***Review Article***

# POTENTIAL IMPACT OF NUTRITION ON IMMUNE SYSTEM:

# PREVENT OR ASSIST COVID-19 RECOVERY

**Abstract-** In human beings, infection risk and severity differ according to immune competence based on how the immune system grows, matures and declines. Many factors affect the immune system and its competencies, including diet. A number of clinical trials are under way to determine treatment options for coronavirus disease 2019 (COVID-19), caused by extreme acute coronavirus syndrome. Considering Covid-19, enhanced nutrition including micronutrient supplementation to improve the immune system has been recognized as a viable solution to both preventing and alleviating infection severity. Micronutrient deficiencies, especially vitamins A, B complex, C, and D including trace minerals zinc, iron, and selenium, are prevalent among vulnerable populations in general, and among COVID-19 patients in particular, and may likely increase mortality risk. A systematic review of the literature was conducted to identify nutritional strategies that might prevent or assist COVID-19 recovery. There is still unmet need for covering the treatment of the geriatric and pediatric patients.

**Keyword**- Covid-19, Immunity, Micronutients, Vitamins, Trace minerals, Geriatric Patients, Pediatric Patients

**INTRODUCTION-**

The COVID-19 epidemic in 2019–2020 occurred in Wuhan, China. Cases of illness, serious, and death are most likely to belong to male and older people, and are mainly those with chronic disease, such as obesity, diabetes, and coronary disease. The decisive range of spread and consequence of this epidemic is not clear ~~till~~ to date as the situation is still evolving. There are approximately 30 corona viruses that can affect humans and animals and their associated respiratory problems are common both to humans and animals. (2)

Our immune system is the best defense, as there is no registered COVID-19 drug or vaccine. The immune system maintains the innate capacity of our body to protect against pathogens that include viruses, bacteria, fungi, ~~and~~ protozoan~~'~~s and worms. We don't notice infections likeCOVID-19 as long as the immune system is running smoothly. Our immune system is classifiable into three groups. They are, namely, innate immunity (rapid response), adaptive immunity (slow response) and passive immunity (Fig. 1).

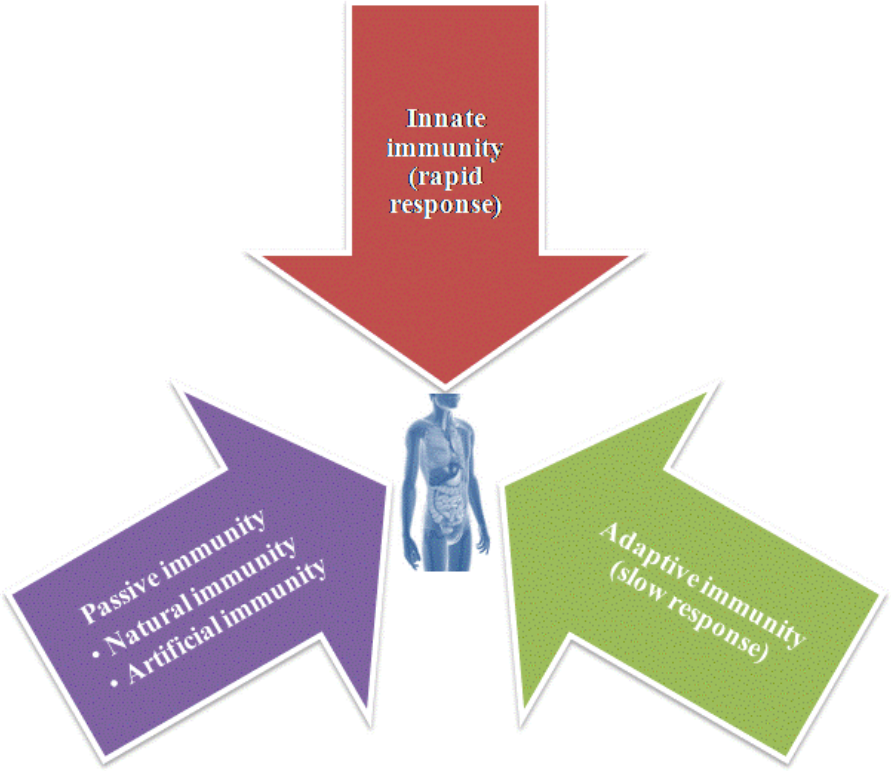


Fig.1. Immunity with subclasses

Passive immunity ~~is again~~ also has two forms, and we derive natural immunity from our mother and artificial immunity from medication. When our body is affected, skin and the inflammatory response starts. But when our body first experiences certain germs or pathogens, the immune system can't function properly and we get ill.(3) This paragraph is not clear and appears to be contradictory.

The first line of defense against pathogens is the innate immune response, consisting of physical, chemical and cellular defenses. The adaptive immune response is the second line of defence and is pathogen-specific. Innate immunity emerges immediately as adaptive immunity evolves after exposure to pathogens and is long-lasting, highly selective and maintained by T cells in memory (1)

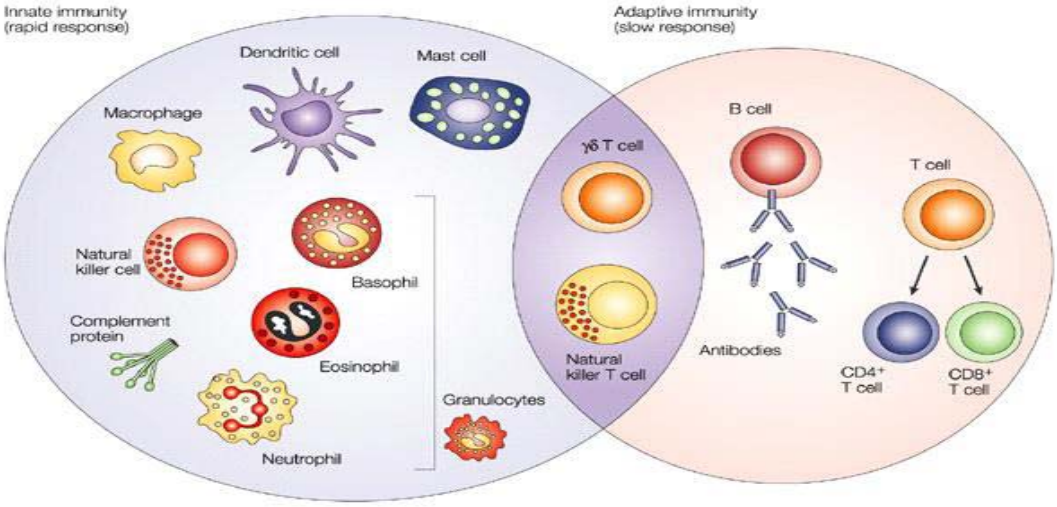


Fig.2. Cells involved in immune responses (3)

A healthy immune system relies on adequate immune functions. In addition, adequate nutrition is vital to maintaining a good supply of the energy sources, macronutrients, and micronutrients needed for immune system growth, maintenance, and expression. (4)

Immunological maturity is achieved by adolescence, and young adults should be well fortified against attack by pathogens. However, many lifestyle factors impact immune skills in healthy adults and raise their risk of infection (Figure 3). In particular, a poor diet, frequently seen in adults with a hectic and stressful lifestyle and ready access to fast food or energy-dense, micronutrient-poor convenience food, may compromise the nutritional status.(4)

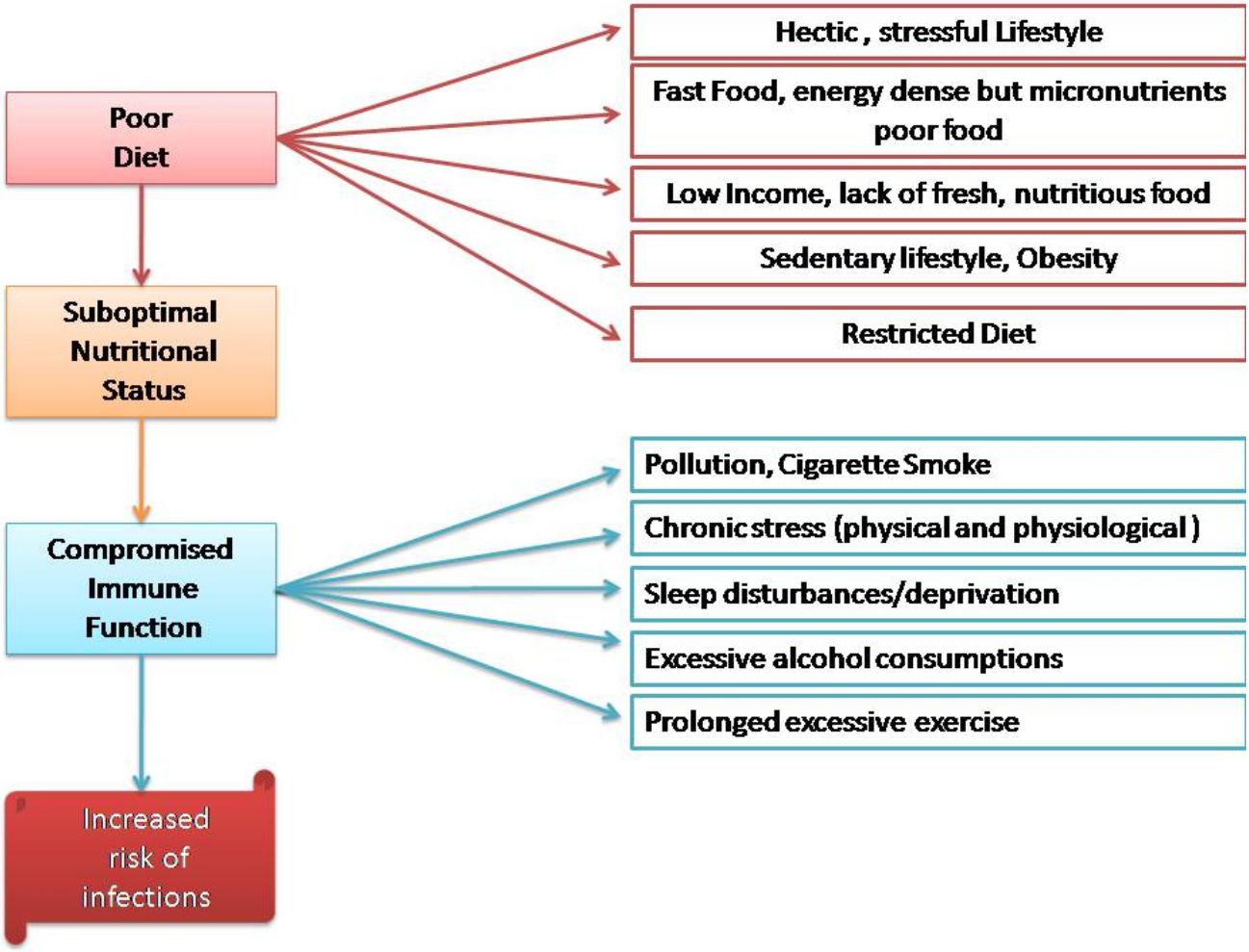


Fig.3. Life-style factors affecting immune function during adulthood.

The risk of infection is also

Influenced by gender, early programming, vaccination history, pathogen exposure, specific health conditions, and diseases (4)

**Nutritional needs of human**

Micronutrients are dietary components that contribute significantly to a strong immune system. Important micronutrients including vitamins A , D, E, C, B6, B12, and folate as well as trace elements such as iron, zinc, and selenium, accessible in a range of fresh animal- and plant related foods, help the body 's ability to combat infections (Fig.4).(5) It is debatable whether vitamins A, D, E etc. are micronutrients – clarify this statement.

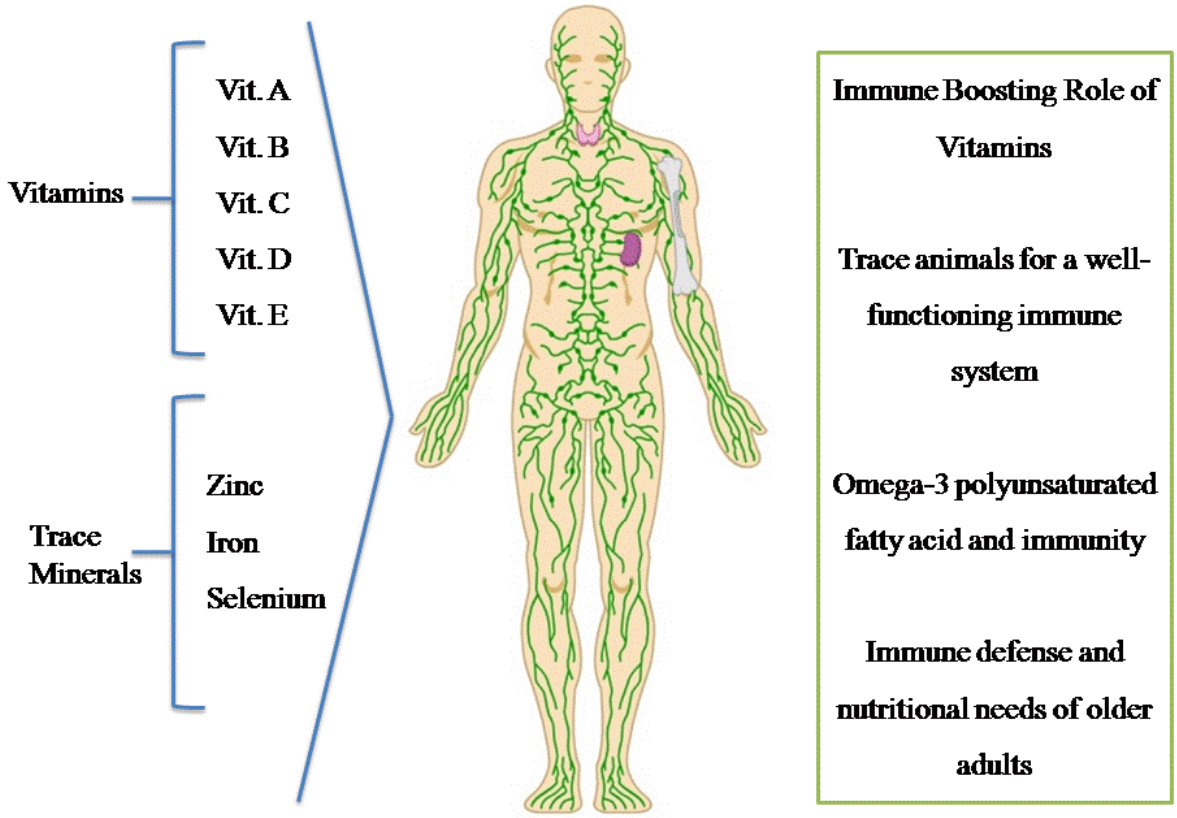


**Fig.4 Nutrients to prevent and assist (5)**

**The comment "Trace animals for a … is not clear!**

Prolonged under nutrition and lack of micronutrients affect the cytokine response and the transport of immune cells. Is it better to say "malnutrition" rather than "under nutrition" if this review is directed at the Western (developed) World? Chronic inflammation and malnutrition association affect immune response. However, not only is under nutrition a problem, patients with obesity (excess fat storage) have demonstrated chronic low-grade inflammation in the systemic circulation with higher concentrations of inflammatory markers. What is the literature citation for this statement? The fatty acid content of immune cells influences the modulation of the immune response. It is normal to see altered T-lymphocyte and decreased TNF-a development in this population. The polyunsaturated fatty acids (PUFAs) influence on the immune system through the diet specially focused on omega-3 PUFAs a-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).(6) we will discuss The last few words need to be deleted or addressed.

The potential antiviral activities and the possible viral targets of A,B,C D, and E vitamins. An in-depth review of the regulatory role of vitamins A,B,C, D and E in the proper functioning of the Immune System against Pathogens is beyond the reach of this paper. Therefore, we will present in brief our current understanding of each vitamin's essential activities in modulating a wide range of Immune processes and regulating immune response to pathogens.

**Vitamin A**

Vitamin A and its metabolites are capable of controlling both endogenous and adaptive immune response strength, enhancing the secretion of IL-2 and modulating proliferation , differentiation and signaling as well as the development of cytokines in both T, B and antigen-presenting cells.Please cite literature supporting this statement. Metabolites of vitamin A also modulate more complex functional features of the immune response, such as TH1–TH2-cell balance and TReg cell differentiation and TH17 cells. Vitamin A is capable of activating IFN-type intracellular network conducting antiviral activities.(7)VA demonstrates several pharmacological mechanisms against SARS-CoV, namely, cytoprotective action, anti-viral activity, anti-inflammatory effects, and immunity-based immunomodulation. The anti-coronavirus benefits may be the dual efficacy of a nutrient agent and bioactive compound to treat complex disease by synergistically modulating all presumptive multi-targets and multi-pathways. Adjuvant VA supplementation can increase the therapeutic effectiveness of current anti-viral clinical agents and immunotherapy to treat potentially fatal COVID-19.(8)

**Vitamin B**

Vitamin B complex was historically supposed to be the single vitamin but later it was found that it consists of several different compounds that can be grouped into different categories according to their functional distinctions, members of B complex include thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9) and cobalamins (B12). Several members of vitamin B complex are used in our body to promote the defensive role for better health and prevention of diseases by boosting-up the immune system. Vitamin forms falling under this group of vitamin B complex play a vital role by functioning as antioxidants in the body, thus improving the efficacy of the immune response. Members of vitamin B complex that have such roles in immune response efficacy include vitamin B6, B9 and B12. (9)

Folic acid, the synthetic source of folate, is a water-soluble vitamin that plays an essential role in cell division, both in blood-forming organs both bone marrow cell growththis statement is

confusing. It is also essential in power generation. The body transforms folic acid into tetrahydrofolic acid and is, in effect, an essential part of nucleic acid (DNA and RNA) and protein synthesis. Enlarged red blood cells are found in deficiency of folic acid as well as defects of white and red blood cells due to macrocytic anemia. Literature citation needed hereVitamin B12 also plays an important role in the development of the immune system as it is responsible for cell division and production. White blood cells can't grow and expand while B12 is in short supply. Healthy older immunocompetent adults with low serum concentration of vitamin B12 had impaired antibody responses to the pneumococcal polysaccharide vaccine.(10)

**Vitamin C**

Often recognized as antioxidant and/or enzyme cofactor, Vit C had been developed as an efficient reducing agent. The effect of Vit C on lymphocytes is not fully evident, however it was observed that Vit C controls genes that are responsible for the production of B cells and T cells, and promotes their differentiation similar to their proliferation. Impaired immunity and decreased susceptibility to infection had also been documented after Vit C deficiency, and vitamin C supplementation proved to be useful in the prevention and/or treatment of serious respiratory and systemic infections such as COVID-19 infection.(11) Atherton et al. Reference needed here reported that vitamin C improved immune functions of chick embryo tracheal organ cultures against coronavirus infection. When sepsis happens, the immune cells such as the cytokine are activated, and neutrophils accumulate in the lungs, destroying alveolar capillaries. Vitamin C may help to prevent the excess activation and accumulation of neutrophils, and decrease alveolar epithelial water channel damage. A controlled, randomised trial found that 200 mg/day of vitamin C improved respiratory symptoms and lowered the mortality rate in severely ill elderly patients. However, a meta-analysis reported that vitamin C administration is associated with no significant effect on survival, length of ICU or hospital stay. Further studies are needed to investigate the association of vitamin C with COVID-19.(12)

**Vitamin D**

Vitamin D is unique: it is a pro-hormone released in the skin during sunlight exposure (UVB radiation at 290–315 nm), typically with lower quantities obtained from food. Many people, especially those living in the northern latitudes (such as the United Kingdom, Ireland, Northern Europe , Canada and the northern parts of the United States, Northern India and China) have low vitamin D status, particularly in winter. Chronic vit D levels are endemic and this should be mentioned. Low vitamin D status may be exacerbated during this COVID-19 crisis (e.g, due to

indoor living and hence reduced sun exposure), and anyone who is self-isolating with limited access to sunlight is advised to take a vitamin D supplement according to their government's recommendations for the general population (ie, 400 IU/day for the UK7 and 600 IU/day for the USA (800 IU for >70 years))8 and the European Union (EU).(14) These supplement levels are probably too low to be effective- 2000 IU might be more suitable.

Vitamin D agonist, calcitriol, exhibited protective effects against acute lung injury by modulating the expression of members of the renin–angiotensin system such as ACE2 in lung tissue, supporting the role of vitamin D deficiency as a pathogenic factor in COVID-19. Again, literature citation needed here for this statement. Vitamin D receptors (VDRs) are extensively distributed in respiratory epithelial cells and immune cells (B cell, T cell, macrophages, and monocytes). 25-hydroxyvitamin D (25OHD), the major circulating form of vitamin D can be converted to the active form (1,25-dihydroxyvitamin D) in the bronchial epithelium and immune cells. The enzyme, 1α-Hydroxylase (CYP27B1), required for vitamin D activation, is induced by diverse stimuli, including cytokines and toll-like receptor ligands in the respiratory tract. However, adequate serum levels of 25(OH)D is required to increase levels of 1,25-dihydroxyvitamin D and consequently improve the immune response to respiratory virus infections.(13)

**Vitamin E**

Vitamin E is essential to preserving older people's physical wellbeing and their immunity. Vitamin E is an effective antioxidant able to ~~protect you~~ provide protection against various pathogens, bacteria and viruses. To get the daily dosage of vitamin E, soaked almonds, peanut butter, sunflower seeds, and even hazelnuts should be eaten.(15) Vitamin E has been shown to have a beneficial impact in enhancing the production of T-cell immune synapse and activating signs of T-cell activation. Vitamin E supplementation has restored interleukin-2 (IL-2) development when administered to humans, which increases the overall functioning of T cell proliferation and immune system Need literature citation for this statement Thus, increasing dietary sources of vitamin E (Table 1) in the diet of an elderly may be advantageous for their immune function, may provide resistance to infection, and may decrease morbidity because of infections. As the elderly population is more vulnerable to infection, investigating vitamin E for possible health benefits against COVID-19hich would be advantageous for improving T cell proliferation and the overall functioning of the immune system. (16)

**Table 1:** Different type of vitamins which helps in enhancing immunity

| Vitamins | Metabolism | Natural Sources | Mechanism to enhance immunity | Marketed products |
|---|---|---|---|---|
| **Vitamins A (23.24,25)** | It is ingested as retinyl esters or carotenoids and further metabolized to active compounds such as 11-cis-retinal. | It is obtained from the diet either as *all-trans*-retinol, retinyl esters or β-carotene, The food supplements are carrots eggs, sweet potatoes, milk etc | It plays rigid roles in cellular immune responses and humoral immune processes. It is a micronutrient that works in promoting growth, maintaining vision, and developing, and protecting epithelium and mucus. (26) | Nutrova Antioxidant Protection, etc. |
| **Vitamins B (27,28, 29)** | It is engrossed by the epithelial cells of the small intestine through intrinsic factor (IF), a gastric glycoprotein. | The major sources are Meat (red meat, poultry, fish), Whole grains (brown rice, barley, millet), Legumes (beans, lentils), Eggs and dairy products (milk, cheese) etc. (30) | Vitamin B6 works for immunity and works towards keeping the immune system strong. It also helps in building new red blood cells, and further transporting oxygen in the body. (31) | Sanliv Forte B-Complex, Enzyme with Vitamin B complex Syrup, cyanocobalamin, Nascobal etc |
| **Vitamins C (32)** | It is known that about 70%–90% of vitamin C is captivated at moderate intakes of 30–180 mg/day. But if body has above 1 g/day then absorption falls to less than 50%, unmetabolized ascorbic acid is eliminated in the urine | It is a water-soluble vitamin and it is naturally present in some foods, and is also available as a dietary enhancement. Humans, unlike most animals, are not able to synthesize vitamin C endogenously, so it is an essential dietary component | It is required for the biosynthesis of collagen, L-carnitine, and some neurotransmitters; It is also involved in protein metabolism. Its biosynthetic and antioxidant functions have an important role in immune enhancement (33) | Eucee Vitamin C chewable Tablets 500 mg. NOW Foods C-1000, Viva Labs Vitamin C etc |
| **Vitamins D** | For metabolism $VD_3$ is converted in the | It is synthesized in the skin from 7- | It helps to promotes a more tolerogenic immunological status. The | Calosto, alfado, Hira D3, Calcit |

| | | | | |
|---|---|---|---|---|
| | liver to 25-dihydroxyvitamin $D_3$ (25(OH)$VD_3$). Further, 25(OH)$VD_3$ is metabolized in the kidneys to 1,25$(OH)_2VD_3$ which is active $VD_3$ metabolite (34, 35) | dehydrocholesterol5, which depends on sunlight, specifically ultraviolet B radiation (36) | expression of the nuclear vitamin D receptor can be seen on vitamin D-activating enzymes in both T- and B cells (37,38) | 5G etc. |
| **Vitamins E** | Metabolism of vitamin E begins with one cycle of CYP4F2/CYP3A4-dependent ω-hydroxylation followed by five cycles of subsequent β-oxidation, and forms the water-soluble end-product carboxyethylhydroxychroman (39) | Main dietary sources of vitamin E are fresh green grass and supplemental forms. Wheat germ oil. Sunflower, safflower, and soybean oil. Sunflower seeds. Almonds. Peanuts, peanut butter etc | Vitamin E deficiency induces the impairment of both humoral and cellular immunity. Vitamin E deficiency induces the impairment of both humoral and cellular immunity. (40.41) | Benvite, Bio 3Sg, Bio 8888, Bio-E |

**Trace Minerals**

**Zinc**

Zinc comes under the trace minerals category. The body wants it in a very limited amount. It assists in immune cell growth and defense. Zn is known to prevent viral entry, block the production of polyproteins or prevent viral RdRp activity. Literature citation and an explanation of RdRp is needed. Zinc is one of the main factors regulating the activity and proliferation of neutrophils, NK cells, macrophages, and T and B lymphocytes as well as the production of cytokines by the immune cells. Zn also provides protection against the adverse effects of ROS Define what ROS is!, typically produced during inflammatory processes. Free intracellular Zn2+ is essential in extravasation to the site of the infection and uptake and killing of microorganisms by neutrophils. (42) Using recombinant SARS-CoV nsp12, teVelthuis et al. showed that Zn2+ directly inhibited the in vitro RdRp activity. They also reported that specifically, Zn2+ was found

to inhibit the SARS-CoVRdRp elongation and template binding. Earlier, it was also shown that Zn2+ inhibited the proteolytic processing of replicasepolyproteins.(43) Altogether, the available data concerning the immunomodulation effect of zinc proposed further study to explore the clinical evidences and to prove the conditional statement of the association with chloroquine (CQ) and Hydroxychloroquine (HCQ). Several theoretical investigations increased intracellular Zn2+ concentration by (CQ) might modulate antiviral effect against SARS-CoV-2. In this perspective, zinc supplementation in the absence of CQ might produce similar effects without adverse side-effects of CQ treatment.(44)

**Iron**

Iron is one of the most important minerals for every age group. People suffering from iron deficiency are more prone and at risk in developing acute respiratory tract infections. What about anemia? Reduced level of iron results in thymus atrophyand affects the activity of naïve T lymphocytes like zinc. T lymphocyte proliferation decreased up to 50 to 60% due to low iron level. (16) Evidence also suggests that iron chelators can exhibit antiviral effect on HIV through the elevation of intracellular iron efflux and increasing iron exporter ferroportin expression. Despite to date little is known about iron regulation in COVID-19 patients, it could be deduced from other viral infections that iron chelation might be an alternative beneficial adjuvant in treating COVID-19. However, it is important to point out that there is no empirical research to date, so further investigation is needed.(46)

**Selenium**

Selenium has important effect on both innate and acquired immunity. Selenium enhances the function of T lymphocyte and B lymphocyte and also increases the activity of natural killer cell. A study found that selenium supplementation improved immune function in the human body. The common sources of selenium are fish meat, egg and nuts. Supplementation of selenium also has some adverse effects on the body. (45)The amount of trace elements present in food varies according to the geographical differences of the soil. In this regard, soils in different regions of China have been reported to have the highest and lowest selenium levels in the world. Zhang *et al.* (2020) have found that infected patients from the areas with high selenium levels were more prone to recover from COVID-19. (47) What about Se in fish…which is best?

**Effect on the Geriatric Patients**

The basic symptoms experienced by patients suffering from COVID-19 consist of fatigue, fever and cough (dry). (48) Less common symptoms include anosmia, headache, production of cough with sputum, chills, joint pains vomiting, and diarrhea.The media report that anosmia is relatively common following COVID-19 infections. Apart from that in some old age patients unusual symptoms are tachycardia or tachypnea, delirium and hypoxia, sore throat. This sentence needs to be tidied up as it does not make sense. The symptoms usually lead to critical illness. The major symptoms which involve lungs dysfunction and shortness of breath are seen in 14% of the patients, and there are 5% that develop critical condition.(49) These complication which result in death of the patient include acute respiratory distress syndrome (ARDS) which leads to extended ventilator hold and other problems like cardiac damage, rhythm disturbance, and shock. (48)

The treatment pattern for the patients is in general supportive. For the patients or suspects the management pattern is isolation in anticipation of successful treatments or new vaccine that could cover the disease. In mild cases home isolation is normally preferred but if the patient in later stage develops symptoms like respiratory distress or hypoxia then preference is given to the ventilator support. [50] It has been noted that geriatric patients are mainly vulnerable to severe outcomes in SARS Cov-2 contagion and evaluation and management is challenging. For better care the longer-stay inhabited care homes and hospitals require ~~to~~ an urgent health care strategy for older patients. [51]

**Effect on the Geriatric Patients previous paragraph has the same title!**

The frequency of COVID-19 is just about 2 percent in children and adolescents. Kids had slight signs and other kids or adults were hardly contaminated.Please explain this statement. It should be taken into account that children are the most susceptible to respiratory contaminants, but lethal SARS-like viruses have not caused serious cases. [52, 53] Most of the cases reported in children at this time are clustered cases caused by close contact, refersed to as "second generation" infection [54]. Nutritional initiatives to increase immunity are something to be discussed for a viral disease such as COVID-19, where no pharmacological approaches for prevention or treatment are currently available and where the exact duration of the termination of the troubling situation is uncertain. [55] The formulating of food-based immune enhancers for

COVID-19 patients to enable the proper intake of macro- and micronutrients and, at the same time, to help reduce the severity of disease may be promising approach food related chemistry. [56] Clarify whether you are talking about a healthy diet or supplementation.

As we understand that children have a very poor immune system, special care must be taken to enhance immunity by increasing the consumption of food and dietary supplements in the form of vitamins and nutrients. Not all children have "a very poor immune system" – it depends on diet, environment and genetics!

**Table 2** Major nutrient food sources that benefit the Immune system [57-58]

| Macronutrients | Food Nutrients |
|---|---|
| Zinc | Vegetables: green beans, kale<br>Animal sources: beef, molluscs (raw), lamb, cheese<br>Seeds: flax seeds, squash seeds |
| Iron | Fruits: apricots (dehydrated), sunflower seeds<br>Vegetables: peas, tomatoes, spinach, kale<br>Animal sources: molluscs, egg, veal (ground), organ meat<br>Cereals: whole grains, fortified cereals |
| Omega-3 PUFAs<br>Seeds: | chia seeds, flax seeds<br>Animal sources: shell eggs, fish, seafood<br>Nuts: walnuts |
| Selenium | fish, meat, egg and nuts |
| Copper | Nuts, shelfish |



## Conclusion

People with low immunity low immunity or a compromised immune system? are more prone for this world pandemic named as COVID-19. To help or boost the immunity, the plant-based foods play vital role by promoting beneficial bacteria in the body. Many vitamins and minerals are ingested through other protein sources such as meat, fish and nuts. Various vitamins like A, B, C, D, and E are investigated to provide important aspects for improving immunity. Fruits like oranges, papaya, kiwi, and guava are rich in vitamin C, while vegetables like eggplant, bell peppers, beetroots, spinach, and cauliflower are known to be quite rich in vitamin C and are good

for immunity. Low- and middle-income countries should strategize to ensure the population at large has access to optimal nutrition to boost the immune system and should provide specific supplementation for treatment of COVID-19 patients, especially those with severe disease. Older adults represent a high-risk population and may be prioritized to receive care in nursing facilities and to receive specialized nutritional support to improve physical and mental outcomes of the COVID-19 pandemic. In the same way, it would be important to carry out separate studies in men and women since it appears that men are more negatively affected by this disease. All this will contribute to making a personalized nutritional approach, and therefore more successful.



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