



Impact of Different Dietary Patterns and Micronutrients on the Immune System and COVID-19 Infection

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Abstract

Globally, the pandemic of coronavirus disease -2019 (Covid-19) has increased people's focus on the importance of consuming a healthy diet to promote their immune defenses. It has been established that many factors influence the immune system, including genetics, hormonal, and nutrition status. This study reviews the effect of the different dietary patterns and some selected micronutrients that most populations suffer from its deficiency, such as vitamin D, zinc, selenium, and iron, on the immune system. The aim was to focus on the impact of different diets and many nutrients on immunity which may protect or ameliorate COVID-19 patients. Mediterranean diet (Med Diet) is characterized by excellent vegetables, fruits, seeds, seafood, and moderate meat. This dietary pattern is linked to a well-functioning immune system. Med Diet contains many antioxidants as vitamin C, beta-carotene, and polyphenols that exert immunomodulatory and anti-inflammatory effects. Med Diet may be considered an effective and reasonably simple way to attenuate the intensity of COVID-19 infection. The vegetarian diet (Veg Diet), the plant-based diet, is also linked to healthy immune responses. It plays a criteria role in activating and strengthen both innate and adaptive immunity. It increases gutmucosa health and reduces autoimmunity related disorders. Contrariwise, the western diet (West Diet) is a popular pattern intake rich in carbohydrates, salt, saturated and trans lipid, while lacking in complex carbohydrates and fibers. This dietary pattern leads indirectly to increase inflammatory markers, obesity, and many diseases. Available evidence indicates that several micronutrients, including vitamin D, zinc, selenium, and iron, play an immune-supporting role, modulate the immune activity, and lower the possibility of infection. Optimizing vitamin D and zinc status definitely has advantages in COVID-19 patients. Evidence showed that various diet and different micronutrients play a role in the immune system and COVID-19 patients.



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Introduction

During the global pandemic of coronavirus disease-19 (COVID-19), many people have sought to improve their health by eating a healthier diet. The World Health Organization (WHO) released guidelines for healthy eating during the lockdown period.¹ Despite the fact that there is no specific food or dietary pattern that can prevent the infection with COVID-19, it has been a well-established impact of nutrition on immune system developments and responses.¹ Dietary intake has a central role in shipping the gut microbiome, which is the main factor influencing immune cells' development and immune responses.^{2,3}

Nutrition or dietary factors can be described as a single or a whole diet. A single diet such as protein, vitamin D, mineral iron, or a bioactive substance such as polyphenols. The whole diet, such as the Mediterranean diet (Med Diet).³⁻⁵ Studies showed that the dietary pattern containing vitamins (E, C, B2, and A), minerals (zinc and iron), and bioactive components (polyphenols) are related to a healthy immune system.⁶ Vitamins, minerals, and polyphenols act at several levels in the gastrointestinal tract, thymus, and immune cells of the circulating blood. Diet components can affect the immune system depending on concentration, interactions with other vital nutrients, internal environmental conditions, and host genetic expression. When a person consumed a healthy balanced diet, the immune system cells can deal with carbohydrates, proteins, and fats and keep a well-functioning immune system regardless of the life stage.⁶⁻¹⁴ Furthermore, evidence shows that poor or healthy dietary pattern has a significant influence on the functional of the immune system.³⁻⁵

Inadequate nutrition, either undernutrition or over-nutrition, was associated with complications to the immune system. In situations of a nutrient imbalance, the duration of the host's altered condition and age are also often critical factors. It has been emphasized that insufficient intake of certain nutrients adversely affects body defenses towards pathogens and impacts sickness and symptoms. In some cases, such as the infection of measles, the health outcome can result from a patient's nutritional status. While coping with an infection can be improved by consuming the deficient nutrient. On the other hand, the superabundant of certain foods or nutrients may

put immunity at significant risk.^{6,15-17} Besides other dual problems precisely due to the overconsumption of saturated fat and proteins.¹⁸

The overall diet intake during the early life of a person influences his future immunity and allergy reaction.¹⁹ Also, studies found that consuming a varied diet in children's early lives leads to a variety of gut-microbes and poor outcomes of allergy.²⁰ This relationship was explained by the positive effect on gut-microbiome, through multiple effects on the immune system's cellular and responses.¹⁹ Numerous epidemiological studies focus on exploring the impact of the whole diet on human health as a human consumed diet, not isolated nutrients. Moreover, the association between single nutrients such as iron and immune systems has been excessively studied.²¹⁻²⁶

As dietary intake is a key factor for better prognosis in COVID-19 patients. It may also assess disease progression.²⁷ This research aimed at reviewing the impact of the different diet and some selected elements on immunity. The review will focus on certain elements that most populations are suffering from its deficiency such as iron, zinc, and vitamin D. Furthermore, it will give insight into the importance of promoting the population's nutritional status to decrease the fraction of infectious diseases and the death rate attributed to immune deficiency.

Immune System

The immune system is an exceptionally complex structure. It is the protection that defends humans from pathogens such as microbes, fungi, viruses, and parasites that occur in the ecosystem. It consists of various cells, tissues, and organs. The immune system also contains thymes, bone marrow, and other secondary organs such as lymph nodes, spleen, and gut-associated lymphoid tissues.²⁸⁻³² Because there are no proven drugs or vaccines to fight COVID-19, the immune system is regarded by most scientists as the important shield that boosts the body's natural immunity against the virus infection. Diseases like COVID-19 go simply if the immunity is working properly.³³

The immune system destroys harmful enemies by two mechanisms: the innate or natural immune mechanism and the acquired or adaptive immune mechanism. Both mechanisms work together to

protect the body from pathogens.^{28,29} All people are born with natural immunity, known as innate immunity. It is the primary body defensive strategy against any pathogens, but it is less effective than the acquired immune reaction. Innate immunity is made of different barriers, including physical barriers such as skin and respiratory tract. This type of immunity also has mechanism defenses such as mucosa, bile, saliva, and inflammatory responses. There are cellular defenses, such as phagocytic cells. The phagocytic cells as neutrophils, basophils, eosinophils, monocytes, and macrophages, identify some organisms that invade the body as strange and potentially dangerous and get rid of them through phagocytosis and sterilization with their soluble factors.^{31-32,34}

The other type of immunity is the adaptive immune that a person acquires by the passage of time during his life after protecting the body from germs. It is the immune system that remembers its former enemies, which are antigens of the invading pathogen, and eliminates them through the antibodies that recognize them, which are "lymphocytes". Every lymphocyte bear surface receptors specific to a particular antigen that makes this type of immunity highly specific.^{29,32,35} For several days after the triggering antigen's prime activation, the adaptive immune responses become effectual, leaving immunological memory cells that is further a defining attribute of the adaptive immune response. This is the foundation for a better and more successful immune reaction after reinfection with the same pathogen. The major features of the acquired immune responses are humoral immunity and cell-mediated immunity. The humoral immunity features produce large amounts of antibodies, B cells to fight against extracellular pathogens, while cell-mediated immunity feature by producing cytokines and T cells that fight against intercellular pathogens. The healthy immune system acts fast, specific, and effective in fighting any pathogen. While the impaired immune system can result in infection and even death for the host.^{29,31,32}

Undoubtedly, the microbiome plays a critical role in shaping future immune tendencies. It has a vital role in developing the immune cells and their function.³⁶ Most of the immune cells are present within the gut-associated lymphoid tissue (GALT). This structure plays a significant role in the immune reaction and preservation of human health. The GALT

provides many efficient immune tasks. Dendritic cells and M cells sample the gut content while IgA is generated by plasma B cells within the lamina propria, which protect against infectious microbes.³⁶ The human intestinal microbiota can guaranty antigens and impulses inside the gut lumen itself accompanied by the capacity for interaction with local and generalized immune cells. The intestinal microbiota formation varies over the life cycle concerning nutritional factors and ecological factors, including exposure to antimicrobial drugs.³⁶ The implementation of a vegetarian Diet (Veg Diet) can bring various nutrients reaching the gastrointestinal tract microbiota. The non-digestible vegetable cell walls allow peptides and fats that might be absorbed in the upper gastrointestinal tract to attain the gut bacteria.³⁷ There may be situations where immune GALT cells fall into closer contact with foods and intestinal microbiome, including decreased wall strength or leaky bowel observed in both immediate and long term inflammation of the intestine.^{3,38} Also environmental factors influencing immune function, which include psychological, physiological stress, obesity, alcohol consumption, smoking, and imbalance nutrition.^{3,14,39-41}

Dietary Patterns and Immunity

Consuming an optimal diet is associated with improving the quality of human life.⁴²⁻⁴⁴ More importantly, it reserves a healthy immune system that can protect the host from any infection or illness.^{3,45} An ideal diet supplies the body with the extreme amount of necessary nutrients needed to develop, sustain, and enhance the immune reaction.

Mediterranean Dietary Pattern

Med Diet, a healthful diet, is characterized by a significant intake of vegetables, fruits, seeds, pulses, olive oil, seafood, and moderate meat and processed foods. This dietary pattern is linked to a well-functioning immune system,^{4,46} and reducing the risk of various diseases such as cardiovascular disease, obesity, type 2 diabetes, cancer, and some neurological disorders.^{44,47-50} One explanation of the role of the Med Diet on the body's health is reducing the immune-inflammation attributed to several diseases and improving the blood lipids profile.⁴⁵ Med Diet has a positive impact on gut-microbiome health and production. An important factor in the role of the Med Diet on the immune system is its antioxidants contents as vitamin C,

beta-carotene, and polyphenols. These antioxidants exert immunomodulatory and anti-inflammatory effects and hence reduce the risk of many diseases. Studies show a relationship between higher intake of the Med Diet and lower levels of the inflammatory cytokines. The Med Diet also reduces oxidative stress biomarkers.^{4,44,45} Another feature of the Med Diet is that it provides the body with an excellent balance of fatty acids⁵¹ as this diet is based on natural plant foods with a moderate intake of meat and low intake of processed foods. It is rich in monounsaturated fatty acids and low in trans and saturated fatty acids. Lab and animal studies show important fundamental roles of well-balanced, healthy fat intake in the immune cell membranes' growth. The unbalance of fatty acids intake in terms of quality and quantity may have disrupted the body's immune system, which increases the chances of infections.^{51,52}

Since COVID-19 is represented by excessive concentrations of pro-inflammatory cytokines, including CRP, IL-6, and TNF-alpha, successful inflammation-reducing therapeutic approaches may be followed to avoid the chance of infection or to minimize the virulence. The major constituents of the Med Diet, such as whole grains, vegetables and fruits, fish, and 'balanced' fats, including monounsaturated (MUFA) and polyunsaturated (PUFA), are all linked to reduced inflammation.⁵³ Compliance to the Med Diet has a good effect on heart disease and metabolic syndrome, which predispose to COVID-19 infection and severity. Via its strong antioxidant, anti-inflammatory, and possible antimicrobial and immunomodulatory activities, Med Diet may be considered an effective and reasonably simple way to attenuate the intensity of COVID-19 infection.⁵⁴

Vegetarian Dietary Pattern

Veg Diet or plants based dietary patterns are also linked to healthy responses of immunity. The Veg Diet is a plant-based dietary pattern rich in fibers, nutrients like vitamin C, E, and beta-carotene known for their antioxidant effect.⁵⁵ Veg Diet is a source of bioactive components, including flavonoids and polyphenol. Its favorable impact on health has proven as an antitumor. It also plays a significant role in activating and strengthening both innate and adaptive immunity. In innate immunity, polyphenols (PP) receptors are expressed on many immune cells that alert them

against any pathogens. It increases gut-associated mucosa health and reduces autoimmunity related disorders. It has antioxidant and anti-inflammatory activities. In addition, it reduces many inflammatory biomarkers, such as C-reactive protein.⁵⁶ They have been shown to modify the inflammatory reaction through multiple mechanisms: (a) modifying the signaling and enzymatic pathways engaged in the inflammation, including tyrosine and serine-threonine protein kinases, implicated in stimulation B-lymphocyte and multiplication T-cell. The major inflammatory markers like nuclear factor kappa β (NF κ β), and inducible nitric oxide (NO) synthase, the pro-inflammatory enzymes like inducible cyclooxygenase (COX-2), mitogen-activated protein kinase, and protein kinase-C have also been known to be inhibited by PP; (b) by decreasing the inflammatory cell discharge; (c) by neutralizing ROS including superoxide anions and hydrogen peroxide; and (d) by modifying inflammatory cytokines, peptides, and arachidonic acid.⁵⁷ Flavonoids have double actions in response to the homeostasis of reactive oxygen species (ROS). They function as antioxidants during normal circumstances and are effective pro-oxidants in tumor cells, which activate the apoptotic cell death and decrease pro-inflammatory signal transduction.⁵⁸

Peoples on Veg Diets have low rates of viral illnesses. In countries in the region to be on a Veg Diet for the reasons of religious or animal rights activists, a quick search of the COVID-19 global data indicated the lowest diseased cases.⁵⁹

Dietary Fiber

Fiber is an important element of a healthy balanced diet. The diets rich in fiber are the Med Diet and Veg Diet.⁵¹ Certainly, higher fiber intake is associated with lower body weight. Consequently, it is also important to maintain a normal weight, thus preventing inflammation attributed to adipose tissues in obese people.⁶⁰ Fiber also participates in the immune response. It causes the intestinal bacteria to produce short-chain fatty acids through the microbial fermentation of high-fiber diets and short-chain fatty acids. Hence, a fiber-containing diet improves the microbes in the gut and gut barrier function, reduces intestine inflammation, and improves the conditions of some diseases like Crohn's disease and irritable bowel syndrome.^{61,62} In addition, increased fiber intake can reverse the impaired T helper cell (Th)

function caused by consuming an unhealthy diet as the Western diet (WestDiet). Fiber intake can work selectively to shut down part of the impaired immune system while operating another part that is unconnected to the healthy immune system by activating the th17/regulatory T (Treg) cell axis and improving the production of mucus.⁶³

Western Diet and Dietary Pattern

A healthy diet should be adequate, varied, moderate, and balanced as excessive intake of certain nutrients has proven to impact human immunity in some cases.⁶⁴ At the same time, poor nutrition can affect the immune system adversely as well. Unfortunately, dual nutritional problems highly prevalent across many countries, including obesity and malnutrition.⁶⁵ This can result from the global nutrition transition, as many nation's diet intake shifted from consuming traditional cultural food to the WestDiet patterns and fast food.^{66,67} The WestDiet is a popular pattern intake rich in salt, trans, and saturated lipid, simple carbohydrates, however poor in complex carbohydrates and fibers. It is also described as a diet high in calories while low in nutrients, including vitamins and minerals.

The consumption of the WestDiet and/or fast food is associated with the high prevalence of obesity and chronic diseases such as Type 2 diabetes. Thus, this dietary pattern leads indirectly to increased inflammatory markers.⁶⁸ Evidence shows that the WestDiet and another western lifestyle, such as physical inactivity, have been identified as a risk factor of 'metaflammation', which is a metabolism-induced inflammation.^{5,69} The suggested reason, however, is the enhanced absorption of lipopolysaccharide (LPS), which is a component of the cellular membranes of gram-negative bacteria, from the intestinal microbiota leading to excessive gut leakage, recognized by innate immune system cells via toll-like receptor 4 (TL4) and by its activation of inflammatory response. This allows the infection to occur through the gut to the bloodstream. The WestDiet can lead to less variety of the gut microbes because of the low intake of fiber, while high in salt, sugars that alert inflammation and lead to some type of cancers, and other immune-related diseases.^{3,62,68,70}

WestDiet negatively impacts adaptive immunity while increasing inherent immunity, causing severe

inflammation and significantly hampering the protection of the individual towards virus infection. In populations who are more susceptible to inflammatory modulators, the use of WestDiet could raise the risk of extreme COVID-19 pathology.⁷¹

Selective Micronutrient Elements and Immunity Vitamin D

Vitamin D is critical for the innate antimicrobial response.^{72,73} Several immune cells possess receptors for vitamin D that influence their activity after ligand attachment. Therefore, this vitamin has a profound effect on immunogenicity. Vitamin D enhances monocytes' transformation into macrophages, improves their killing ability, modifies inflammatory cytokine secretion, and helps antigen presentation. In addition, vitamin D metabolites tend to control the development of unique antimicrobial proteins that destroy pathogens straightforwardly. It is, therefore, effective in mitigate the lungs' infection in kids and adults.⁸

Globally, most populations have an inadequate vitamin D.⁷⁴ It can act in a local immunological environment in an autocrine manner because vitamin D receptor is presented on different lymphocytes (B lymphocytes, T lymphocytes, and antigen-presenting cells). This vitamin can ameliorate both the natural and acquired immune reaction. Insufficiency in vitamin D is positively correlated to autoimmune disorders and raised vulnerability to pathogens.⁷⁵

Vitamin D beneficial effects on immune response are partly because of its impact on the innate immune response. Macrophages are reported to distinguish LPS, a bacterial contagion representative, via the toll-like receptors (TLRs). TLR involvement contributes to a series of incidents generating peptides with strong antibacterial action, including cathelicidin and β -defensin. These peptides collocate with bacteria phagocytosed inside macrophages, where they destroy bacterial cell membranes and possess a significant bactericidal action.⁷²

Vitamin D often influences physical and biological barriers because calcitriol controls antimicrobial proteins (cathelicidin and β -defensin), which are capable of changing the gut microbiome to a healthy system and maintaining the intestinal barrier.^{76,77} Calcitriol enhances the macrophage's oxidative

burst capacity, boosts superoxide production, lowers pro-inflammatory cytokines, and raises the anti-inflammatory cytokines.⁷

When assessing the magnitude of COVID-19 infection, the concentration of vitamin D plays an important role. A recent study showed that, in peoples suffering severe COVID-19 disease who need ICU admission, vitamin D deficiency is much more common. On the same hand, vitamin D deficiency COVID-19 sufferers reported higher concentrations of inflammatory cytokines.⁷⁸ A literature review analysis has also been carried out by Laird et al. concluded that optimizing vitamin D status definitely has advantages in COVID-19 patients.⁷⁹

Zinc

Zinc is important for cell-mediated immunity. This mineral supports many immune cells' works, such as natural killer cells, leukocytes, and dendritic cells.⁹ Zinc is known for its antioxidant function. It also possesses anti-inflammatory actions. The richest food of zinc is meat, while zinc from plants is not well absorbed. Thus some people who followed a Veg Diet may have a low intake of zinc.⁸⁰ Zinc deficiency is found to weaken the natural and adaptive immune responses, while abundant of this mineral improves human immunity.⁶⁶ The addition of zinc lowered oxidative stress indicators and the production of inflammatory interleukins.⁸¹ The value of zinc regarding the immune response is crucial at all ages. It is a cofactor and part of hundreds of enzymes in the human body. It helps to protect the natural barriers, including the skin and cell walls. It has a valuable role in cell proliferation and the formation of healthy mature immune cells. A notable property of zinc is that it regulated cytokines' secretion during the cell-mediated adaptive immune responses.⁸¹⁻⁸⁴ Zinc plays a critical role in regulating T cell receptors and T lymphocytes.⁸⁵ It is found to play a significant role in the immune response. Individuals with zinc deficiencies may face greater vulnerability to a wide range of pathogens. T-cell activities are negatively impacted by zinc deficiency since thymus dysfunction and immunoglobulin malformation are caused by zinc deficiency.^{86,87} Acute zinc malnutrition leads to suppressed natural and acquired immune responses, while a prolonged inadequacy raises inflammatory response. The development of pro-

inflammatory cytokines is augmented during chronic zinc insufficiency, affecting the outcome of a wide variety of disorders like rheumatoid arthritis.⁸³

Notably, in antiviral immunity, zinc plays a significant role as well.⁸⁸ Zinc is a popular component in both preventative and therapeutic COVID-19 clinical trials utilizing dietary supplements. Many clinical trials employing zinc in COVID-19. These studies might indeed give some insight into zinc's effectiveness against in vivo viral diseases.⁸⁹

Selenium

Selenium is an important component of the immune system. As an antioxidant, it plays a vital role in protecting the immune cells. It has vital functional, structural, and enzymatic responsibilities. Selenium works together with glutathione (GSH) to remove excess damage produced during oxidative stress.⁶ Bad selenium condition entails a greater risk of chronic illness, such as tumors and heart diseases.^{3,90} Selenium has great capability to affect the immune function since GSH peroxidase (an important antioxidant enzyme) is likely to defend neutrophils against ROS that are generated to destroy the foreign phagocytosed pathogens.

Selenium affects the dual types of immune function innate and acquired. Insufficiency selenium caused the inability of lymphocytes to proliferate, affect humoral immunity, and lowered immunoglobulins.^{86,91}

Selenium is a component of immune systems enzymes such as the seleno-enzyme thioredoxin reductase that is important to protect cells from damage by free radicals and important components of s anti-inflammatory activator protein (AP)-1, NFκβ, which is vital to activate the expression of cytokines and other protein components contribute to immune response.^{86,92} Selenium-dependent GSH peroxidases are important to reduce the damage of lipid and phospholipid.⁹³

Selenium depletion boosts infection susceptibility.⁹⁴ Seleno-proteins are an essential element of the endogenous host antioxidant defense mechanisms that affect the function of leukocytes.⁹⁵

Selenium condition has recently been observed to equate favorably with the survival of COVID-19

victims as opposed to non-survivors.⁹⁶ In COVID-19 suffers, a shortage of elemental selenium and its transporter protein levels were identified.⁹⁷ Furthermore, the findings of a recently published empirical investigation indicate that medication with selenium could be useful in minimizing the symptoms of the COVID-19 virus.⁹⁸

Iron

Anemia or iron deficiency a common problem among the population, especially children and women internationally.⁶⁵ Through the years, many studies have discussed in details the importance of iron on the immune system.²¹⁻²⁴ Iron plays a central role in the immune response. Evidence reported that iron deficiency and overdoes have an impact on immunity responses. Adequate iron intake is vital for maintaining healthy innate and adaptive responses. Iron has many roles in the immune system. It is important for cell-mediated immunity more than humoral immunity. It also plays a significant role in promoting natural immunity, such as the phagocytic cells. It also plays a role in defenses against a pathogen by neutrophils, and it is essential for many chemicals in fighting a photogene and the inflammation responses. Iron shortage can affect T-cells' production and elevated the cytotoxic T-cell. While overdoes of iron adversely affect the immune system, since this mineral plays a role in many microorganisms' growth and function.¹⁷

In COVID-19 cases, serum iron reduction was observed. The seriousness and mortality of the illness were closely associated with iron status. In COVID-19 sufferers, decreased serum iron level was a significant cause of mortality.⁹⁹

The Recommended Amount of Nutrients during Covid-19 Pandemics

WHO recommended eating 2 cups of fruit (4 servings), 2.5 cups of vegetables (5 servings), 180 g of grain, and 160 g of meat and beans on a daily basis. It has recommended a total daily consumption of salt to less than 5 g (about 1 teaspoon).¹⁰⁰ The average daily recommendation of vitamin D is 600 IU,¹⁰¹ zinc 10 mg,¹⁰² selenium (15-60 µg),¹⁰³ and iron (0.27-27 mg).¹⁰⁴

Conclusion

This review of the published studies showed a close relationship between dietary patterns and their components on the immune system. The Med Diet was one of the most important diets in enhancing the immune response and defending against microbes. The Med Diet was recommended to protect against COVID-19 infection. The review also presented the essential immunostimulant role exerted by many micronutrients, especially zinc and vitamin D. These elements may have an important role in COVID-19 infection and severity.

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List Of Abbreviations

AP = Activator protein

COX-2 = Cyclooxygenase

GALT = Gut-associated lymphoid tissue

GSH = Glutathione

Ig = Immunoglobulins

LPS = Lipopolysaccharide

MidDiet = Mediterranean diet

NCD = Non-communicable diseases

NF κ B = Nuclear factor kappa β

NO = nitric oxide

PP = Polyphenols

ROS = Reactive oxygen species

Th = T helper cell

TL4 = Toll-like receptor 4

TLRs = Toll-like receptors

Treg =Regulatory T

VegDiet = Vegetarian diet

WestDiet = Western diet