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Nutrition within and beyond covid-19: A review to explore the immunity boosting potential of nutrients to strengthen the adaptive immunity response

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The immunocompromised disease is a health condition characterized by weakened immunity due to comorbidities (like cancer and HIV), medical procedures (including surgeries, bone marrow, organ, and stem cell transplantation), and treatments resulting in susceptibility, the severity of disease or recurrent infections. An immunocompromised individual is at increased risk of getting infected and progressing of disease present. In the presence of a global pandemic amidst several communicable infections, there is an increase in so many burdens related to health and wellness; a lot of individuals have become more concerned about their health, nutrient intake, and wellbeing. A healthy functioning immune system is very essential for body function and the need for immune-modulatory micronutrients, for instance, zinc, vitamin A Vitamin D emerges either through supplementation or from a natural source (which is optimum) for a healthy population. The immune systems are comprised of important cells (innate and adaptive immune response) responsible for performing defence and regulatory functions in the body. This review focuses on the implication of micronutrients in the regulation and maintenance of the immune system for the proper functioning and prevention against disease development, progression, or severity of these diseases.

Keywords: Adaptive immunity; COVID-19; Immuno-compromised Disease; Micronutrients; Supplementation, Stem cell Transplantation.

INTRODUCTION

Immunocompromised disease is a health condition characterized by depleted immunity produced by a particular recurrent chronic infection, comorbidity, medical procedures or treatment resulting in decreased functioning and protection against infection alongside other ailments. (Cahill et al) Conditions or treatments leading to weakened immune system, making an individual immunocompromised or immunodeficient include: Cancer, transplant (bone marrow, organ, stem cell, HIV), use of immunosuppressant among others. It is classified into primary (genetic condition where by an individual is immune impaired from birth) and secondary (acquired either from environment or disease) types (Raje and Dinakar 2015).

Immunocompromised individuals have increased risk of contracting an ailment and longer healing period than healthy individuals.

Immune System is the collective line of defence (Abbas et al 2019) classified as an innate and adaptive immune response (Childs et al .2019) that protects the human body at the time of infection from the multiplication of Microorganism that causes infectious diseases, regulates tissue injury and synthesis, identifies and sends feedback to protein synthesis and transportation of tissues through grafting, and also damages cells to activate therapeutic inflammation (Abbas et al. 2019) (Parham et al. 2014). The immune system is very crucial in the survival of humans. Absence or low immunity may lead to death most especially during childhood due to slow development (Parham et al .2014). Any stimulation may result in inflammation which is a sign of feedback made by the immune cells. A Modern sedentary lifestyle and lack of proper intake of adequate nutritious food may lead to the slowing of defence rate in the body (Childs et al. 2019) (Parham 2014)

The natural (innate) and adaptive immune feedback are the cells responsible for immune system coordination (Childs et al. 2019). The innate immune response is known as the upfront immediate defence opposing the disease-causing microorganisms; this is usually present at birth. The innate immune response detects the appearance of antigen and gives immediate feedback alongside the adaptive response involved with the advancing of infections. Phagocytes are the biological composition of natural feedback of the immune system (Portou et al. 2015)

Adaptive immune feedback protects body system from infections following the detection of a foreign body. B cells and T cells are the chief antigen receptors present on the biological surfaces in adaptive immune responses (Hemmer et al. 2015). T cells are composed of cytotoxic and T helper cells responsible for antigen detection and immune response regulation.These cells function in immediate detection and destruction of affected injured and a tumour cell, exhibit CD4 receptors, and regulates other responses (Childs et al. 2019). B cells play a role in the synthesis of specialized immunoglobulin separated into five categories: IgA, IgM, IgG, IgE, and IgD. IgA is found in the blood, mucosal linings and defends against bacterial and viral infections. It is also essential in hindering allergy from food. IgM amid maturation binds an antigen to detect and fight infections. IgG identifies antigen present producing efficient disposal. IgE functions as an extracellular parasite cleanser. IgD is constituted in the plasma in fewer concentrations (Childs et al.) (Berin 2012). Both B and T lymphocytes remain in memory to detect subsequent transgression by microorganisms.

Any stimulation may result in inflammation which is a sign of feedback made by the immune cells. Modern sedentary lifestyle and lack of proper intake of adequate nutritious food may lead to slowing of immune response (Childs et al .2019) (Calder et al 2015)

IMMUNOCOMPROMISED DISEASE

CORONAVIRUS

Coronavirus (COVID19) is a respiratory tract viral infection also identified as Severe Acute Respiratory Syndrome (SARSCoV2). It is characterized by respiratory malfunction, causing damage to the respiratory system and other vital body organs specifically when an underlying immunocompromised disease is present and other comorbidities. The symptom which manifest after incubation period of 2- 14 days includes; fatigue, dyspnoea, dry cough, pharyngitis, sometimes diahrrea and vomiting. The virus is transmitted through direct face to face contact with droplets of infected individuals (Al Shamsi et al. 2020). Some individuals turn out to be asymptomatic. The W.H.O announced Coronavirus as a global pandemic in the early 2020. Several vaccines are currently in trial while medication approved for different regions treatment (Marano et al. 2016) (Verma et al. 2020). Preventive measures are currently taken worldwide through maintaining optimum hygiene, social distancing and wearing of protective mask (BourBour et al. 2020).Recent studies indicates that rate of COVID19 transmission is three times higher than influenza (Syal 2020) (Vallamlondu et al .2020). Another data obtained showed that the virus increasingly affected every region in the world and above 50 percentage has received treatment (Verma et al. 2020). A data obtained in the Mid 2020 by the World Health Organization indicated above 8 million individuals confirmed positive while more than 400 thousand deaths. Reports from the WHO showed globally, there have been 31.4million confirmed cases of COVID-19, about 1 million deaths in the late 2020. According to region, data obtained by the WHO showed as follows

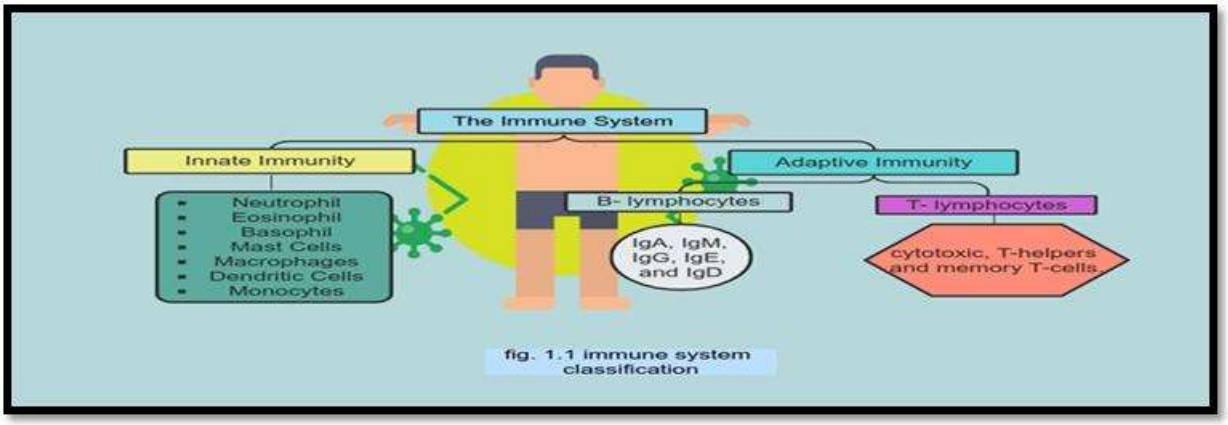

Figure 1 : Classification of Immune System

Table.1 Summary of studies

Form of Nutrient	No. of participants	Dosage/ Amount	Duration	Outcome	Reference
Ergocalciferol	36	250000IU/500000IU	84 days	Length of hospital stay of mechanically ventilated participants ICU of 250000 group reduced from 36 in control group to 25 days and 500000IU to 18 days	(Han et al 2016)
Vitamin D Status	50		3 month	Vitamin D status was higher in dengue fever participants than participants of dengue haemorrhagic fever.	(Mahmud et a 2018)
Ergocalciferol supplements	20	1000IU/d and 4000IU/d	10 days	The Dengue fever participants with higher dosage showed lesser infected cells than those with lower dosage	(Martinez et al 2020)
Zinc Tablets	4	115mg to 184mg	10-14 days	Improved recovery in COVID19	(Alexander et al 2020)
Zinc Sulphate	3	220mg	5 days	The supplements enhance the recovery of COVID19 participants	((Alexander et al 2020)
Zinc Powder	50	15mg, 3 times daily	5 days	Dengue participants had shorter stay in hospital than placebo patients	(Rerksuppaphol 2018)

respectively: Americas; almost 16 million confirmed, South-East Asia; 6.3 million confirmed, Europe; 5.3 million confirmed Eastern Mediterranean; 2.2 million confirmed, Africa; 1.1million confirmed, Western Pacific; about 600 thousand confirmed. In Pakistan, around 300 thousand cases have been confirmed and about 6,500 deaths (WHO 2020)

Studies have shown that most reported cases were seen most in the Elderly with no gender susceptibility difference and also in patients with comorbidities including chronic diseases like hypertension and diabetes which was associated with advancement of disease severity (Hu et al ..2020)

At the inception of the virus, it first aims the host major cells related to the respiratory system and binds through a systemic pathway that

attacks the immune response (innate and adaptive response).It then debilitates the lymphocytes presents subsequently, multiplication of the viral cells increases thereby damaging the pulmonary capillaries, erythrocytes, emphasizing the inflammatory response and invading the phagocytic cells. Studies from autopsies have shown thickened and blockage of walls in the bronchioles, singular nuclear cells, and Phagocytes.As the virus advances, rapid blockage increases and clotting occurs in the respiratory cells (Weirsinga et al. 2020) (Marietta et al. 2020) When the viral burden hits its peak (i.e. at the time of maximum of symptoms), antigen is released by the phagocytes resulting in t lymphocyte and synthesis of chemokines as a result there is an effective immune response and inflammation in infected cells occurs (Li et al. 2020)

DENGUE FEVER

Dengue fever is a viral infection caused by female mosquito (Aedes aegypti sp.) found in Anglo American and other warm regions in the world. Four closely related serostrain generates dengue virus infection and interacts differently alongside immunoglobulins present. Clinical manifestation include: hyperthermia, myalgia, cephalgia, ophthalmalgia, and arthralgia. It ranges from mild fever to severe haemorrhagic fever. As the infection advances, it leads to other comorbidities and organ failure.

The first barrier for defence against dengue is the skin succeeding the bite from the infected mosquito. The virus then attacks the accessory cells present and phagocytes and attaches to the cellular structures responsible for the transfer of the response. The virus further multiplies on the internal structure of the cells; Antibodies are produced as a result to directly attack the infected cells. Some antibodies divert and attach to viral cells leading to multiplication of the viral cells (Heilman et al. 2014) (Tremblay et al. 2019) (Arboleda and Urcuqui 2016). Vaccines and various medications are currently in use. Majority of the population worldwide are at risk with millions of cases reported yearly. A study has shown that the immune system only gives protection for one serotype at a time (Uno et al 2018) In Pakistan the first case was reported at the teaching hospital at the KPK province and from then, 47 thousand cases were confirmed and close to 80 deaths in the late 2019, around the four provinces (Cahill K)

MICRONUTRIENTS AND IMMUNE FUNCTION

Optimum nourishment obtained from nutrients (vitamins, minerals, trace elements) either through diet or supplementation is a foundation for a functional immune system. A study has shown that at the onset of infection there is a higher demand for energy thereby increased metabolic rate (Childs et al. 2019). Apart from immune functions, it is optimal for overall sound cell function and health status of the body. Deficiencies or lack of these micronutrients may result in low immunity, susceptibility to infection, deficiency or severity of disease, excessive (Lange and Nakamura 2020) (Maggini et al. 2018). Every Micronutrient has a unique role in the body function. Zinc is crucial for response of neutrophils and monocytes to stimulus. Vitamin D plays a regulatory function in immune response (Fantacone et al. 2020).Vitamin A derivatives plays a regulatory and functional role in basophils, dendritic cells, eosinophils, monocytes and macrophages (Huang et al. 2018)

One of the factors to consider is the bioavailability of nutrients especially during supplement selection for desired results (Gombart et al. 2020)

VITAMIN D

The D Vitamin is lipophilic in nature available as Ergocalciferol (D2) and Cholecalciferol (D3) in animal and plants respectively. The active form located at the kidney is 1, 25-dihydroxyvitamind. Due to its nature, products it makes it easier to diffuse into the cell organelles enabling attachment of 1α-25$(OH)_2D_3$ to its receptor and forms to bind with the response element resulting in its ability to function in metabolisms, inflammatory control, cell growth among others (Arboleda and Urcuqui 2016).Several clinical studies are in agreement that the normal blood level for Vitamin D3 was 75- 150nmol/l, below 30ng/ml was inadequate and below 50nmol/l showed deficiency of the vitamin (Nedjadi et al. 2015)

Vitamin D is essential in the regulation and anti-inflammatory effect of the immune system. It is also effective safeguarding against viral and microbial infection through activity of its compounds known as catheliriden and defensin. It facilitates regulation of inflammatory levels that affects the homeostasis of tissues (Arboleda and Urcuqui 2016).Cholecalciferol is the fundamental form of vitamin D obtained from precursor sources (from the skin and diet) after conversion and absorption through biochemical process in the

duodenum then further transported within the lymphatic vessels there by attaching to the globular proteins or vitamin binding proteins. These globular proteins are mainly produced in the liver. The vitamin is converted in the liver through enzymes present to 25-hydroxyvitaminD and further to 1, 25-hydroxyvitaminD. 1, 25-hydroxyvitaminD is an antibody or hormone that attaches vitamin d receptors that binds with DNA sites called vitamin d response. This response is effective in immune modulation. It is present in the skin as 7-dehydrocholesterol.

For a virus to thrive in the human system it first destroys the Vitamin D receptors present, therefore individuals with low levels are susceptible to these infections. Resent findings indicates assessment and therapy of the vitamin was necessary to improve positive outcome in infected patients. Also, patients with decline in Vitamin D levels especially at regions with decreased availability of sunlight may be linked with the risk or intensity of COVID19, as result require intensive care in the hospitals (Radujkovic et al. 2020) (Munshi et al. 2020) (Pizzini et al. 2020). Deficiency of this vitamin can be reversed through supplementation or sunlight which could enhance fighting infections (Galmes et al. 2020)

A recent findings indicated high dosage of Cholecalciferol decreased the severity of COVID-19(40) A study of 36 mechanically ventilated ICU patients grouped into 250,000IU 500,000IU were given ergocalciferol supplementation which resulted to the Length of hospital stay of 250000IU group reduced from 36 in control group to 25 days and 500000IU group to 18 days (Han et al. 2016)

Randomised control trials experiment is highly recommended for standard amount of Vitamin D levels that would be effective in the treatment of COVID19 due to the fact that there are current few RCT trials studies on the link between COVID19 and Vitamin D supplementation. Several RCT trials have been conducted on UTI, Pneumonia, ARTI and Vitamin D levels which shows its relevance in COVID19.Cholecalciferol especially signals for the necessary action to be taken to combat the virus or infection present and prevents tissues damage via its immunomodulatory capacity which makes its response effective for COVID19 (Siddiqui et al. 2020)

A 3 month study conducted to check Vitamin D levels in Benazir Bhutto hospital, Pakistan among 50 patients, between ages 19 to 70 years, half of the participants were diagnosed with Dengue fever and remaining half with dengue haemorrhagic fever showed Dengue Fever had levels of (21.5 ± 13.6 ng/ml) and Dengue Haemorrhagic Fever patients had(12.4 ± 5.6 ng/ml) there by mean the D vitamin status was higher in participants with dengue fever than those with dhf which also verified Vitamin D levels was significant in lowering dengue fever severity (Mahmud et al. 2018). A study also conducted in Mexico among five patients were given supplements of Cholecalciferol at concentrations of 0, 0.001, 0.01, 0.1, 1, and 10 μM after every 12 hours showed significant increase in platelet count and reduction in infected cells (Ahmed et al. 2014)

A study conducted within 2015-2016 in 10 days between 20 donors classified in two categories with the first group given 1000 IU/d and 4000IU/d respectively to check the effect of Cholecalciferol supplementation of on DENV-2 infections showed that those who received 4000iu/d had significant increase in Cholecalciferol levels with decreased frequency of infected cells than those who received 1000iu/l. this study showed high dosage of Cholecalciferol supplementation had positive effect on reducing the dengue infection (Martinez et al. 2020)There was no report indicating hypocalcaemia or Vitamin D toxicity during intake of supplement. But there might be possible chances of toxicity if high dosages are used on long term.

ZINC

Zinc is a trace element easily adapted by the body cells and mostly found in muscles and the bones. Zinc is critical in the immune system; it is involved with cells function as well as regulation of plasma membranes and inflammatory response including during sepsis, aids enzymes requiring numerous minerals known as metalloenzymes. With the help of zinc these metalloenzymes carry out various activities in cells including metabolisms, production and transport of nutrients respectively (Whitney and Rolfes 2018). Zinc from dietary form is distributed as free ions during digestion are assimilated in the small intestine. These free ions may bind to the ligands before they are transferred to the intestinal absorptive cells in the upper and middle part of the small intestines. It is transported into the liver and to other tissues where it carries out regulatory, immune modulatory and homeostatic functions.

Decrease or deficiency in Zinc concentrations in the body which is very rare may result in impairment of immune response and susceptibility

to microbial infection. Zinc concentration in the serum decreases at the time of infection due to transfer to organs in need (Mayor and Robles 2020). Zinc was also said to be effective in the treatment of diahrrea mostly in children. Studies has shown the inflammatory response of Zinc was shown to be effective in immune mediators' response present in patients with severe COVID19 (Doboszewska et al. 2020). Another study showed 1-Hydroxypyridine-2-thione along with low amount of Zinc hinders multiplication of SARS- COV hence, Zinc supplements was effective on not only COVID19 related symptoms but also pneumonia (Zhang and Liu 2020). A case history conducted in 10- 14 between 4 COVID19 patients administered 3 times daily with 115mg to 184mg zinc tablets, between 26 -63 years showed all patients recovered well. Another case history that was carried out in 5 days between 3 patients that were administered with 220mg of zinc sulphate alongside other medication showed improvement in the patients. The efficacy of Zinc was not properly established due to the fact that it was case histories (Alexander et al. 2020). An RCT trial conducted in Thailand for 5 days between 50 dengue fever patients with 15mg of elemental Zinc prepared in powdered form and dissolved in water and a placebo (oral rehydration solution with similar flavour and packaging) was administered 3 times daily. Result from the study showed patients given zinc supplementation had a shorter stay in the hospital than patients who had the placebo indicating a positive effect of zinc in dengue fever infections (Rerksuppaphol 2018) also the study showed patient with normal zinc serum levels had shorter stay in the hospital.

A study conducted in Malaysia on impact of different levels of zinc in dengue fever viral cell necrobiosis revealed that zinc enhanced death of dengue viral cells, and this should be improved through supplementation in patients. Recent reports conducted with human malignant tumor revealed that low $ZnSO_4$ levels (<20 μM) was effective in safeguarding affected cells (Ahmed et al. 2014)

VITAMIN A

The A Vitamin is Lipophilic in nature also known as retinoic acid, food sources contains carotenoids which is a precursor of vitamin A. (Whitney and Rolfes 2018)

Vitamin A is known for various body functions including regulation of immune cells response (particularly innate immunity) and inflammation, internal body function, skin, bone and eye health.

Vitamin A breakdown occurs in the duodenum like other lipophilic vitamins then released and merged with other dietary fats and bile acids. This enables intestinal absorptive cell to engulf them into fat globules from its precursor forms and transferred by the lymphatics.The liver cells disintegrate preformed vitamin A to retinol and merge it to the retinol binding protein. The TTR is mixed with the retinol binding protein and then released into the codocytes by the blood. When the retinols esters are not in use it is stored in the liver.

Vitamin A enhances synthesis of glycoprotein found in the digestive and respiratory tract thereby enhancing the immune functions in these sites.

A recent report showed the vitamin was efficient in relief of contagious breathing ailments in children which proves the need for supplement for children between 6-60 months old in developing countries (Huang et al. 2018). Another study revealed Vitamin A supplementation showed positive effect in patients with chronic bronchitis.

A clinical study was conducted on supplements that were effective in the increase of antibody response in bovine coronavirus in animals which showed low Vitamin A levels indicated epithelial tissue damage. There are currently few studies that shows the impact of vitamin A on COVID19 (Jovic et al. 2020) A recent study showed that low levels of retinol and β-carotene are linked with dengue fever severity (Ahmed et al. 2014). There is need for more investigation in roles of vitamin A and viral infections and dosage forms required to enhance treatment in these diseases

CONCLUSION

Micronutrients are very crucial in regulation of the immune system. It is also essential in immunocompromised diseases. The Immune system is also very essential in the maintenance of the Human System. All go hand in hand with each other to assist in defence of the infections caused by microorganisms, control immunosuppression caused by and thereby it is necessary to obtain these nutrients from preferably natural sources and through supplements.

Sources of the Vitamin D can be obtained from oily fish and egg yolk or naturally from sunlight through physiological process. Vitamin A sources include liver, carrots, dark green leafy and yellow vegetables and fortified or enriched cereals. Lastly Zinc sources include liver, carrots,

dark green leafy and yellow vegetables and fortified or enriched cereals.

Currently there are limited studies which need to be carried out on these micronutrients and their roles mentioned above and few studies mentioned healthy natural sources that could be taken by patients who are moderately Ill rather it suggested supplementation which could cause toxicity when high doses are ingested for a very long time

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

All authors shared in the writing of manuscript and reviewing it. All authors read and approved the final version.

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