D (approximately 40 ng/mL), ingestion of 4000-6000 IU daily is required, especially when exposed to the sun is reduced [26]. In view of vitamin D status assumptions, geo-mapping is usually considered an approach taking into account the different amounts of sun to which people are exposed. The majority of vitamin D (up to 90%) is acquired via the sun action on the skin, and hence geographical location is accounted as the most important factor to ensure adequate vitamin D levels. However, data referring to countries with abundant sunlight, such as Brazil or Thailand, have indicated a higher prevalence of vitamin D insufficiency. This finding suggests the probable increase in vitamin D deficiency at a global level gives dimension to other influent factors, such as individual exposure to the sun, lifestyle, age, gender, skin pigmentation, dietary intake, and air pollution since living in urban areas was related to low serum 25(OH)D levels [27, 28]. One comment pointed to Africa as a region where the vitamin D status is even worse in a context of a worldwide vitamin D deficiency, opposite to the extensive sunshine [29]. Sun exposure is considered the main tool leading to optimal vitamin D status compared to diet. Since vitamin D is not highly abundant in food, postulating other alternatives to overcome poor statuses, such as food fortification or vitamin D supplementation. In a group of oily, vitamin D_3-rich fish are salmon, mackerel, and sardines, with egg yolk being another important food source, significantly variable in vitamin D amounts, which is not preferred due to the relatively high cholesterol content [30].

As previously noted, many people are deficient in vitamin D and supplement with this vitamin to become sufficient and to optimize immune function and bone health. Furthermore, recent studies have correlated vitamin D sufficiency with a lower risk of death from COVID-19. According to Grant *et al.* [31] vitamin D stimulates the production of cathelicidins and defensins that can destabilize microbial membranes thus lowering the viral replication rates. Vitamin D analogues may increase the expression of antimicrobial peptide cathelicidin in macrophages, natural killer (NK) cells and epithelial cells lining the respiratory tract, and hence reduce susceptibility to nasocomial infections such as pneumonia, sepsis and central line infection [32]. Cathelicidin synthesis may be induced through activation of vitamin D when an invading microorganism triggers toll-like receptors (TRLs) to increase the activity of the mitochondrial enzyme 1α-hydroxylase, which subsequently stimulates the intracellular conversion of 25(OH)D to $1,25(OH)_2D$ (Figure 2). The last is an active form that binds to and activates the vitamin D receptor (VDR) via autocrine mode. Hereupon, retinoid X receptor (RCR) complexes with the VDR and binds to the allied vitamin D response element (VDRE) in the promoter region of $1,25(OH)_2D$ target genes. It activates transcription of the vitamin D responsive genes such as cathelicidin gene leading to increased cathelicidin production [33]. Moreover, an active metabolite of vitamin D, calcitriol ($1,25(OH)_2D$) can modulate tolerance in antigen-presenting cells (APC) by decreasing the expression of major histocompatibility complex class II (MHC-II). A reduction in the proinflammatory cytokines is associated with an inflammation of the lining of the lungs, leading to pneumonia and increased levels of the anti-inflammatory cytokines.

The most justified role that may be interesting for the prevention and treatment of patients with severe cases of COVID-19 regarding frequent coagulopathy is high vitamin D supplementation showing decreased generation of thrombin and clot density *in vitro* [34]. However, without studies confirming specific benefit to COVID-19 patients, administration of vitamin D in high doses (above 4000 IU/day) is rather based on a high prevalent poor vitamin D status in critically ill patients, such as a retrospective study reporting mortality to be significantly correlated to low vitamin D levels (< 20 ng/mL) [35]. Five-month lasting

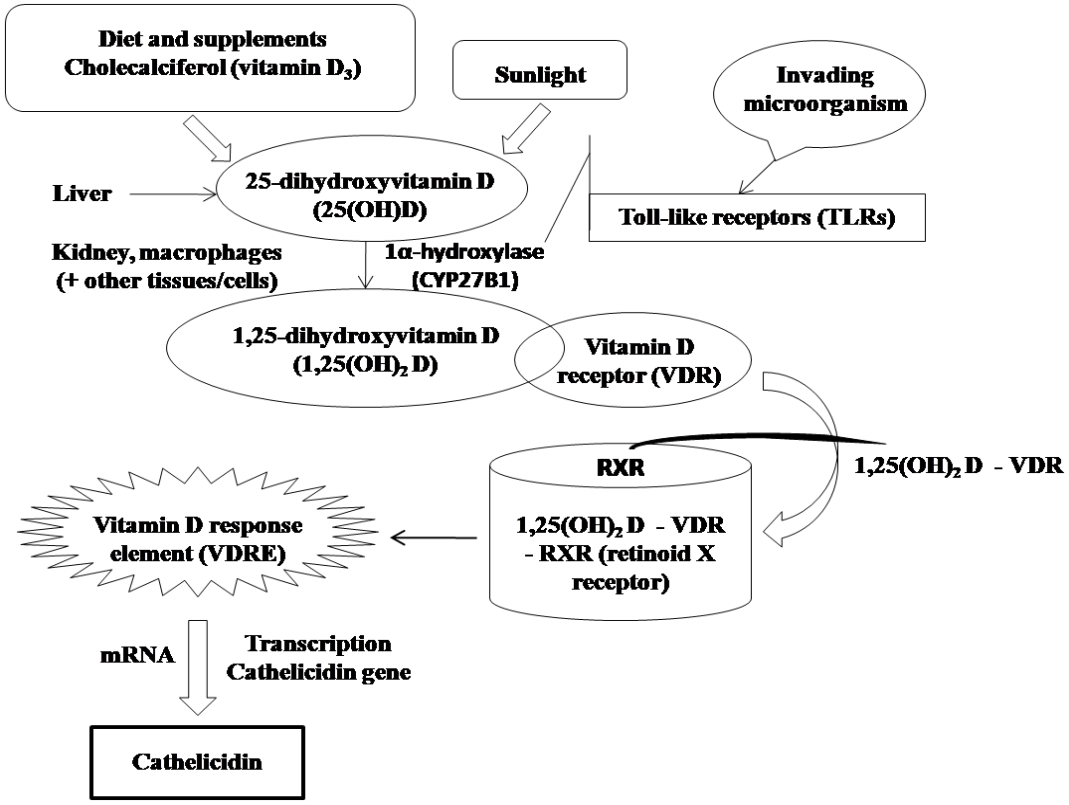

Figure 2. Antimicrobial peptide synthesis (e.g., cathelicidin) through activation of vitamin D and toll-like receptors (TLRs) induced by invading microorganism

multicenter, double-blind, randomized, placebo-controlled trial comprising 240 hospitalized patients with severe COVID-19 conducted in Brazil, revealed that a single dose of 200,000 IU vitamin D_3 are safe and effective in increasing 25-hydroxyvitamin D levels, without significant difference in any other investigated clinically relevant outcomes (admission to intensive care units (ICU), length of hospital stays, mechanical ventilation requirement, mortality rate) [36]. It was concluded that vitamin D_3 supplementation could not support the treatment of COVID-19 patients with certain limitations of the study underlined by the authors, such as heterogeneity and size of the sample and co-existing diseases of the patients appealed complex medical treatment. An observational cohort study of 175 critically ill COVID-19 patients with vitamin D deficiency (25(OH)D < 12 ng/mL) who received a single dose of 300,000 IU vitamin D_3 intramuscularly failed to confirm a reduction on the need for intubation, length of hospital stays as well as inhospital mortality [37]. Lakkireddy *et al.* [38] have reported that vitamin D oral supplementation of 60,000 IU daily for a specific period of time determined by the individual's BMI, the initial level of vitamin D and the formulation significantly reduced the inflammatory markers associated with COVID-19 by improving the serum vitamin D level to 80-100 ng/mL without any side effects. A short-term high dose vitamin D regimen is widely investigated among moderate to severe ill COVID-19 patients, and it is generally reported as a safe approach. In the hope of preventing COVID-19, it is suggested that adults likely to be deficient receive a higher dose of 4000 IU vitamin D per day for the first four weeks and then reduce to 800 IU-1000 IU/day [39]. In general, doses above the maximum limit of 4000 IU/day should be avoided since it is well known that excess amounts of vitamin D are toxic.

Safety concern

In particular, long-term vitamin D consumption in excess of 4000 IU could lead to hypercalcemia because vitamin D increases calcium absorption in the gastrointestinal tract. Vitamin D toxicity may result in marked hypercalcemia with total calcium greater than 11.1 mg/dL, hypercalciuria, and high serum 25(OH)D levels, usually greater than 150 ng/mL [40]. Hypercalcemia, in

turn, can lead to plethora of adverse events such as nausea, vomiting, muscle weakness, neuropsychiatric disturbances, pain, loss of appetite, dehydration, polyuria, excessive thirst, and kidney stones. In postmenopausal women, 50 to 79 years of age, randomly assigned to long-term (seven years) combined administration of 1000 mg/day elemental calcium and 400 IU/day vitamin D or a placebo, the risk for kidney stones increased by 17% [41], while shorter clinical trials (from 24 weeks to five years) of vitamin D supplementation alone or with calcium in adults pointed to higher risks of hypercalcemia and hypercalciuria [42, 43]. The US Food and Nutritional Board established upper limits for vitamin D [44]. The note that signs and symptoms of vitamin D toxicity are unlikely at daily doses up to 10,000 IU, but even intakes lower than the upper limits might have manifest adverse health effects over time. Since they found serum levels in a range of 30-48 ng/mL to be associated with increase in rates of all-cause mortality, risk of certain types of cancer (e.g., pancreas) and cardiovascular events, and falls and fractures among older adults, a general recommendation is to avoid serum 25(OH)D levels above 50-60 ng/mL. Regarding this suggestion, experts considered that gaining vitamin D levels through safe sun exposure cannot lead to excessive amounts and toxicity because vitamin D_3 is thermally activated and partially converted to non-active forms [44]. However, according to two case reports, frequent use of tanning beds may significantly contribute to an increase in vitamin D, which often leads to 25(OH)D levels in a range of 150-200 ng/mL [45, 46]. People should avoid excessive doses of vitamin D in hopes of preventing or treating COVID-19 with reference to cases of renal failure, calcification of soft tissues, including coronary vessels and heart valves, cardiac arrhythmias, and even death associated with consumption of dietary supplements that contained excessive vitamin D amounts [40, 47, 48]. Overall, people should continue to adjust daily vitamin D consumption in consistence with the recommended daily allowance and tolerable upper intake level (Table 1).

Vitamin E

Biological function and potential application in COVID-19 management

Vitamin E, comprising eight biologically active tocopherols and tocotrienols, is a micronutrient with antioxidant properties naturally found in the oily fraction of nuts and oilseeds. It is important for the maintenance of good vision, reproduction, and the health of the brain and skin [49]. The most biologically active is alpha-tocopherol, but beta-, gamma-, delta-tocopherols, 4 tocotrienols, and several stereoisomers may also have important biologic activity. Vitamin E deficiency is known to impair both humoral and cellular immunity, leading to increased viral pathogenicity and the generation of specific viral mutations [50]. Few mechanisms have been postulated as being responsible for an improved immune response, such as decreased production of nitrogen oxide resulting in prostaglandin E2 down-regulation and inhibition of cyclooxygenase-2, initiation of T-lymphocyte signals, and modulation of the Th1/Th2 balance, as well as inhibition of protein kinase C, thus reducing superoxide free radical production in neutrophils and macrophages [51, 52] (Figure 3). Regarding this potential, the effectiveness of vitamin E supplementation for the prevention of respiratory diseases is discussed but has not been demonstrated yet since it has not been confirmed in randomized controlled trials. Daily vitamin E supplementation in 33 elderly subjects with immune deficiencies improved the immune system activity at a comparable level to immune system of the control group consisting healthy adults [53]. Daily supplementation with 200 IU of vitamin E for a period of one year indicated reduced incidence of upper, but not lower respiratory tract infections in nursing home residents [54]. A study considering 50-69 years old adult smokers revealed that vitamin E supplementation increases the risk of pneumonia [55]. Because of disturbed oxidant-antioxidant balance resulting in excessive lipid peroxidation of biological membranes and serious outcomes in the most severely affected patients with COVID-19 (e.g., alveolar damage, pulmonary edema) [1], vitamin E ingestion may be effective to reduce the production of superoxides, but further research must unravel this potential.

Safety concern

Common consumption of vitamin E reach foods is not associated with adverse health effects, neither relatively large amounts of vitamin E (up to 1500 IU/day of the natural form or 1100 IU/day of the synthetic form) taken by adults for months to years were noticed to cause apparent harm [21]. Occasionally, muscle weakness, fatigue,

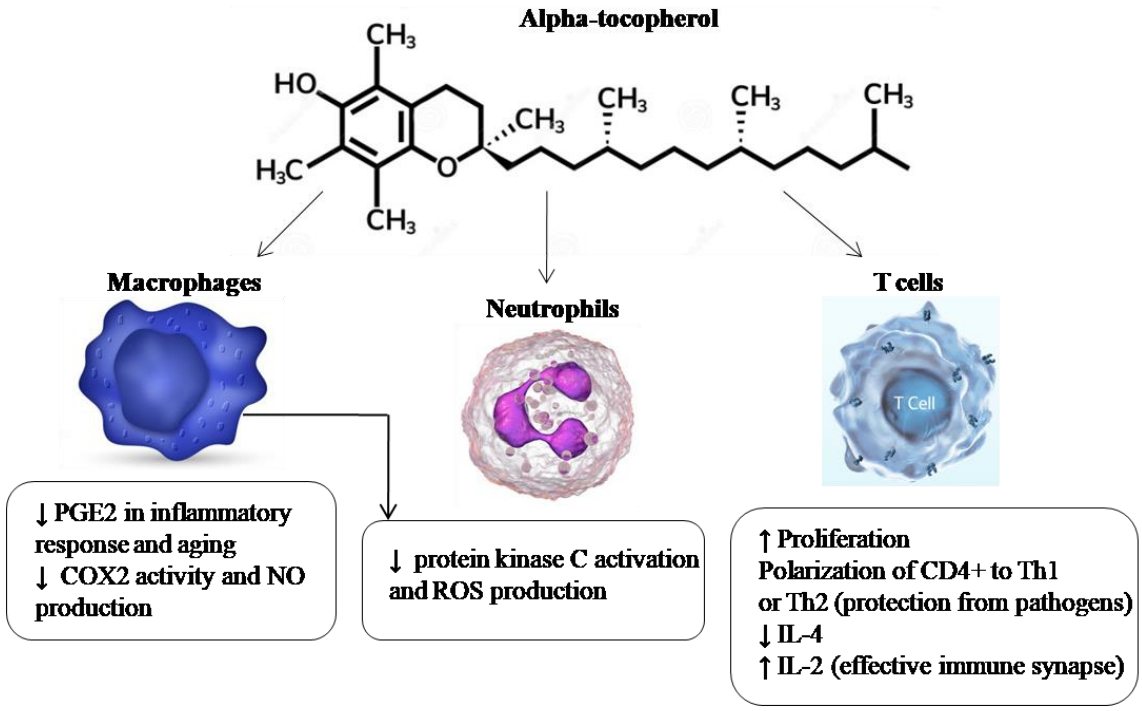

Figure 3. Effects of vitamin E on the immune system. Treatment with vitamin E leads to proliferation of T cells (e.g., CD4+), activation of immune system and modulation of regulatory cytokines (e. g. IL-2, IL-4) [51, 52]. PGE2 - prostaglandin E2; COX2 - cyclooxygenase 2; NO - nitric oxide; ROS - reactive oxygen species (e.g., superoxide free radical); Th/Th - T helper cells; IL-2 - interleukin 2; IL-4 - interleukin 2

nausea and diarrhea may occur. The most significant risk is bleeding that is uncommon unless the dose of vitamin E is > 1000 mg/day or concomitantly administered with oral anticoagulant drugs coumarin or warfarin. However, even lower doses of alpha-tocopherol supplements inhibited platelet aggregation *in vitro*. An increased risk of hemorrhagic stroke has been noticed in Finnish male smokers who consumed 50 mg alpha-tocopherol per day for an average of six years [56]. As well as in a large US trial in which participated male physicians consumed 400 IU (180 mg) of synthetic vitamin E every second day for eight years [57]. In the second trial, the vast majority of the participants took aspirin, which may also contribute to bleeding.

Depending on the potential of vitamin E to induce hemorrhagic effects, the Food and Nutrition Board of the US Institute of Medicine [21, 24] has established upper limits for vitamin E intake (Table 1). The defined upper limits by the US Institute of Medicine [21] (≤ 1000 mg/day) refer to all supplemental forms of alpha-tocopherol with the risk of adverse effects appears to be very low at the highest intakes, but long-term intakes above 1000 mg/day increase the risk of adverse health effects. According to two meta-analyses of randomized trials, even significantly lower doses of vitamin E than the established upper limit is a safety concern. The first meta-analysis included 19 clinical trials in total, of which nine tested vitamin E alone, and the rest tested vitamin E combined with other vitamins or minerals. All analyzed trials involving 135 967 patients with chronic diseases receiving an average dose of 180 mg or 400 IU vitamin E per day (dosages ranged from 7.5 to 900 mg/day), and pointed to increased risk of death, particularly for dosages greater than 150 IU/day [58]. The second meta-analysis included 68 randomized trials with 232 606 participants, has shown that average dose of 569 IU (256 mg/day) of vitamin E administered alone or in combination with up to four other antioxidants (vitamin A and C, selenium, β-carotene) and aiming to prevent diseases, in fact may increase mortality [59]. In contrast with the belief that high-dose of vitamin E supplements (up to 900 mg/day) may protect against certain chronic diseases, such as cardiovascular

disorders or decrease the risk of prostate cancer, one study reported an increased risk of prostate cancer with vitamin E supplementation (180 mg/day as *dl*-alpha-tocopheryl acetate) [60]. Unlike, Huang *et al.* [61], reviewing published articles failed to find a clear relationship between vitamin E supplementation benefits and safety concerns in healthy individuals at risk of certain chronic diseases (cardiovascular diseases, cataract, macular degeneration, cancer).

Regarding benefits and risks associated with vitamin E supplementation for prevention and treatment of COVID-19, available data are insufficient. This is partially due to the lack of validated biomarkers for vitamin E intake and status, which may help to relate intakes to possible clinical outcome. However, well-controlled clinical trials are required to provide a relevant answer to whether high doses of vitamin E (equal or even above 1000 mg/day) are appropriate to reduce the risk of SARS-CoV-2 infection and/or disease severity.

Zinc

Biological function and potential application in COVID-19 management

Zn can be naturally found in high concentrations (> 1.2 mg/100 kcal of a product) in certain foods, such as meat (lamb, beef), shellfish, root vegetables and leafy grains, while other types of meat (pork, poultry), nuts, legumes and whole grain cereals are reported to be good food sources of zinc (< 1.2 mg/100 kcal) [62]. Zn is recognized as an essential trace element in the human nutrition due to its structural role (integrity of proteins and cell membranes), regulatory action (regulation of gene expression via action on transcription factors) and catalytical function (works as a co-factor for different metalloenzymes known as Zn dependant enzymes). Zn homeostasis might affect ACE-2 expression [63], which is mainly expressed on pneumocytes type 2 and metallothionein and matrix metalloproteinases [2]. Zinc-deficient subjects, especially within the older population, may lead to delayed wound healing, lymphopenia and increased susceptibility to infection [64]. These authors examined the impact of chronic Zn deficiency on T and B cell lymphopoiesis, myelopoiesis and erythropoiesis in mice and based on the obtained results hypothesized that both anemia and T cell lymphopenia associated with chronic zinc deficiency may be consequence of a greater sensitivity of their precursor cells to Zn deficiency and elevated corticosterone in humans also. In a case of COVID-19, leukocytosis with neutrophilia and lymphopenia was associated with poor prognosis, whereas the retrieved lymphocite counts were observed to improve patients' clinical state [65]. Regarding the immune function, Zn is crucial for T-cell maturation and differentiation, thus preventing the premature apoptosis of immature T cells, consequently altering Th1/Th2 ratios or even decreasing total T-cell count [2]. Zn deprivation leads to a decreased ratio of type 1 to type 2 T-helper cells with reduced production of T-helper type 1 cytokines like interferons (IFN), and compromised T-cell mediated immune defense [66]. In this context, Zn supplementation may help to stimulate endogenous interferon production and to inhibit SARS-CoV-2 replication, in addition to unspecific reactions of innate immunity cells such as production of type-I IFN as well as chemokine and tumor necrosis factor alpha (TNF-α), which provide activation of endothelial cells and better vascular adhesion [67]. Beside the essential role in cell-mediated immune function, Zn is an important component of the pathogen-eliminating signal transduction pathways leading to neutrophil extracellular traps formation. Further, it is a modulator of the proinflammatory response targeting the main regulator of the proinflammatory response, transcription nuclear factor kappa B (NF-κB) and regulating the level of inflammatory cytokines [68]. Effects of Zn on different immune cell types and inflammatory factors are rather described as balancing than activating or inhibiting [2]. According to Wessels *et al.* [2], it sounds contradictory that Zn increases induced production of reactive oxygen species in platelets since it prevents tissue disruption by reducing the high levels of inflammatory mediators (e.g., reactive oxygen species). Nevertheless, a certain level of reactive oxygen species is vital to inhibit platelet aggregation and exactly to this reason, Zn might be effective in preventing vascular complications in COVID-19 patients. Additionally, the possible benefit of Zn supplementation in COVID-19 may be related to inhibiting the ability of Zn ions to the coronavirus RNA-dependent RNA polymerase activity *in vitro* [69]. Wessels *et al.* [2] reviewed the potential impact of Zn supplementation on COVID-19 pathogenesis due to improved mucociliary clearance, strengthened epithelium integrity, decreased viral replication, preserved antiviral immunity, reduced risk of hyper-inflammation

as well as minimized secondary infections. In this review, preventive supplementation of subjects from risk groups was suggested, however the need of randomized and controlled trials to assess the effect of Zn as a therapeutic option for COVID-19 was also accentuated. One retrospective study showed a positive correlation between the high prevalence of Zn deficiency and the COVID-19 cases in Asian countries. The study stated that it is not clear whether Zn supplementation after hospital admission can reduce the severity of COVID-19 due to insufficient data on the relationship among Zn levels, COVID-19 infection and mortality [70]. In a randomized clinical trial of ambulatory patients diagnosed with SARS-CoV-2 infection, 10-days treatment with high-dose Zn gluconate (50 mg), ascorbic acid (8000 mg), or a combination of the two supplements did not significantly decrease the duration of symptoms compared with the standard of care [71]. Pal and coworkers [67] recently reviewed interventional clinical trials (some of these still ongoing) which included Zn intake alone or in combination with other micronutrients (vitamin C, D, B_{12}) and drugs (hydroxychloroqine, choroquine, azithromycin) and concluded that the ratio benefit-risk is in favor of Zn supplementation in COVID-19 patients, arguing the importance of the results of incomplete trials.

Conclusions of meta-analyses assessing the Zn supplementation effect in common cold are variable depending on characteristics of studied participants and dosage regimen, type of given Zn salt, cold duration [72, 73], and thus cannot be used as a baseline to predict eventual benefit in COVID-19 infected individuals. In addition, compared to placebo, Zn supplementation revealed adverse effects such as nausea, vomiting, and changes in taste.

Safety concern

According to US Institute of Medicine [74] Zn is well tolerated, but acute adverse effects of high Zn intake include loss of appetite, abdominal cramps, diarrhea, and headaches. One case report has described severe nausea and vomiting occurred within 30 minutes of ingesting 4 g of Zn gluconate (570 mg elemental Zn) [75]. Zn toxicity can also occur in chronic forms such as low copper status, altered iron function, reduced immune function, and reduced levels of high-density lipoproteins, resulting in Zn daily intake in 150-450 mg [76]. Significantly lower Zn intakes of approximately 60 mg/day for up to 10 weeks have been found to negatively affect the copper status [74].

Long-term Zn supplementation of 80 mg/day that lasting 6.3 years on average was associated with increased number of hospitalizations for genitourinary problems, indicating that chronic Zn administration may induce deteriorations in normal functioning of genitourinary tract [77]. Moreover, the long-term intake of Zn and in particular in large doses (300 mg/day) can suppress the immune function [67]. The Food and Nutrition Board of the US Institute of Medicine has established upper limits for Zn intake (Table 2) suggesting that long-term intakes above these limits increase the risk of adverse health effects [74]. Having in mind the uncertain risk benefit ratio of Zn supplementation, when COVID-19 patients choose to take Zn in larger doses than 40 mg/day as a part of a medical treatment, they should be under the care of a physician for continuous monitoring of the levels of Zn to obtain maximum therapeutic efficacy as well as initiation of possible adverse health effects.

Selenium

Biological function and potential application in COVID-19 management

The most often naturally existing form of Se is selenoproteins, with several other chemical forms typical for biological materials including organic Se compounds (selenomethionine, dimethylselenide) and inorganic selenites and selenates. Selenomethionine is a predominantly present form in foods, known to be an important dietary source of Se and commonly used in nutritional supplements, beside selenite and selenate. Naturally, Se-rich foods are Brazil nuts, broccoli, green tea, spirulina, and edible fungi such as shiitake and golden mushrooms [78]. It is generally believed that Se and its compounds are antioxidants. This observation is attributed to its role as an essential co-factor of the antioxidant enzyme glutathione peroxidase, which protects against oxidative stress. It is well known that Se increases the proliferation of natural killer cells. Se deficiency can lead to immune dysfunction and increased virulence of pathogens [50]. Regarding Se oxidizing capacity as a most important feature of its antiviral property, it seems probable that Se supplementation protects coronavirus. Further, Se reduces thrombosis in the blood vessels [79]. It thus can be seen as a valuable tool

Table 2. Age and gender related tolerable upper intake levels for mineral zinc and selenium [21, 24, 74]

Age (years)	Zinc (mg/day)		Selenium (µg/day)	
	Male	Female	Male	Female
0-0.5	4	4	45[1]	45[1]
0.5-1	5	5	60[1]	60[1]
1-3	7	7	90	90
4-8	12	12	150	150
9-13	23	23	280	280
14-18	34	34	400	400
Pregnancy		34		400
Lactation		34		400
19+	40	40	400	400
Pregnancy		40		400
Lactation		40		400

[1]Only recommended selenium sources are breast milk, food and infant formula

to reduce the formation of micro-clots as a significant cause of death in patients with COVID-19 [80]. Khatiwada and Subedi [81] critically reviewed relevant studies of the major databases, PubMed and Scopus, investigating the selenium effects in COVID-19 and concluded that this nutrient has a potential to support COVID-19 management due to immune function strengthening, oxidative stress and inflammation reduction, although more studies are necessary to ascertain the assumption. Similar conclusion was launched by Zhang *et al.* [82] who hypothesized that both selenoproteins and redox-active selenium species could attenuate virus-triggered oxidative stress, down regulate the excessive inflammatory response, and thus improve immune-system function as well as the outcome of COVID-19 infection.

Safety concern

Se can display toxicity to humans depending on the chemical form, and in general organic Se compounds are known less toxic than inorganic. The US Institute of Medicine [21] considered that long-term high intakes of the organic and inorganic forms of Se have similar effects. At the same time, in one clinical trial, relatively high doses of selenite (up to 2000 µg/day) were reported to be well tolerated and were found to reduce mortality from septic shock [83]. In humans, it is generally accepted that mild symptoms of toxicity in the form of reversible hair loss and fingernail brittleness start to occur at a dose of 1000 µg/day during one year of supplementation. Early indicators of excess intake are a garlic odor in the breath and a metallic taste in the mouth. Other symptoms include lesions of the skin and nervous system, nausea, diarrhea, skin rashes, mottled teeth, fatigue, irritability, and nervous system abnormalities. Even regular consumption of Brazil nuts which contain very high amounts of Se (68-91 mcg per nut) could cause Se toxicity. Acute Se toxicity has been reported as a result of an ingestion over-the-counter product containing very large amounts of Se [84, 85]. Further, a liquid dietary supplement containing 200 times the labeled amount of Se induces severe adverse reactions [86]. In addition, acute Se toxicity can cause serious gastrointestinal and neurological symptoms, as well as an acute respiratory distress syndrome, myocardial infarction, hair loss, muscle tenderness, tremors, lightheadedness, facial flushing, kidney failure, cardiac failure, and, in rare cases, death [21, 84]. Considering the amounts of Se associated with hair and nail brittleness, the Food and Nutrition Board of the US Institute of Medicine [21, 24] has established upper limits for Se intake through food and supplements (Table 2).

Regarding COVID-19 treatment, a correlation between high quantum Se supplementation in adults (more than 550 µg/day) and the therapeutic effect has been made, conferring a higher cure rate [87]. The authors believe that a few weeks (average duration of acute infection phase in COVID-19) supplementation with daily doses of 1 mg Se (as selenite) would markedly increase the formation of redox-active Se species, and are still comparable to the doses have been used in critical care applications. In addition, mild symptoms of toxicity (reversible hair loss and fingernail brittleness) have been observed after one year of the administration of sodium selenite at a dose of 1

mg/day [79]. It was reported that Se concentration in human serum may range between 0.4 and 30 mg/L, while concentrations above 1,4 mg/L are still considered non-toxic [88]. However, it is logical that high Se doses (starting from 0.6 mg/day) [79] will reach a level normally associated with toxicity and in consideration of narrow dose range exerting beneficial and adverse effects of Se, should not be used as a regular strategy to manage moderate to severe COVID-19 cases prior ascertain in randomized and controlled trials.

Conclusion

Herein, the effects of vitamins C, D, E, and minerals zinc and selenium on the immune system and the possible benefits of preventing and improving SARS-CoV-2 infection outcomes are presented. Compared to the known and possible benefits, the risk profile of nutritional supplementation seems to be small, in a case of well-established intake of these vitamins and minerals in both the prevention and treatment of COVID-19. However, in clinical studies of vitamin D, vitamin C, Zn and other micronutrients that gain some new insights applicable to COVID-19 patients, doses significantly higher than tolerable upper intake levels are often applied, which may be a safety concern. Even more important is lacking firm clinical evidence that can justify the high-dose administration of specific nutrients, especially in healthy and well-nourished individuals. A further and more detailed investigation is required to support high-dose supplementation considering the ratio between efficacy and risks, especially in the elderly and those patients suffering from moderate to severe COVID-19. Meanwhile, the best way to ensure patient safety as well as to other people who are at risk, is to be educated by healthcare providers about potential harm related to food supplements, known contraindications and interactions with drugs and other nutrients as well as the need certain parameters related to the selected food supplement to be monitored.

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