Nutritional Interventions for a Healthy Life during COVID-19 Outbreak: Prospective Association with Healthy Dietary Pattern

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Abstract

Coronavirus disease of 2019 is a global pandemic and is a life-threatening public health problem all over the world. In view of the prevalence of this deadly disease caused by severe acute respiratory syndrome coronavirus 2, prevention and prophylactic strategies to prevent or minimize the havoc on mankind are now the topic of growing interest. This review focuses on various measures, as mentioned below, that will help to lead a healthy life, to improve the condition of patients for recovery, and to reduce the risk of deleterious effects. The aim of this review is to present an updated summary of most, although not all, preventive strategies. The adverse ill effects on health can be prevented or minimized by boosting the immune system. The immunomodulatory and anti-inflammatory actions of various micronutrients, particularly vitamin D are highlighted. The role of antioxidant nutrients in the prevention of coronavirus infection is emphasized. Diet plan to improve immunity has been discussed.

Keywords: Coronavirus, Immunity, Nutrients, Antioxidants, Diet plan

1. Introduction

Immune regulators are the first line of defence against the deterioration of health during coronavirus disease of 2019 (COVID-19) pandemic. A number of vitamins (A, D, C, E, B_{12} and folate) and trace elements (zinc and selenium) play a key role in supporting the human immune system. Micronutrients with the strongest evidence for immune support in preventing the risk of inflammation are vitamins (A, D, C) and zinc. Immunomodulatory, anti-inflammatory and anti-fibrotic action of micronutrients will be useful in possible prevention and management of COVID-19. Thus, well-functioning immune system is required for healthy life. Similarly dietary interventions with proper diet plan, is essential for the maintenance of health. Functional foods, such as nutraceuticals provide health benefits beyond the basic nutritional values. Proteins of high biologic value should be provided to enhance immunity function. During COVID-19 pandemic individuals are susceptible to abnormal behavioral problems due to social isolation. The individuals may suffer from depression, aggression, hostility and paranoid behaviour. The COVID-19 patients are more prone to stress, depression and abnormal behavioral problems. It is noteworthy to mention that omega-3-fatty acids [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and resolvins derived from DHA] may play a crucial role for optimal brain function and thus, can improve mental function (Cardosa et al. 2016). Lack of omega-3-fatty acids may lead to abnormal social and behavioral problem as mentioned above in COVID-19 patients. Oxidative damage due to mitochondrial dysfunction has been correlated with depressive symptoms. Furthermore, oxidative damage due to reactive oxygen species (ROS) may activate pro-inflammatory cytokines, which may aggravate inflammation of the airways and lungs caused by coronavirus. The beneficial effects of probiotics and prebiotics have been discussed in detail in this review.

2. Vitamin D

It is the main immune regulator having direct effect on the function of immune cells. It modulates the function of main immune cells, such as T cells, dendritic cells (DCs) and regulatory T cells (Tregs) (Poole et al, 2018). Tregs can inhibit inflammatory

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responses through the secretion of anti-inflammatory cytokines (Noval et al, 2016). Inhibition of DCs maturity and differentiation is an important immunomodulatory effect of active vitamin D (calcitriol) (Griffin et al. 2004; Barragan et al. 2015) and related D_3 analogs. Vitamin D_3 metabolite calcidiol can promote the development of Tregs (IL-10) by activating DCs (Bakdash et al. 2014). DCs of lymph node and skin are the antigen-producing cells (APCs). APCs are also known as accessory cells. APCs digest and present pieces of the antigen on their surface. In APCs, products of antigen digestion after coupling to protein products of the major histocompatibility complex (MHC) are presented on the cell surface (Ganong 2003). The MHC peptide complex on the surface of APCs binds to T cells. APCs act as messengers between the innate and the adaptive immune system. APCs are the key players in all aspects of T cell responses, including the generation of memory cells.

Vitamin D and inflammatory markers: The expression of inflammatory cytokines, such as IL-6, IL-8 and IL-17 has been found to be reduced by treatment with Vitamin D. Gut dysbiosis caused by COVID-19 is one of the common features. Vitamin D may enhance antimicrobial function in human oral keratinocytes by increasing cathelicidin production (Wang et al. 2013). Cathelicidin can maintain intestinal barrier integrity and also enhances the expression of protective mucin (Otte et al. 2009). Acute respiratory distress syndrome (ARDS) due to COVID-19 is caused by excessive and damaging inflammation of the respiratory tract, termed as "cytokine storm". Negative correlation between vitamin D status and number of COVID-19 cases, and mortality rate was observed (Ilie et al. 2020). Release of pro-inflammatory cytokines (IL-1â and IL-18) by activated macrophages and type 1T helper (TH1) immune cells results in inflammation and fibrosis of the lungs. TH1 helper cells are concerned with exaggerated cell-mediated response, acting against intracellular bacteria. They are activated by cytokines (IL-12, IFN-ä and IL-2). Expression of inflammatory cytokines, such as IL-á, IL-â and tumor necrosis factor-á was found to be inhibited by vitamin D and hypovitaminosis D was caused by overexpression of TH1 cytokines (Hughes et al. 2009). In addition to immunomodulatory action, vitamin D acts as an important antioxidant agent (Ebadi and Montano-Loza 2020).

3. Vitamin A

It was termed as "anti-infective" vitamin at the beginning of the 20th century. It takes part in modulating immune response function, such as activation and proliferation of lymphocytes, T-helper cell differentiation, production of specific antibody isotypes and so on (Mora et al. 2008). It plays an important role in preventing or treating inflammation and autoimmunity. Hypovitaminosis A results in reduced natural killer cell activity, decreased T- and B- lymphocytes and abnormal cytokine function. Vitamin A supplementation decreases child mortality and decreases the severity and duration of diarrhea (Ramakrishnan 2004). Retinoic acid derived from oxidation of retinal (vitamin A aldehyde) takes part in the synthesis of glycoprotein and glycosaminoglycans. Thus, vitamin A takes part in promoting growth and differentiation of tissues, and lubrication between the joints. This function of vitamin A may be hampered by COVID-19. Vitamin A deficiency causes metaplasia, leading to keratinized stratified squamous epithelium in the respiratory passages. This metaplasia of respiratory epithelium may facilitate replication and survival of SARS-CoV-2, which binds to angiotensin converting enzyme 2 receptors in the respiratory tracts of patients. Hypovitaminosis A causes infection of the lungs due to loss of mucociliary epithelium that will aggravate inflammation and fibrosis of the lungs caused by SARS-CoV-2.

4. Additional Immune Regulators with Special Emphasis on Vitamin C

Dysregulation of the immune function increases susceptibility to infection with increased morbidity and mortality. Intestinal infections hamper the absorption of both macronutrients and micronutrients, leading to dysregulation of the immune system, as well as malnutrition/undernutrition (Farhadi and Ovchinnikov 2018). Downregulation of immunity is a cause of malnutrition, which in turn, causes immune dysfunction (bidirectional interaction). This is typically observed in protein energy malnutrition (PEM) which is a disease of infants/children of poor mother. Chronic poverty is the main cause of PEM in developing countries. Lack of micronutrients status may lead to suppressed immunity, which predisposes to malnutrition. The individuals having BMI less than 18kg/m^2 are susceptible to COVID-19 infection. Vitamins (A, D, C, E, B_{12} and folate) and minerals/ trace elements (zinc, iron, copper and selenium) work

in harmony to support the human immune system and play significant synergistic roles to reduce the risk of infection (Gombert et al. 2020). Micronutrients deficiencies or insufficiencies are common in people with eating disorders (for e.g. anorexia nervosa), in smokers, chronic alcoholics and immunocompromised individuals (for e.g. pregnant women and elderly people), which suppresses the immune function (Wintergerst et al. 2007).

Deficiency/insufficiency of micronutrients inhibits immune function by affecting the innate T-cell mediated immune response and adaptive antibody response. COVID-19 patients should have adequate amount of vitamin C as the scorbutic individuals suffer from gum bleeding and subcutaneous hemorrhage in any part of the body due to defective collagen formation and brittle intercellular cement substance. Bone fracture with minimal trauma occurs as the bones are rarified. Deficiency of vitamin C may lead to depletion of muscle carnitine due to defective synthesis of lysine hydroxylase. This may lead to fatigue of the scorbutic individuals. Nitrites, used as preservatives in food can be converted to nitrosamines (Chakrabarty and Chakrabarty 2019). Vitamin C can prevent the formation of nitrosamine, which is a potent carcinogen. The risk for infectious disease is increased with zinc deficiency. Impaired zinc absorption causes acrodermatitis enteropathica characterized by eczematous skin on the hands and feet, impaired immune function, increased susceptibility to infections, diarrhea, poor wound healing, hypogeusia and hemorrhagic dermatitis around the mouth and eyes. Selenium is an anti-inflammatory micromineral. It is essential for immune function. Deficiency of selenium causes cardiomyopathy, resulting in enlargement of heart and ultimately heart failure (Keshan disease) (Gibney et al. 2009). Selenium and zinc are useful in preventing respiratory infections (Jayawardena et al. 2020).

5. Antioxidants

Vitamin C, vitamin E, carotenoids, flavonoids, and selenium are radical-trapping antioxidants, which prevent oxidative damage by inactivating oxygen free radicals. Carotenoids contain beta-carotene, beta-cryptoxanthine, lutein, zeaxanthine and lycopene. Flavonoids are antioxidant nutrients present in a variety of foods (Scalbert and Zamora-ROS 2015). Carotenoids are a variety of carotenes and give rise to retinal aldehyde, which is converted to retinol (vitamin A). Highly toxic ROS causes oxidative stress and damage by modulating various enzymes and transcription factors. Oxidative damage due to ROS activates pro-inflammatory cytokines, resulting in inflammation of the airways and lungs and causes bronchitis and thus, will aggravate the inflammation of the airways and lungs caused by coronavirus. Vitamin E and selenium act synergistically to prevent lipid peroxidation. Zinc/Copper superoxide dismutase (Zn/Cu SOD) prevents oxidative damage by converting superoxide to hydrogen peroxide, which is degraded by catalase. Antioxidants prevent oxidative damage caused by ROS and modulate various enzymes (kinases 1 and 2) and thus, immune function by regulating redox-sensitive transcription factors. Activated transcription factors travel from the cytoplasm of the cell into the nucleus and cause alteration of the gene expression, resulting in cell senescence. Antioxidant sources in the diet are shown in Table 1.

Table 1 Antioxidant sources in the diet

	Antioxidants	Main sources
1.	Carotenoids	Yellow vegetables, carrots and fruits
2.	Vitamin D_3	Cod liver oil, liver, egg yolk, meat, butter,fortified milk and edible mushrooms
3.	Vitamin D_2	Fortified food and mushrooms
4.	Vitamin E	Vegetable oils, wheat germ, tomatoes, nuts,green leafy vegetables and seeds
5.	Vitamin C	Orange, lemon, guava, amla (Indian gooseberry),tomatoes, broccoli and green leafy vegetables
6.	Zinc	Meat, liver, cheese, nuts, beans, wheat bran andoat meal
7.	Selenium	Garlic, cereal grains (jowar and bajra), Bengalgram, meat, shellfish, chicken and egg yolk
8.	Flavonoids	Onions, berries, apples and green tea containingcatechin
9.	Melatonin	Vegetables, fruits, flowers, seeds and a variety of herbs

6. Dietary Interventions/Diet Plan

(a) Nutraceuticals are functional foods with health benefits beyond the basic nutritional values for e.g. diets rich in fruits, vegetables, fish, cereal grains and olive oil.

(b) Omega-3-fatty acids (EPA and DHA) are found in fish oils. EPA can be converted to prostaglandins and leukotrienes that are essential for fluidity and renewal of the membrane. COVID-19 patients are not able to face minor stress. Isolation syndrome of Covid patients aggravates stress due to increased glucocorticoids. Social isolation, helplessness, dejection and loss of interest in daily activities may lead to aggressive behavior and domestic violence. Suicide is common due to extreme depression. Brain cells require EPA and DHA in order to stabilize mood and emotion (Cardosa et al. 2016).

(c) Probiotics are live microorganisms, the good bacteria that increase resistance to pathogen invasion by forming a physical barrier. Probiotics have many important functions including enhancing the immune function and also helping in the treatment and prevention of diarrhea, colitis, irritable bowel syndrome, diverticular disease etc. Yoghurt is a very good source of probiotics. Beneficial effects of probiotics is shown in Table 2.

Table 2 Beneficial effects of Probiotics

Facilitation	Inhibition
Formation of B vitamin (folic acid)	Gastrointestinal infections
Overall immunomodulatory response	Protein expression of pathogenic bacteria
IgA formation	Toxic compounds like ammonia
IgG formation (allergen specific)	IgE formation (allergen specific)
Th1 cytokine production	Th2 cytokine production
Treg formation and function	Cholesterol levels
Antiinflammatory mechanisms	Superoxide radicals
SCFAs formation	
Lactose tolerance	
Growth of intestinal beneficial flora	

(d) Prebiotic fibers are nondigestible food ingredients and include galacto-oligosaccharides, fructose-oligosaccharides (fructosans) and lactulose. Some dietary fibers are major sources of prebiotics. Fermentable fiber is present in prebiotic supplements which induce growth of beneficial bacteria (Lactobacillus and Bifidobacteria). Prebiotics increase the formation of important vitamins. They stimulate the activity and growth of intestinal bacteria. Colonic flora ferments carbohydrates and releases short-chain fatty acids (SCFAs). SCFAs are acetate, propionate and butyrate. They maintain the integrity of colonocyte DNA. SCFAs increase the secretion of bile. Propionic acid decreases cholesterol synthesis in the liver, leading to hypocholesterolemia. SCFAs result from fermentation of fibers by the gut microbiota and reduce the risk of type 2 diabetes mellitus (T2DM), metabolic syndrome, obesity and inflammatory diseases. Beneficial effects of prebiotics is shown in Table 3.

Table 3. Beneficial effects of Prebiotics

Facilitation	Inhibition
Growth of intestinal beneficial flora	Pathogenic bacteria
Formation of B vitamin (folic acid)	Risk of colonic cancer
Immune function	Triglyceride and cholesterol levels
Peristalsis	Risk of intestinal infection
Mineral absorption like calcium	
Bowel movement	

(e) During COVID-19 pandemic, the non-infective individuals or the patients suffering from coronavirus should take anti-inflammatory food (fruits, vegetables, dietary fibers, etc) and avoid pro-

inflammatory inducing diets (for e.g. processed and junk food), preventing inflammation. Intake of minimum 400g/day of fruits and vegetables is desirable. Diets rich in PUFA and MUFA should be preferred.

Effects of Various Factors on COVID-19 are summarized in Figure 1.

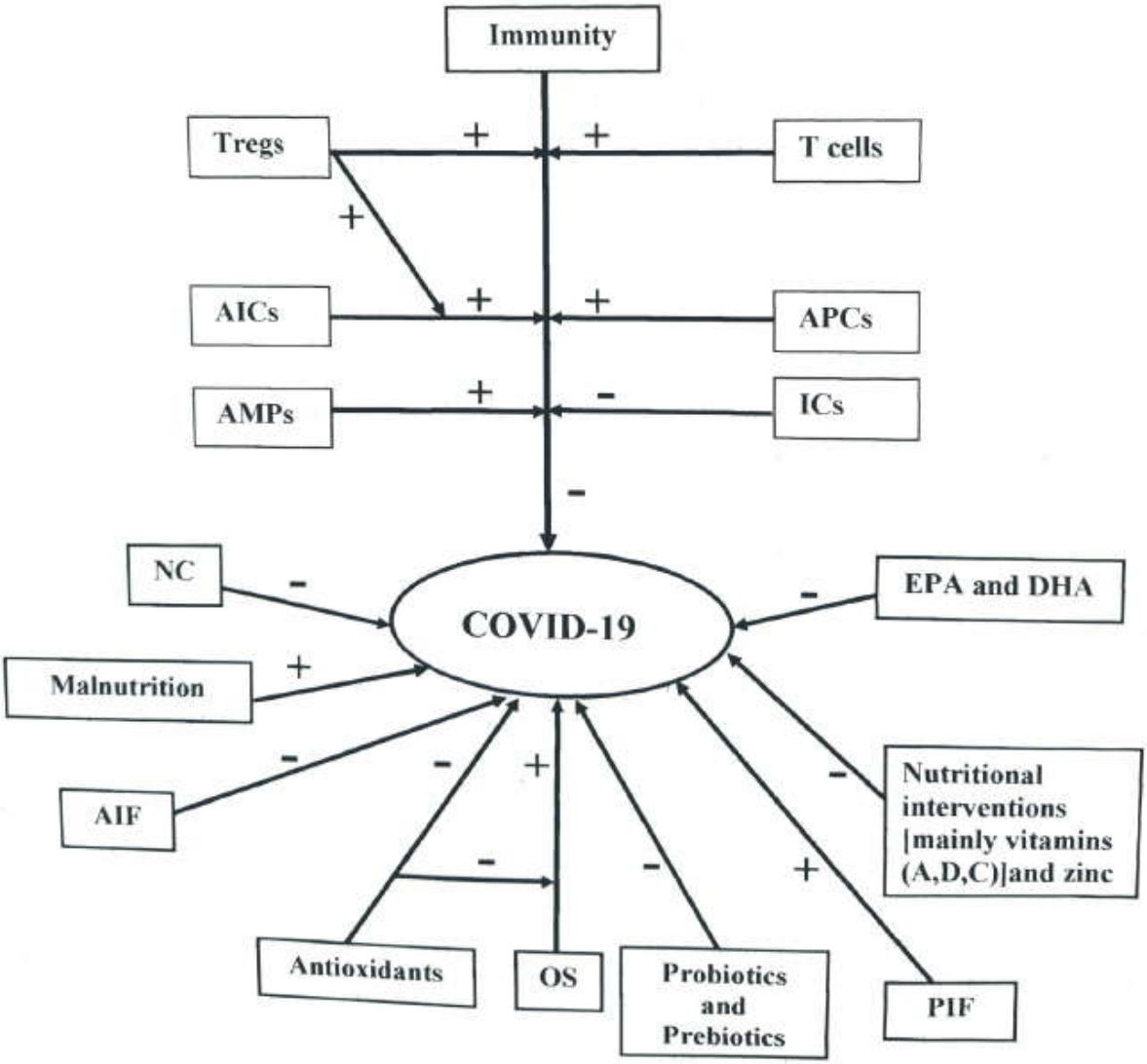

Figure 1 Effects of various factors on COVID-19. + indicates facilitation and - indicates inhibition; Tregs=Regulatory T cells; AICs=Anti-inflammatory cytokines; AMPs= Antimicrobial peptides; APCs=Antigen presenting cells; ICs=Inflammatory cytokines; NC=Nutraceuticals; EPA=Eicosapentaenoic acid; DHA=Docosahexaenoic acid; OS=Oxidative stress; AIF=Antiinflammatory food; PIF= Proinflammatory food

7. Summary

Possible benefits of vitamins, trace elements and functional foods including nutraceuticals in Covid-19 patients are summarized. The role of probiotic and prebiotic fibers, omega-3-fatty acids, pro-inflammatory and pre-inflammatory diets in ameliorating immunity in non-infective individuals as well as in patients suffering from SARS-CoV-2 disease has been emphasized. Balanced diet should be followed. Daily supplementation of nutrients should be higher than the RDA to support immune function. In conclusion, nutritional interventions may prevent cytokine storm in COVID-19 patients.

8. Future Directions

During COVID-19 pandemic, endogenous cutaneous production of vitamin D_3 (cholecalciferol)

from 7-Dehydrocholesterol is negligible due to limited exposure to sunlight in indoor population, especially immunocompromised individuals (for e.g. pregnant women and elderly persons). Dietary sources of vitamin D are not adequate to maintain vitamin D levels in the body. Vegans are very much susceptible to vitamin D deficiency as they do not consume any animal products including eggs and dairy products. Similarly obese people suffer from vitamin D deficiency as vitamin D, a fat soluble vitamin, is mainly stored into greater volume of adipose tissue because of its lipophilic properties. As a result, bioavailability of vitamin D is negligible due to volumetric dilution effect, as well as due to less endogenous cutaneous production. UV radiation falls in the autumn and becomes very less in the winters. Vitamin D status may be extremely low in vegans and obese individuals, especially in autumn and winter. To my knowledge, no study till date has measured serum vitamin D level in indoor vegans and obese individuals (both coronavirus infected and non-infected) during COVID-19 pandemic. It may be interesting to investigate the same at different seasons and different duration of sun exposure (from <1h/day to >2h/day). Different doses of vitamin D should be administered to find out the optimal vitamin D status. High dose of vitamin D should be avoided because of calcinosis. Well-designed randomized clinical trials may be warranted to evaluate or determine nutritional interventions with special emphasis of diet plan in preventing/minimizing the risk of deleterious effects of COVID-19.

Conflict of Interest: The author declares that there is no conflict of interest.

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