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REVIEWING THE POTENTIAL ROLE OF NUTRITION AND ITS IMMUNE RESPONSE AGAINST COVID - 19

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ABSTRACT

The outbreak of the novel coronavirus has created a threat to humanity as there is neither specific treatment to cure the disease nor a vaccine to prevent the spread. Hence prevention of the disease by other measures is the need of the hour. Dietary intake of macronutrients and micronutrients that possess antiviral effects and immunomodulatory effects could be an adjuvant to boost host defense thereby preventing the disease or improve the prognosis of the disease when infected. The present manuscript aims to review the published data on the role of nutrients in immunomodulation for the prevention of COVID 19.

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Introduction

The 2019 novel coronavirus (SARS-CoV-2) epidemic, attacked the world in December 2019 in Wuhan Province in China, and has been declared a public health emergency with severe morbidity and mortality by the World Health Organization, and has spread to major continents in the world transforming into a pandemic.SARS-CoV-2 is genetically similar to the SARS-CoV virus that caused 8096 confirmed cases in more than 25 countries between 2002–2003.[1] SARS-CoV-2 is the seventh coronavirus known to cause disease in humans; SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe infections whereas HKU1, NL63, OC43, and 229E cause only mild symptoms.[2] The wide spectrum of SARS-CoV-2 pneumonia could range from mild to critically ill cases requiring ventilation and critical care. Health authorities all over the world have suggested social distancing measures to prevent the rapid spread of this disease as it is known to spread by droplets. Despite ongoing research in laboratories all over the world a successful therapeutic measure in the form of a drug or a preventive vaccine against SARS Cov 2 has not come up. It is known that food and its constituent macro and micronutrients could prevent and cure many diseases and infections. This has been a yesteryear healing practice all over the world. This comprehensive review sheds light on the relationship between nutrition and its role in the prevention and management of the SARS Cov 2 infection.

The Immune System SARS Cov 2 Pathogenesis

It is well known that pathogenic invaders like bacteria and viruses are first recognized by the immune system of the human body. This applies to SARS Cov2 also. Once the virus gains entry into the human system, it binds to cell surface Angiotensin 2 which is documented to be the SARS Cov 2 receptor. [3] Following this some proteases like furin[4] and cathepsin S [5] cleave the S glycoprotein unit of the virus and make the cellular entry of the virus possible. Following cellular entry, the virus replicates within the cell using the host machinery and releases virions which causes the host cells to undergo a phenomenon called pyroptosis.[6] Consequent to this, numerous damage-associated molecular patterns are also released such as ATP, nucleic acids, and ASC oligomers. These molecules are identified by

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the neighboring epithelial, endothelial, and immune cells which respond by producing huge amounts of pro-inflammatory cytokines and inflammatory mediators such As IL -1, IL-6, MCP 1 which further cause more of immune cell infiltration and more cytokine production. This mechanism is referred to as a cytokine storm which causes severe damage to vital organs mainly the lung leading to pneumonia.[7] The cytokine storm also travels to other organs leading to multi organ failure that causes severe morbidity and mortality. It can hence be inferred that the immune system plays a central role in the pathogenesis of SARS Cov 2 infection.

Nutrition As A Modulator Of The Immune System In Viral Diseases.

One of the important modulators of the immune system in states of health and disease is nutrition or intake of a well-balanced diet. Food has been an important constituent of all cultures. It has been understood that malnutrition or impaired intake of nutrients can cause severe bacterial and viral infections. Epidemiological observations have ascertained that infection and malnutrition aggravate each other. Good nutrition with an ample amount of not only macronutrients but also micronutrients is required for a robust immune system to fight infections. A "primed" immune system poses greater demand on the body for energy and nourishment during diseased states. Thus, optimal nutrition for the best immunological outcomes would be the intake of a balanced diet that would help in preventing and managing infective invaders. As the popular saying of Hippocrates quotes "Leave your drugs in the chemist's pot if you can heal the patient with food". The above saying is very appropriate in the current situation where in the world is being tormented by the deadly viral disease COVID 19. At present, there is neither a specific therapeutic strategy nor a specific vaccine for prevention. It is a well-known fact is that adequate nutrition can boost the host immune response. Nutrition plays a vital role in the immunomodulation of viral diseases. Also, the prognosis of viral diseases is influenced by the nutritional status of the affected individual.[8] Studies have shown rotaviral infection and ARI is more severe in children with malnutrition in comparison with well-nourished children. [9–11]Al-Nakib et al have reported reduced clinical symptoms in volunteers who had Zinc supplements before exposure to Rhinovirus.[12] Studies have shown

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that Vitamin A-deficient children have been affected by severe measles. [13] Thus, nutrition plays a vital role in prevention and improvement in the prognosis of viral infections through immunomodulation. In the same manner, nutrition could modulate the susceptibility to COVID 19 infection as the disease is viral in origin. The following sections will describe in detail a few micronutrients and probable mechanisms to prevent COVID 19. A Schematic diagram representing the preventive and beneficial role of nutrients in the pathogenesis of SARS Cov - 2 infection has been represented in Figure 1.

Role Of Vitamin C In The Prevention And Management of COVID 19

Vitamin C also denoted chemically as ascorbic acid is one of the important water-soluble vitamins. This vitamin was discovered in the early twentieth century. It was Alfred Hess who wrote a commentary consequent to a scurvy epidemic. He documented that lobar pneumonia of the lungs could be cured by administration of an antiscorbutic compound which is nothing but vitamin C. [14] Another observation by Casimir Funk in Sudan found that the administration of vitamin C could cure a scurvy epidemic in the African country Sudan. [15]

Vitamin C is synthesized in most mammals except guinea pigs. This vitamin plays a major role in normal homeostasis. Vitamin C is a potent antioxidant. Therefore, it could play a role in conditions when oxidative stress is increased. Infections lead to the activation of phagocytes, which release reactive oxygen species (ROS) and free radicals. These play a role in pathogen destruction to ward of the infection as a nonspecific or innate response.[16] But the generation of oxidative radicals to mediate pathogen destruction has destructive effects on the host cells also.[17] Vitamin C hence plays a major role as an antioxidant preventing host cellular damage in ongoing bacterial and viral infections. Phagocytes such as neutrophils and monocytes harbor a specific transport system by which the oxidized form of vitamin C (dehydroascorbic acid) is imported into the cell where it is converted into the reduced form of vitamin C.[18] Vitamin C has also got profound effects on the immune system. Vitamin C levels are exponentially higher in the white blood cells compared to plasma showing that Vitamin C could be the predominant antioxidant protecting the cells of the immune system from oxidative damage.[19]

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Other immune effects of Vitamin C include inhibition of viral replication, increasing the maturity of T lymphocytes, and the production of interferon. [20] The effects of Vitamin C in promoting collagen hydroxylation thereby maintaining connective tissue integrity is well known. [21]Vitamin C is known to mediate the production of enzymes such as dopamine and carnitine which are neuroendocrine peptides.[22] Experimentally induced vitamin C deficiency has hence found to cause depression and tiredness. Vitamin C has been found to cause mood elevation in hospitalized patients. [23,24]

A large dose of IV ascorbic acid could help in treating SARS Cov 2 disease. [25] It is believed that ARDS is the main cause of COVID 19 morbidity and mortality. A study demonstrated that out of 99 Covid19 patients, 17 suffered from ARDS complications and 11 patients died. [26] Like influenza, coronaviruses cause rapid lung destruction by stimulating excessive cytokine production referred to as a cytokine storm that further interacts with the endothelial cells to stimulate oxidative stress and pulmonary damage.[27] The transcription factor nuclear factor-erythroid-2–related factor 2 (Nrf2) is an important regulator of antioxidant response element (ARE) driven cytoprotective protein expression. Ascorbic acid is an important compound of the antioxidant system in cells and tissues.[28] It is now understood that viral infections result in increased production of cytokines and free radicals. Hence a large dose of antioxidants like Vitamin C can be given taking into account that no specific drugs or vaccines are available to manage the pandemic. This is further supported by positive findings that a large dose of IV Vitamin C has shown successful clinical improvement and resolution in viral ARDS and influenza. [29]

It can hence be inferred that Vitamin C could be used for managing viral infections as an adjuvant taking into account its antioxidant and neuroendocrine effects. Concerning the SARS Cov 2, there is definite evidence to support the use of Vitamin C as an adjuvant. In fact, in Shanghai, several hospitals have resorted to administering high dose intravenous Vitamin C to patients as above mentioned. Hence it can be concluded that Vitamin C could be used both for prevention and non-specific management of COVID 19.

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Role of Zinc in the Prevention and Management of COVID 19

Zinc is an essential mineral required for the effective functioning of the body's defense mechanism, mitosis, growth, wound healing, and carbohydrate metabolism. As the name suggests, approximately 750 zinc-finger transcription factors required for gene transcription require Zinc as an essential constituent. About two thousand enzymes that are hydrolases, transferases, oxidoreductases, ligases, lyases, and isomerases require Zinc as a catalyst. [30,31] Free and bound zinc are 2 compartments in which this metal exists in the human body. Free zinc levels are very low while a predominant amount of zinc remains bound to proteins and enzymes.[32] The free and bound state of Zinc levels in the body is regulated by human proteins that prevent toxicity during excessive consumption of Zinc and deficiency during reduced dietary intake. However jeopardized state of Zinc homeostasis, may result in copper deficiency induced by increased consumption of zinc. [33] Several in-vitro studies have demonstrated the antiviral activity of Zinc. However, the concentrations of Zinc used for assessment of antiviral activity was higher than physiological concentrations.[34,35] The intracellular concentration of zinc ranges between 10s to 100s of μM, and free zinc concentrations are maintained at picomolar to nanomolar range by buffering actions of metallothioneins which are zinc-binding proteins. [36,37] Thus, the availability of zinc ion would play a significant role in determining the efficacy of specific antiviral activity of zinc.[38] Studies have reported the antiviral effects of zinc on respiratory viruses. In vitro studies have demonstrated that zinc ionophore pyrrolidine dithiocarbamate significantly inhibits RNA-dependent RNA polymerase(RdRp) thereby inhibiting the replication of influenza(PR/8/34). [39,40] Interestingly, in vitro studies have demonstrated the antiviral activity of Zinc against the SARS coronavirus. The study reported that Zinc was found to inhibit severe acute respiratory syndrome (SARS) coronavirus RdRp template binding and elongation in Vero-E6 cells. [41] Incubation of HEp-2 cells with Zinc salts was shown to inhibit the respiratory syncytial virus even after the removal of zinc before exposure with the virus.[42] Zinc, not only exerts antiviral activity but also plays a major role in innate and adaptive immune signaling pathways. Thus zinc could prevent SARS Cov 2 thorough antiviral activity and immune

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modulation.

The only limitation with zinc is in determining the clinical dose that may be required to prevent and cure SARS Cov 2. If a proper extrapolation of the in vitro scenario is extended to the clinical setting zinc could be exploited as a drug for its antiviral properties in the coronavirus crisis

Role of Iron in the Prevention and Management of COVID 19

Iron is one of the most important trace elements required for various functions of the body. It is a well-known fact that iron is a part of hemoglobin and is essential for oxygen transport. Iron is required for certain metalloproteins and certain enzymes required for the immune system. Immune cells require iron for cytochromes a,b,c, and activation of catalase for their metabolism. [43] Studies have demonstrated that iron deficiency causes decreased thymocyte proliferation and thymic atrophy in mice.[44] Decreased lymphocyte count has also been demonstrated in iron deficiency anemia. [45,46] The proposed mechanism for decreased lymphocyte count is that iron deficiency causes a reduction in translocation and activation of protein kinase C that causes impaired lymphocyte proliferation. [47] Studies have demonstrated decreased levels of serum IL2 and IL6 in children with iron deficiency. [48,49] Thus, it is shown that iron is essential for the normal functioning of the immune system. On the contrary, Weinberg has reported that iron withholding could be a probable mechanism for defense against viral infections.[50] Hence the exact role of iron in viral infections remains unclear and the protective role of iron in COVID 19 has to be explored further for definitive conclusions.

Role of Antioxidants in the Prevention and Management of COVID 19

Free radicals and antioxidants play a major role in influencing several regulatory pathways of the body including the immune system. The balance between free radicals and antioxidant systems is essential for cell membrane integrity, signal transduction, gene expression, cellular proteins, of immune cells. Moreover, the immune cells are very sensitive to free radicals and oxidative stress due to the high content of polyunsaturated fatty acids in the plasma membrane in these cells. Free radicals cause lipid peroxidation of PUFA and phospholipids that leads to formation of various aldehydes and lipoperoxides thereby

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leading to plasma membrane damage of immune cells. This in-turn results in dysregulation of gene expression, membrane related signaling which are the critical function of immune cells. [51–53] Thus, antioxidants such as Vitamin C, Vitamin E, beta carotene, Zinc, Selenium could aid to combat oxidative stress, thereby regulate the immune response and prevent diseases.[54] Oxidative stress has been implicated in several viral infections although the exact mechanism remains unclear. Semba et al [55] have reported increased mortality rates of vitamin A deficient children suffering with pneumonia. Similarly Beck et al [56] have reported increased virulence of Cocksakie virus B3 in Vitamin E deficiency. In-vitro studies have demonstrated increased replication of HIV through NF kappa B when subjected to free radicals. Thus, antioxidants could play a major role in preventing viral infections. In COVID 19, based on the clinical features it has been postulated that the respiratory disorder caused is an outcome of inflammation and oxidative stress. [57] Hence antioxidants could play a significant role in prevention and improve the prognosis of COVID 19 through immunomodulation.

Role of Amino Acids in the Prevention of COVID 19

Amino acids are molecules that combine to form proteins and hence are considered as the building blocks of life. Aminoacids have several functions including regulation of immune response. They are essential for the synthesis of proteins such as antibodies, cytokines that regulate metabolic pathways of the immune response to pathogens, cellular redox state, gene expression, the proliferation of lymphocytes, activation of T lymphocytes, B lymphocytes, macrophages. [58] Although all the amino acids directly or indirectly influence immune response, arginine, glutamine, and cysteine possess well defined specific roles.[59–64] Also, branched-chain amino acids play an important role in the regulation of immune response as they are needed for lymphocyte proliferation, regulation of protein synthesis, activation of cytokines, and production of antibodies. [65] Thus, a deficiency of amino acids could exert a negative impact on the immune system. Furthermore, there is an increased protein and amino acid requirement during acute and chronic infections due to the negative nitrogen balance and hypermetabolism that occurs during

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infections. [66] It has been hypothesized that dietary glutamine supplementation could meet the host's increased metabolic demand for glutamine for the functioning of immune cells, cells of the gastrointestinal tract, and synthesis of glutathione, which could thereby prevent muscle wasting in HIV. [67] Thus, dietary supplementation of amino acids could enhance host immune response and aid in prevention of COVID19. However further studies in this regard is warranted for conclusive results.

Conclusion and Future Directions

The available scientific evidence suggests the role of nutrients such as vitamin C, zinc, iron, antioxidants, amino acids in immunomodulation. Since there is no specific treatment for the novel coronavirus, dietary supplementation with adequate micronutrients and macronutrients could not only aid in preventing the disease but also could be an adjuvant in improving the prognosis of the affected individuals. However, further specific studies in this regard have to be conducted to assess the specific role of these nutrients in modulating the immune response to COVID 19.

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Figure 1. Preventive role of nutrients in the pathogenesis of COVID 19