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Review Article

Association between Nutrition and Immune System: A Review

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ABSTRACT

Many human diseases are caused by infection with either viruses or bacteria. The proper functioning of the immune system is essential for the survival of any individual throughout life. The optimal immune response depends on an adequate nutrition and appropriate food pattern to prevent infection. For example, getting enough protein is important for optimal antibody production. Minerals and vitamins are forms of nutrients (called micronutrients) that have the appropriate capacity to support the immune system by providing preventive mediators of infectious diseases to reduce the rate of destruction of cells transported by free radicals or to help the better functioning of T-cells. Reduced intake of micronutrients such as vitamins A, E, C, D, B6, B9, and B12, as well as minerals such as zinc, magnesium, iron, selenium, and copper can decrease resistance to infections. Therefore, it is necessary to design a review study that looks at the role of micronutrients in preventing infectious diseases.

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Introduction

Since birth, our bodies are encountered by pathogens that live and replicate in an individual's body. Not all microorganisms are detrimental, for example, microbiota that have a symbiotic association with our digestive system (1). However, many pathogens can grow and multiply in the host body using certain mechanisms. These mechanisms cause disease in human beings. The body's defense system includes biochemical and other barriers that fight pathogenic microorganisms (2). Every step of the immune response is dependent on the existence of certain nutrients. For example, scurvy is caused by a lack of vitamin C. Therefore, this indicates the effect of nutrients on the functioning of the immune system (3). Also, vitamin D deficiency increases the risk of respiratory infections. An association has been observed between vitamin D deficiency in the blood and increased susceptibility to acute respiratory infections (4). In 2017, Martino conducted a systematic review and meta-analysis of (n=10933) participants and reviewed 25 clinical trials. Vitamin D supplementation was associated with a 12% reduction in respiratory infections (5).

A balanced diet containing a range of minerals and vitamins is essential for immune cells to function optimally to prevent infection (6-11). So immune cells need a good energy source, macronutrients, and micronutrients to fill in the articulation and preserve the immune response. The role of a healthy diet in immune function has become widely recognized, and the influence of various nutritional components on explicit aspects of the immune role has been extensively researched (12). Proper nutrition modulates oxidative and inflammatory stress processes (13). Dietary compounds with anti-inflammatory and antioxidant properties include omega-3 fatty acids (14), vitamin C (15) vitamin A (16). and selenium (17). Also, probiotic bacteria and bovine colostrum are effective in improving the functioning of Th1 and the immune system. Docosahexaenoic acid (DHA) and omega-3 fatty acids can reduce the damaging effects of inflammation. Therefore, the purpose of designing this review study is to investigate the known mechanisms of micronutrients that are essential for the functioning of the immune system and to determine the effects of an inadequate diet on the risk of infection.

Immunity

Resistance to pathogens has been referred to as immunity. Inflammation is a biological reaction of the immune cells that can be caused by a diversity of factors, including pathogens, tumors, and damaged cells. The immune system consists of two parts of acquired and innate (18, 19).

Innate immune Response

The innate immune system is the initial reaction to infection. The innate immune system can be characterised by three protection mechanisms including (i) physical barriers; (i) cellular components; and (iii) humoral responses. The innate reaction is quick, but not specialised (3, 18, 20, 21).

Physical Barriers in Innate Immune System

The first line of the immune system includes the surfaces of the body (mucus membranes and the skin), which form chemical and physical barriers against pathogens. Micronutrients are involved in the proper functioning of this line of defence. For example, iron is essential for cell growth (22). Vitamin A and zinc are essential for maintaining the integrity of mucous and skin cells, and vitamin C is essential for enhancing collagen synthesis (22). Intestinal microbiota compositions are affected by vitamins A, D, B9, B6 and B12 (23). Antioxidants such as vitamins C and E are effective in protecting cell membranes against free radicals (24).

Cellular Components in Innate Immune System

Some pathogens cross the first line of defence, but encounter the second line of defence, such as phagocytes, interferons (IFNs), and Natural killer (NK) cells. Interferons are antimicrobial agents that inhibit the growth of pathogens. Selenium increases the production of IFNγ (25). Iron, zinc, and vitamin C are effective in its production (22). Neutrophils and NK cells produce antimicrobial peptides such as cathelicidins. These peptides absorb and kill bacteria (26).The active form of vitamin D is effective in the gene expression of these peptides (27).

NK cells kill pathogens via cytotoxins (2). Vitamin A is effective in maintaining the function of NK cells and vitamins B6, B12, C, and E, and folate are involved in their cytotoxic activity (2). Next, neutrophils and macrophages migrate to infected areas. Neutrophils kill the infection and macrophages clear the cellular waste (28). Macrophages need iron and vitamin D for their normal function (29). Vitamin D also enhances the phagocytic activity of macrophages. Vitamin C facilitates the movement of neutrophils (30).

Phagocytes digest microbes and reactive oxygen species (ROS) is produced during this process. Finally, a combination of digestive enzymes, peptides, and oxidants causes phagocytes to die and burst (12). Vitamins C and E have antioxidant properties and are effective for optimal oxidative explosion performance (2). Selenium acts as a regulator of cellular antioxidants (via glutathione peroxidase) and is therefore effective for the function of leukocytes. Zinc also improves the function of phagocytes by modulating oxidative explosion activity (31). On the other hand, zinc has antioxidants that have a protective effect against ROS (32).

Inflammatory Reaction

Cells can be damaged by pathogens. Raising body temperature is an inflammatory response to eliminate any foreign matter. Fever can exacerbate the effects of IFNs and the body's reactions to tissue repair. Following cell damage, the capillaries constrict and histamine is released from the mast cells, leading to dilation and increased capillary permeability. Basophils and platelets migrate to the infected site. Increased blood flow dilutes infections and bacterial toxins. Prostaglandins, bradykinin, and leukotrienes also help capillaries increase the number of neutrophils to kill pathogens. Finally, macrophages phagocytose dead cells (33). Vitamin A activates macrophages (12). Vitamin D increases the expression of anti-inflammatory cytokines by macrophages through positive regulation of MAPK phosphatase-1 and suppression of p38 activation (34), and vitamin E modulates the production of prostaglandin E2 (which has inflammatory properties) (12) and vitamin C reduces histamine levels and cytokine production (35).

Acquired Immune Response

The obtained immunity is dependent on the ability of the immune cells to differentiate between their own cells and unwanted invaders. Pathogens that overcome initiate immune response biochemical mechanisms quickly, identify pathogens, and eliminate the risk through plentiful immune cells. The acquired immune response has the capability to precisely recognize a pathogen and 'remember' it if exposed to it again. Acquired immunity is the defence that we gain through life when we face with numerous illnesses or defences against them for vaccination. This immunity produces antibodies when it spots a microorganism in the body. Specific offensive agents can initiate slower-acquired immune operations that use B and T cells. They detect antigens present on the pathogens and produce antibodies against them; they can also neutralize or detect pathogens being attacked by other immune cells (20, 36). Acquired immunity takes 5 to 10 days to produce antibodies, and during this time, innate immunity becomes aggressive to preserve the levels of pathogens (18, 20, 21).

There are three types of T cells. Cytotoxic CD8+ T cells kill pathogens after identification of peptide antigens on the pathogens membrane. CD4+ T helper (Th) cells support B and other T cells to accomplish their functions. Regulatory T cells (Tregs) prevent excessive immune reactions (37). Th cells differentiate into Th1 and Th2 cells. Th1 cells secrete IL-2 and IFNγ in response to viruses and bacteria. Th2 cells also produce several other ILs (IL-4, IL-5, IL-10 and IL-13) against pathogens. Vitamin A is essential for the development and differentiation of Th1 and Th2 cells (12). Vitamins E, B6, and B9, and zinc are involved in improving Th1 function, while vitamin D inhibits its activity (12). Lymphocytes begin to multiply after exposure to antigens and their detection. Vitamins C, E, B12, and B6 are involved in the differentiation and proliferation of lymphocytes, while calcitriol prevents the proliferation and differentiation of lymphocytes (38). The acquisition of mucosal-homing properties by lymphocytes is facilitated by vitamin A (12).

Effect of Nutrients on Immune System

The immune system and nutrients interact in four steps (39). Steps 1 and 2 do not play a role in providing essential nutrients to the immune system, so these two steps are called inactive. Steps 3 and 4 play a role in regulating the immune response, for example, through gastrointestinal receptors, so these two steps are called "active methods" in increasing the immune system. Step 1 includes nutrients such as protein, vitamins (vitamins A, E, and C), and minerals (Fe and Zn) that are provided to improve the function of the immune system (39). Step 2 involves the supply of glutamine, which is a common fuel for immune cells and the body, especially during strenuous exercise. This step plays a role in providing more nutrients than the first stage in the performance and better response of the immune system against invading factors (39). The goal is to communicate with the immune system in order to control how it works.

Step 3 allows dynamic communication with the body's defense system to control its function to the desired goal. For example, probiotic bacteria and bovine colostrum are effective in improving functioning of Th1 and the immune system. Also, docosahexaenoic acid)DHA) and omega-3 fatty acids that can reduce the damaging effects of inflammation (39). Step 4 surveys the relationship between diet, environment, and genome; thus, a good diet can be effective in eliminating disease and improving quality of life (39).

Effect of Micronutrients on Improving Body Defense and Tracking the Incidence of Infection

Optimal amounts of micronutrients are needed for the body's active defense system, and these amounts vary at each stage of a person's life (2). It is recognized that an apparent lack of micronutrients has a negative impact on the immune system and makes people more susceptible to infections (40), and a lack of micronutrients is recognized to increase the risk of illness and humanity. Lack of micronutrients causes destructive effects on the health of the body (34) (Table 1).

The Effects of Nutrients on Infectious Disease

As discussed, minerals and vitamins play an essential role in every stage of the immune system.

Lack of micronutrients is considered the most common cause of secondary immunodeficiency and infection (71). Studies show that many people have an inadequate daily intake of micronutrients (72).

Vitamin A

Vitamin A supplementation (50,000-200,000 IU every 4–6 months) in offspring can decrease the incidence of malaria (73), measles, and diarrhea (74). Serum levels of vitamin A were also low in patients with AIDS (75). However, other studies in children did not find any relation between vitamin A consumption and a decrease in the incidence of pneumonia or lower respiratory tract infections (RTI) (76, 77).

Vitamin D

Vitamin D deficiency is linked to infection diseases. This deficiency has also been observed in

Table 1: The role of micronutrients on the body's defence system.

Micronutrient	The role of micronutrients	Foods rich in micronutrients
Vitamin A	Vitamin A is involved in the cell differentiation of Th1 and Th2 cells (16). It is vital for supporting the gut barrier (23). It also has immunoregulatory activities by decreasing the toxic influence on ROS and modifiable gap-junctional communication and membrane fluidity (41). It controls the amount and role of NK cells, IL-2, and IFNγ production (42) and their involvement in the activity of macrophages (12).	In animal sources including liver, milk fat, poultry eggs, offal, liver, and turkey meat; in plant sources including carrots, spinach, orange juice, sweet potatoes, and cantaloupe (43, 44).
Vitamin D	Calcitriol controls the regulatory proteins of microbiota, which protects the intestinal barrier (45); it grows the protein of tight junction expression in the gut (46). It also improves the defensive system in the lungs and corneal epithelium (47). Calcitriol adjusts antimicrobial protein expression, which puts death to pathogens (48). It preserves renal epithelial barrier role (49) and increases corneal epithelial barrier role (50). Monocytes and macrophages have vitamin D receptors; thus, this receptor increases conversion induction from monocytes to macrophages (22). It also plays a role in the movement of phagocytes (12), prevents IFNγ production (51), and is involved in reducing the expression of inflammatory factors by macrophages (34).	Liver fish, oil fish, butter, cream, egg yolk, liver, and shitake mushroom (44, 52).
Vitamin E	It keeps cell membranes from the negative effects of free radicals (12), increases natural killer cell cytotoxic action (12), prevents the action of macrophages in the production of PGE2 (24, 53), increases the production of IL-2 (22), increases lymphocyte production, and affects the function of T cells (22).	Wheat germ oil, soy, safflower, corn, cottonseed, palm, canola, sunflower, raisins (44), and soaked almonds (54).
Vitamin C	It protects cells against free radicals through collagen synthesis. It preserves intracellular redox homeostasis (12). It reinforces the antioxidant function of Vitamin E and glutathione (32). It modulates histamine and cytokine levels (42). It increases NK cell actions (12). It increases phagocytosis, ROS production, and microbial killing (42). It also has a role in apoptosis (42). It weakens extracellular trap (NET) construction, therefore, decreasing related tissue hurt (55).	Fruits, vegetables, organ meats (44), citrus fruits, red and green peppers, kiwi fruit, tomatoes, broccoli, brussels, strawberries, sprouts, and cantaloupe (54, 56).
Vitamins B6	Vitamin B is involved in regulating intestinal immunity. It promotes lymphocyte migration into the intestine (57). It maintains or increases NK cell cytotoxic activity (12). It promotes lymphocyte proliferation; and it protects the Th1 immune response (22).	Whole grains, vegetables, nuts, potatoes, chicken, bananas, meat, fish, eggs, and dairy products (44).
Vitamin B9	Folate controls the action of T cells (57). It keeps or increases NK cell cytotoxic activity (12).	Liver, mushrooms, spinach, asparagus, broccoli, beef, potatoes, orange juice, and beans (57).
Vitamin B12	Beneficial microbes in the gastrointestinal tract use vitamin B12 to improve the body's defenses (57). Vitamin B12 is involved in the function of T and NK cells (22).	Beef liver, oysters, shellfish, liver, some fish (herring, sardines, salmon, trout), and milk and milk products (44).
Iron	Iron is important for the evolution of epithelial tissue (22) and the complicated control of cytokine function (22). It improves the M2 macrophage phenotype and controls the inflammatory response of M1 (58).	Beans, spinach, liver, potatoes, beef, eggs, peanuts, chicken breast, and broccoli (56).

Zinc	It preserves the skin (59) and increases NK cell cytotoxic function (12). It plays an essential role in the evolution and differentiation of immune cells (60). It increases the phagocytic activity of macrophages and the phagocytic activity of monocytes (24). It produces IFN (42). It is an anti-inflammatory mediator (61). It controls cytokine spread (22) by reducing the growth of proinflammatory cells (62) and affecting the production of IL6, IL2 and TNF (63). It has antioxidant properties too (32).	Meat, fish, poultry, and soy (64).
Magnesium	It preserves DNA against oxidative harm (65). It is involved in DNA duplication and reparation (65). It controls leukocyte activation (66). It is involved in the control of apoptosis (65) and high concentrations of magnesium decrease superoxide anion production (63).	Seeds and kernels, legumes, grains, green vegetables, and milk (67, 68).
Copper	It is effective in the function of macrophages, (69), monocytes, neutrophils (70), and NK cells (71). It also has an antioxidant role (70). It gathers at sites of inflammation (70). It is a key enzyme in preservation, in contradiction to ROS (12). It is a free radical hunter and is vital for IL2 production (70). It also preserves intracellular antioxidant equilibrium, suggesting a vital role in inflammatory response (12).	Chocolate, nuts, legumes, cereals, and dried fruits (69).
Selenium	It increases IFNγ production (42). It also has an antioxidant role (2).	Seafood, offal, meat, and poultry (64).

severe respiratory infections (78) and in COVID-19 patients (79). As a result, adequate vitamin D levels in the body strengthen the lungs' defense system against coronavirus attack (48). Vitamin D has antimicrobial activity that fights several microorganisms, including bacteria, viruses, and fungi. It also fights against several microorganisms, including bacteria, viruses, and fungi (80, 81) and vitamin D (300–3653 IU/day) in children and adults can decrease the risk of respiratory tract infections (RTI) (5). The study supports the benefits of vitamin D in decreasing the risk of upper tuberculosis, RTI, pneumonia, diarrhea, and influenza (82).

Vitamin C

The influence of vitamin C in decreasing the risk of colds has been discussed. The study found no link between participants who received vitamin C supplementation (0.2 g/day) and the occurrence of the common cold (83). Although the other evidence supports a decreased risk of upper RTI and pneumonia (83, 84). In the present study, only the association of vitamin C and the improvement of the immune system function of patients with COVID-19 has been deducted (85).

Zinc

Undernourished children (86) can benefit from zinc (5–50 mg/day) to decrease the incidence of otitis media. Other evidence showed a decrease in the incidence of lower RTI or pneumonia, and diarrhea or dysentery after zinc supplementation consumption (87, 88). However, there is no relation between zinc (5 to 20 mg/day) consumption and the reduction of the risk of malaria or RTI in children, though there was a decrease in mortality connected to RTI, malaria, and diarrhea (89, 90). Patients with tuberculosis and HIV (75) have revealed significantly lower plasma zinc levels than individuals without tuberculosis, regardless of their nutritional status (91, 92).

Iron

Iron supplementation in children decreases the risk of RTI (93).

Selenium

Selenium deficiency may be associated with death in patients with COVID-19 (94) and patients with tuberculosis (91, 95-98) and patients with HIV (75).

Conclusion

Every stage of the immune reaction relies on the existence of certain micronutrients, which are effective for its optimal performance. Acquired immunity requires vitamins A, B6, B9, B12, D, and C, and selenium, iron, and zinc for differentiation, proliferation, and cellular function. Also, chemical reactions such as the release of proinflammatory cytokines require minerals and vitamins (vitamins A, C, and D, and zinc, selenium, and iron). Vitamins A, B6, C, and E, and iron, copper, and zinc regulate inflammatory responses. Micronutrients are essential for the effective functioning of the body defence, and on the other hand, a lack of micronutrients negatively affects the body defence and makes people more susceptible to infection. Intake of micronutrients in developing countries is insufficient and raises the risk of infection (99). Current research suggests that vitamin A (measles and diarrhea in offspring), vitamin C (pneumonia and common), vitamin D (RTI), zinc (otitis media, diarrhea, RTI, and pneumonia), and iron (RTI) have valuable influences on risk reduction (100). Overall, the studies showed that micronutrients can help people stay healthy and boost their immune systems.

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Conflict of Interest

None declared.

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