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REVIEW ARTICLE **OPEN ACCESS**

Multifactorial Utility of Vitamins in Treatment of Covid – 19

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ABSTRACT
The pathogenesis of the SARS-CoV-2 virus responsible for COVID-19 disease is ever unravelling. Researchers are continuously generating evidence regarding the mechanism of the infection and its complications. There is also an attempt to understand the role of various biomolecules in preventing or treating COVID-19 disease and its complications. The focus of this review is to apply our modern knowledge of vitamin D, B12 and C as micronutrients & facilitator of immune competence. We suggest that vitamins D, B12 and C may serve as attenuators to COVID-19 symptoms. Large randomized trials are required to confirm this hypothesis.
KEYWORDS: *Vitamin D, Vitamin C , Vitamin B 12 , Covid -19*

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INTRODUCTION

In December 2019 a sudden rise of acute respiratory distress syndrome cases occurred in Wuhan, china, [1] The pathogen was isolated from Chinese population and identified as severe acute respiratory syndrome corona virus [2] (SARS-COV-2). COVID-19 specially affects respiratory system with most important symptoms being fever, cough, flu and dyspnoea. As SARS-Cov-2 usually disrupts the immune system of humans and animals with the help of a huge release of cytokines as cytokine storms and the hyper activation of the other elements of the immune system [3-6].

VITAMIN D AND MECHANISMS TO REDUCE MICROBIAL INFECTIONS

The overall metabolism and clinical benefits of Vitamin D are widely recognized. Vitamin D3 is generated in skin through the UVB radiation using 7-dehydrocholesterol which is found in the skin, followed by a thermo sensitive reaction. Vitamin D3 is converted to 25(OH)D inside the liver and then to 1,25(OH)D (calcitriol), within the kidneys or other organs as needed. Calcitriol is the active form of vitamin D which is a hormone that enters nuclear D receptor, a DNA binding protein interacting directly with regulating sequences near target genes and recruits chromatin active complexes participating genetically and epigenetically in modifying transcriptional output .Apart from this characteristic of calcitriol is to help regulate serum calcium concentrations, which it does in a feedback loop with parathyroid hormone (PTH) [7].

Coronavirus disease 2019 (COVID-19), often leads to severe respiratory signs and symptoms. Vitamin D treatment has been recognized as an able strategy to deal with COVID-19 and has been found to decrease different viral respiratory infections, mainly in persons with vitamin D deficiency [8-10]. Calcitriol (1,25-dihydroxyvitamin D3) exerts its action on ACE2/AngMasR axis with better expression of ACE-2 in the host cell receptor liable for mediating infection with the aid of SARS-CoV-2. In the lungs, ACE2 is proven to defend acute lung damage. Vitamin D has many mechanisms by which it reduces the chance of microbial affection and early death in COVID-19 patient. A current dataon covid-19suggests that vitamin D aids in three ways: physical barrier, cellular natural immunity, and adaptive immunity. Vitamin D helps maintain tight junctions, gap junctions, and adherens junctions (e.g., by using E-cadherin) [11].

Vitamin D promotescellular innate immunity partly via the induction of antimicrobial peptides, along with human cathelicidin, LL-37, through 1,25-dihdroxyvitamin D , and defensins [12]. Cathelicidins exhibits direct antimicrobial effect in opposition to a spectrum of microbes, which include Gram-positive and Gram-negative microorganism, enveloped and nonenveloped viruses, and fungi .The host-derived peptides kill the invading pathogens through perturbing their cellular membranes and might neutralize

the biochemical activity of endotoxins. In another laboratory study, 1, 25(OH) D reduces the replication of rotavirus both in vitro and in vivo by another method.

Vitamin D partly enhances cellular immunity, by means of lowering the cytokine storm caused by the innate immune system. The innate immune systemproduces anti-inflammatory and proinflammatory cytokines in reaction to viral and bacterial infections [13]. Vitamin D is a modulator of adaptive immunity, itdecreases responses mediated with the aid of the T helper celltype1 (Th1), by repressing production of anti-inflammatory cytokines IL-2 and interferon gamma (INFγ) Also, it promotes cytokine production through the T helper type 2 (Th2) cells [14]. Furthermore, 1,25(OH)2D3 promotes induction of the T regulatory cells, thereby inhibiting anti-inflammatory approaches [15].

Serum 25(OH)D concentrations tend to decrease with age which can be critical for COVID-19 because case-fatality RATIO (CFRs) increase significantly with age. Also a few drugs decrease serum 25(OH)D concentrations by activating the pregnane-X receptor .Such drugs consist of antiepileptics, antineoplastics, antibiotics, antihypertensive, antiretrovirals, endocrine drugs, and a few herbal drug treatments. Several reviews consider the ways inwhich vitamin D reduces the risk of viral infections [16-17]. Vitamin D has many mechanisms by which it reduces the risk of microbial infection and death. Vitamin D supplementation additionally enhances the expression of genes associated with anti-oxidants (glutathione reductase and glutamate–cysteine ligase modifier subunit).

Vitamin D holds an important position in the immune system. Vitamin D interacts with majority of the immune system cells such as macrophages, B and T lymphocytes, neutrophils and dendritic cells . Cathelicidin, a peptide shaped via vitamin D stimulated expression, has shown antimicrobial activity against microorganism, fungi and enveloped viruses, including corona viruses [18].

The metabolite of vitamin D in macrophages and dendritic cells, derived from the precursor 25(OH)D, leads to the activation of VDR, which, after RXR hetero-dimerization, effects inside the expression of diverse proteins of the innate and adaptive immune systems (Treg cells, cytokines, defensinsetc.) . Vitamin D exerts contrary consequences at the adaptive and innate immune system. This correlates and balances the immune response. The active metabolite of vitamin D, 1,25(OH)2D3 may act in T and B lymphocytes and inhibits T cell proliferation and activation . This way, vitamin D may also suppress T-cell mediated inflammation and stimulate Treg cells proliferation, with the aid of increasing IL-10 formation in DC cells, and as a result enhance their suppressive impact [19-22].

Vitamin B12 and COVID-19

Vitamin B12 (cobalamin) is an immunomodulator and is essential in the healthy functioning of the hematopoietic, nervous and immune systems. The occurrence of cobalamin deficiency is seen the most in the elderly, who have difficulty in absorption of the required dietary allowance from diet because of the deficiency of gastric acid or intrinsic factor [23-25].

Niacin acts as a building block of NAD and NADP, each essential at some point in chronic systemic inflammation. NAD+ acts as a coenzyme in various metabolic pathways and its elevated levels are crucial a variety of pathophysiological situations. NAD+ may be responsible for limiting and preventing the cytokine storm resulting in resolution of inflammation. Interleukin-6 (IL-6) which is a biomarker of cytokine storm has been found to be significantly raised in complicated and severe COVID-19. It is therefore evident that management of the cytokine storm is essential to the management of COVID-19. Moreover, niacin reduces neutrophil infiltration and reveals a beneficial effect in patients with ventilator associated lung damage. In hamsters, niacin and nicotinamide prevents lung tissue damage. In addition, nicotinamide reduces viral replication (vaccinia virus, human immunodeficiency virus, enteroviruses, hepatitis B virus) and strengthens the host's defence mechanisms. Taking into consideration the lung protecting and immune strengthening roles of niacin, it could be used as an accessory remedy for COVID-19 patients [26-27].

With the use of molecular modelling technology, it has been found that Vitamin B12, nicotinamide, ribavirin and telbivudine may have a potential role in the treatment of COVID-19. It is being suggested that Vitamin B12 may be a possible inhibitor of the RNA dependent RNA polymerase activity of the SCV2-nsp12 enzyme. This inhibitory action may result in a decrease in the viral infection the severity of COVID-19. It has also been proposed that melatonin, an anti-oxidative molecule, potentially can be used in the management of COVID-19 patients [28].

It is hypothesized that the SARS-Cov-2 virus interferes with Vitamin B12 metabolism. The virus probably impairs the growth of intestinal microbiota which results in the manifestations of vitamin B12 deficiency. Signs of Vitamin B12 deficiency, including the increase of reactive oxygen species, hyper-homocysteinemia, pro-coagulation, thrombocytopenia, raised lactate dehydrogenase (LDH), reticulocytopenia, intravascular coagulation, thrombosis, vasoconstriction and vasculopathies are also manifestations and complications of COVID-19 disease [29]. Symptomatic Vitamin B12 deficiency is treated by the administration of high dose methylcobalamin. It is therefore being extrapolated that

administration of dietaryvitamin B12, mainly methylcobalamin, in patients with COVID-19 could reduce the disease complications. Vitamin B12 supplementation reduces oxidative stress, infection and microvasculopathy related to hyper-homocysteinemia. The majority of Vitamin B12 supplements contain cyanocobalamin which is metabolized and transformed to methylcobalamin in the liver. This conversion may also be occasionally reduced, especially in disease [30].

The methyl component of methylcobalamin stimulates serotonin which is a neurotransmitter responsible for cognition, memory and modulation of mood. Vitamin B12also plays an important role in maintaining myelination, erythropoesis and DNA synthesis. Supplementation with methylcobalamin has been considered in the management of vitamin B12 deficiency, Alzheimer's disease, neruro-regeneration, Bell's palsy and rheumatoid arthritis. The metabolite of vitamin B12 are hydroxo-, adenosyl- and methyl-cobalamin. Vitamin B12 acts as a modulator of gut microbiota and low degrees of vitamin B12 increase methylmalonic acid and homocysteine, resulting in increased inflammation, reactive oxygen species and oxidative stress [31]. Hyperhomocysteinemia causes endothelial dysfunction, activation of platelet and coagulation cascades, megaloblastic anemia, disruption of myelin sheath integrity and reduced immune responses.

A study conducted in Singapore found that patients with COVID-19 who had been given vitamin B12 dietary supplements (500 μg), vitamin D (1000 IU) and magnesium had reduced COVID-19 symptom severity. Dietary supplements appreciably reduced the need for oxygen therapy and intensive care support [32]. Vitamin B12 can potentially be used as a safe and cost effective immunomodulator which can down regulate the pro inflammatory cytokines causing the cytokine storm in COVID-19 patients. It may potentially improve respiratory and gastrointestinal symptoms, prevent hypercoagulability resulting in improved outcome and decreased duration of hospital stay of COVID-19 patients [33].

THE PROTECTIVE ROLE OF VITAMIN C IN THE MANAGEMENT OF COVID-19

Vitamin C or ascorbic acid an inevitable cofactor for mediating enzymatic reactions which can be responsible for several biological activities. It is deemed a significant antioxidant with strong anti-inflammatory and anti-microbial properties [34]. It possesses a variety of biochemical actions like antioxidant, phagocytosis, neutrophil chemotaxis, microbial clearance, and immunomodulatory. It modulates the immune system by enhancing natural killer cell and T cellular proliferation, provoking the activation and response of T lymphocytes, increasing interferon levels and scavenging reactive oxygen species (ROS). Besides, vitamin C is needed for the synthesis of nor-adrenaline, catecholamine, and adrenal steroids. It additionally acts as a cofactor for peptidyl-glycine alpha-amidating monooxygenase that is wanted for vasopressin's endogenous synthesis. [35] It has been significantly used to manage critically ill patient [36-38]. Due to these actions, Vitamin C has a potential in the management of COVID-19 patients [39-41]. Vitamin C supplementation has shown beneficial results in infections and sepsis. As extreme COVID-19 can also induce acute respiration distress syndrome (ARDS) and sepsis, excessive doses of vitamin C supplementation may also contribute to ameliorating inflammation in patients with COVID-19 [42-43]. A series of clinical trials related to COVID-19 have been launched or announced from the very beginning of COVID-19 to evaluate the therapeutic benefit of vitamin C alone or in combination therapy with one or more therapeutic substances (e.g., zinc, vitamin D, hydroxychloroquine, and azithromycin). However, it should be kept in mind that vitamin C is not yet a standard treatment for COVID-19 owing to a shortage of evidence [44-46].

CONCLUSION

It is regarded that a strong immune system can help prevent or treat COVID-19 infection. The use of vitamins especially Vitamin D, B12 and C may have an effect. Supplementation of these vitamins and treatment of their deficiency may significantly improve the anti-inflammatory status of the individual and may have a positive impact on the outcome of COVID-19 disease. Randomized clinical trials of interventions to reduce the deficiencies of specific vitamins must be undertaken to determine whether the interventions could reduce COVID-19 associated morbidity and mortality. The anti-inflammatory and immunomodulatory effects of Vitamins may prove to be very important for the prevention and treatment of COVID-19 infection.

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