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Nutritional support for immune health during infections

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ABSTRACT

Infectious diseases are common in underdeveloped and developing countries. Malnutrition plays an important role in disease etiology, remarkably increasing morbidity and mortality risks during the early stages of life, such as infancy and childhood. Nutrients such as glutamine, arginine, omega-3 and omega-6 fatty acids, zinc, selenium, iron, vitamins A, C, E, D and B6, components of breast milk, and adequate energy intake strengthen the immune system, reduce infection risk, and play a key role in combating diseases. This review highlights the importance of nutrition for the treatment of infectious diseases.

Keywords: Nutrition, immunity, infectious diseases

INTRODUCTION

Adequate nutrition is essential to prevent infections and reduce morbidity and mortality. Nutritional status influences the host's susceptibility to infections and its ability to fight them.[1] Malnutrition is the primary cause of immunodeficiency (Figure).[2]

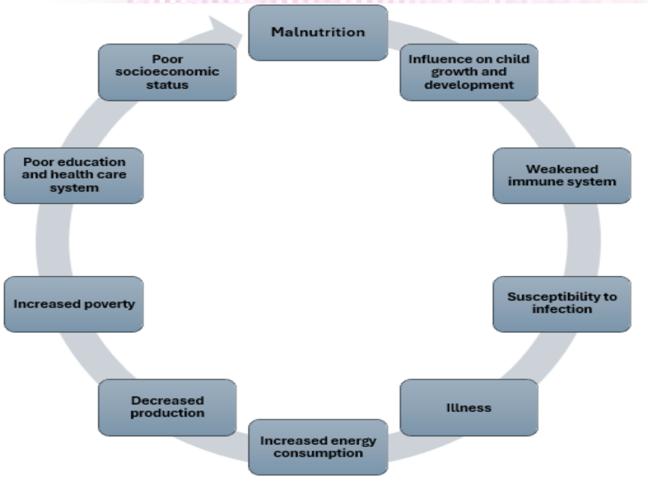

Figure. Cycle of the malnutrition and infection[7]

Owing to the deficiency of some micronutrients, the immune system is adversely affected, causing a weakening of the immune system and infection.[3,4] Therefore, adequate nutrition is critical during fetal development and infancy, when the immune system is not fully mature.[5]

Infectious diseases are differently affected by nutritional intake. Diseases such as pneumonia, infectious diarrhea, measles, and tuberculosis are highly affected by malnutrition, while infections such as influenza, viral encephalitis, and tetanus are moderately or minimally affected by malnutrition.[6]

EFFECTS OF NUTRIENTS ON INFECTIOUS DISEASES

Nutritional habits and food consumption directly impact the immune system. Nutrient deficiency, excessive consumption of sugary and allergenic foods, and high blood cholesterol levels suppress the immune system.[8] Proper nutrition also influences the immune system by affecting the composition of gut microbiota. Moreover, the microbiota produces metabolites such as short-chain fatty acids and ligands of the aryl hydrocarbon receptor that process food components and control the development and activity of certain immune cells, including regulatory T cells.[9] Glutamine, arginine, omega-3 and omega-6 fatty acids, zinc, selenium, iron, vitamins A, C, E, D, and breast milk components are the main nutrients that affect the immune system.[10-12] Deficiency of these nutrients in children may impair the immune system function in later periods.[13]

These nutrients have various functions in the human body.[14] We can list these as follows:

- It acts as fuel for the immune system's activity.
- It forms building blocks for the production of RNA and DNA, proteins (antibodies, cytokines, receptors, acute phase proteins, etc.), and new cells.

- Forms specific substrates for the production of immune-active metabolites (e.g., arginine as a nitric oxide substrate).
- Regulators of immune cell metabolism (e.g., vitamin A, zinc)
- They have specific antibacterial or antiviral effects (e.g., vitamin D and zinc).
- They protect the host from oxidative and inflammatory stress (e.g., vitamin C, vitamin E, zinc, selenium, long-chain omega-3 fatty acids, and many plant polyphenols).
- They act as substrates for gut microbiota, thus modulating the immune system.
- The following are the nutrition and lifestyle recommendations for effective functioning of the immune system:[15]
- Unprocessed products such as vegetables, fruits, seeds, cereals, and legumes should be consumed.
- The consumption of fat and refined sugar should be limited.
- Drink at least 2 liters of water per day.
- Sleep for at least seven hours a day.

NUTRIENTS

Vitamin A

Vitamin A and its derivatives retinoids, are critical for immune functions, including innate immunity, cell-mediated immunity, and humoral antibody immunity.[16] Vitamin A plays an important role in maintaining the integrity and secretion of the epithelial and mucosal surfaces. These systems form a primary nonspecific host defense mechanism. Studies have demonstrated that vitamin A stimulates and strengthens numerous immune processes, including the following:[17]

- Cell-mediated cytotoxicity stimulation against tumors.
- Natural killer cell activity
- Lymphocyte blastogenesis
- Mononuclear phagocytosis
- Antibody response.

Vitamin A supplementation significantly reduces morbidity during the acute and recovery phases of measles infection; increases the total number of lymphocytes in peripheral blood, and measles IgG antibody concentration in these patients.[18]

Vitamin C

Vitamin C plays a critical role in maintaining immune system function and contributes to both innate and acquired immunity, particularly immune cell function (epithelial barrier integrity, chemotaxis, antimicrobial activity of phagocytes, natural killer cell activity, and the immune system), as well as lymphocyte proliferation and differentiation.[19,20] It has been shown that taking 1-3 grams/day of vitamin C for three days a week increases T cell proliferation in the long term.[21]

Vitamin E

Free radicals damage the membrane of immune cells, reducing their response to pathogenic challenges, leading to impaired immune and inflammatory responses, and consequently, the development of inflammatory diseases.[22] Vitamin E is an important antioxidant that cleans free radicals from the body.[23] It protects against oxidative stress, increases the activity of natural killer cells, and contributes to antibody formation.[24] Vitamin E deficiency weakens the immune system, whereas adequate intake supports both innate and acquired immunity.[25] Vitamin E is closely associated with crucial immune cell functions such as macrophages, dendritic cells, B cells, and natural killer cells. Vitamin E supports the interaction between dendritic cells and T cells, especially Th1 cells, and stimulates IL-2 production.14 It has been shown that supplementation with 100 mg/day of vitamin E for eight weeks regulate the development of natural killer cells.[26] Vitamin E supplementation positively affects respiratory tract infections in newborn babies.[27]

Vitamin B6

Vitamin B6 serves as a coenzyme in synthesizing proteins that make up antibodies and cytokines.[28] Vitamin B6 plays an essential role in the production of interleukins and T lymphocytes, and its deficiency results in decreased IL-2 production and increased IL-4 production.[29] In the presence of chronic inflammation, there is an inverse relationship between vitamin B6, IL-6, and TNF-α levels.[30] The liver, kidney, meat, and green leafy vegetables contain high amounts of vitamin B6 (Table 1).[27]

Table 1. Vitamin B6 values in 100 grams of some foods

Food	Amounts of vitamin B6 (mg per 100 grams)
Breast milk	5-22
Cow's milk	50-70
Meat	300-400
Liver	700-800
Kidney	400-1000
Rice flour	30-50
Green leafy vegetables	250-300
Fresh fruits	50-60

The human body cannot synthesize vitamin B6. It can be found in food or in microorganisms in the digestive system, such as Helicobacter pylori, Bifidobacterium longum, Bacteroides fragilis, Collinsella aerofaciens, and Prevotella copri, which make pathways for B6 vitamin synthesis.[30]

Vitamin D

Vitamin D affects both innate and acquired immunity.[31] Vitamin D increases chemotaxis, phagocytosis, and the production of antimicrobial proteins.[32] Vitamin D protects against bacterial or viral upper respiratory tract infections.[33] It has been shown that individuals with vitamin D deficiency have an increased risk of contracting tuberculosis.[34] Furthermore, the treatment of T cells with calcitriol or its analogs, especially vitamin D, inhibits the secretion of pro-inflammatory Th1 (IL2, interferon-γ, tumor necrosis factor α), Th9 (IL9), and Th22 (IL22) cytokines while supporting the production of anti-inflammatory Th2 cytokines (IL3, IL4, IL5, IL10).[35,36]

Vitamin D also has an impact on autoimmune diseases. Vitamin D deficiency is associated with type 1 diabetes (T1D), multiple sclerosis (MS), systemic lupus erythematosus, rheumatoid arthritis, and irritable bowel syndrome.[37]

Vitamin D supplementation has been shown to reduce pain in patients with rheumatoid arthritis, and improvements in mental health have been observed in individuals with MS.[38,39]

Zinc

Zinc is a catalytic component of over 300 enzymes that regulates cell communication, proliferation, differentiation, and survival. It is also an effective mineral for innate and acquired immunity.[40] Zn increases the number of natural killer cells and reduces their cytotoxicity. It decreases the number of T cells, Th1/Th2 ratio, and IL-2 production.[41] Zinc also regulates B lymphocytes and cytokine synthesis.[42]

However, excess zinc can also negatively affect the immune system, leading to zinc deficiency.[41] Zinc prevents the entry of viruses into the body and inhibits their replication.[43,44] Zinc also enables the intestinal microbiota to be modulated.[45]

Iron

Iron is effective in innate immunity because it controls the production of antimicrobial factors such as nitric oxide and hydroxyl radicals. Acquired immunity is effective in increasing lymphocytes.[46] Pathogenic microorganisms and viruses need nutrients in the blood, such as free-floating iron, to sustain their activities. However, the host must have sufficient iron concentration to induce an immune response.[47] Natural killer cells require iron for proliferation and differentiation.[48] Iron is also required for T-cell proliferation. It plays a role in DNA synthesis, especially in Th1 cells.[49]

Iron deficiency decreases the cell-mediated immunity, activity of myeloperoxidase enzyme, and activity of neutrophil and natural killer cells.[50,51]

Glutamine

Glutamine is the most abundant amino acid in the human body.[52] Due to its ability to increase lymphocyte function and IL-6 levels in macrophage cells, glutamine is effective in the immune system.[53,54] A previous study showed that, glutamine supplementation increased the effectiveness of neutrophils against Staphylococcus aureus.[55] Furthermore, glutamine plays a role in cellular protection against oxidative stress by serving as the main substrate for producing the antioxidant glutathione.[56]

When an infection starts in the body, immune cells consume more glutamine than carbohydrates. In mammals, glutamine is produced, stored, and secreted by the skeletal muscles.[57] Increased glutamine consumption by tissues such as the liver and immune cells can lead to glutamine deficiency.[58] A decrease in plasma glutamine levels leads to impaired immune system function. Decreased glutamine levels reduce cytokine production and lymphocyte proliferation, leading to apoptosis in these cells.[59]

Breast Milk

Breast milk plays an active role in the immune system, with its bioactive components, such as immunoglobulins, cytokines, chemokines, and growth factors.[60] Quantitative immunoglobulins are found in breast milk:IgM, IgG, IgD, and IgA (**Table 2**).

Table 2. Concentrations of essential soluble immune factors in human milk under physiological conditions.[60]

Immune factors	Type	Concentrations
IgA (mg/L)	Mature breast milk	160-2435
	Colostrum	1428-8700
	Preterm breast milk	260-3181
IgG (mg/L)	Mature breast milk	14-230
	Colostrum	40-150
	Pretersm breast milk	70-90
IgM (mg/L)	Mature breast milk	7.5-170
	Colostrum	160-660
	Preterm breast milk	380-440
TGF-β2 (mg/L)	Mature breast milk	0.26-99
	Colostrum	1.8-336
	Preterm breast milk	7.5-15.5
EGF (mg/L)	Mature breast milk	2.2-10.8
	Preterm breast milk	0.7-1.9
IL-7 (ng/L)	Mature breast milk	17.2-131.5
	Colostrum / preterm breast milk	75-1088
IL-8 (ng/L)	Mature breast milk	2.3-1704
	Preterm breast milk	309-2542
GRO-α (mg/L)	Mature breast milk	0.05-15
MIP-1β (ng/L)	Mature breast milk	2.7-76

IgA is the most abundant, accounting for 95%, and its levels decrease gradually after birth. IgA protects against enteric and respiratory antigens.[61] Therefore, breastfed infants are more resistant to respiratory tract infections.[62]
Lactoferrin, one of the most abundant proteins found in breast milk, prevents infection, plays a role in iron metabolism, and has important functions in the immune system, owing to its anti-inflammatory and antioxidant properties. It exerts bacteriostatic effects by binding and transporting iron into the body.[63] Lactoferrin enhances the activity of natural killer cells. In addition, it prevents viral accumulation in cells and entry of the virus into the host through the angiotensin-converting enzyme-2 receptor pathway.[64] Lactoferrin mediates changes in the expression of signaling molecules, which control the balance between molecules that cause inflammation and molecules that stop it.[65] The expression of anti-inflammatory cytokines, such as IL-4 and IL-10, and pro-inflammatory cytokines, such as tumor necrosis factor-alpha, IL-1, IL-6, IL-12, and chemokines, such as IL-8, is controlled by lactoferrin.[66] Breast milk contains bioactive growth factors. These bioactive components play an important role in the development of healthy infants because they contribute to the production of red blood cells and exhibit anti-inflammatory and antioxidant properties.[63]

The oligosaccharides found in breast milk prevent respiratory pathogens such as Streptococcus pneumoniae from binding to the respiratory epithelium. Additionally, milk glycoproteins prevent colonization by intestinal pathogens such as Vibrio cholera and Escherichia coli.[67]
Breast milk interacts directly with glycan-binding proteins

expressed in epithelial cells and innate immune system cells.[68] One of the components found in breast milk is long-chain polyunsaturated fatty acids. Omega-3 and omega-6 fatty acids improve Th1 and Th2 immune cell responses.[69] Additionally, although docosahexaenoic acid (DHA) and arachidonic acid make up a relatively small portion of the total fatty acids in human breast milk, they play a role in the development of immunity.[70] If infant formulas are supplemented with these fatty acids for infants who are not breastfed, the number of lymphocytes and cytokines will be similar to those in breastfed infants.[70] Additionally, breast milk contains lactic acid bacteria such as Lactobacillus, Lactococcus, and Leuconostoc as well as bacterial species such as Bifidobacterium, Streptococcus, Enterococcus, and Staphylococcus.[71,72] Breast milk containing more than 820 species of bacteria enhances the development of the infant's early immune system, maintains tolerance to commensal microbial members, and enhances intestinal host defense against pathogens.[73]

Proteins

Some proteins such as lectin, lactoferrin, and whey proteins stimulate immune responses. Lectin and lactoferrin can recognize viruses by binding to their glycoproteins. Whey proteins, however, enhance immunity and reduce certain cancer risks.[74] A protein intake of 3-4 g/kg/day is recommended for infants, while for older children, a protein intake of 1.5-2 g/kg/day is recommended.27

Protein deficiency causes dysfunction in epithelial and physiological barriers, and impairs macrophage, neutrophil, and natural killer cell functions [75] Additionally, protein deficiency in the diet leads to atrophy of lymphoid organs and a deficiency of T lymphocytes, which increases susceptibility to viral and bacterial pathogens, as well as opportunistic infections.[76]

Fats

Fatty acids play a role in regulating many responses, including inflammation and immune function.70 Omega-3 polyunsaturated fatty acids (PUFAs), in particular, play an important role in regulating the immune system due to their antioxidant properties.[77] Omega-3 PUFAs are important fatty acids that strengthen anti-inflammatory responses, block hyperinflammatory reactions, and reduce the incidence of systemic inflammatory response syndrome and infectious complications.[78,79] Furthermore, omega-3 fatty acids regulate the activation of macrophages, neutrophils, basophils and lymphocytes.[80]

CONCLUSION

Nutrition plays an important role in the development of the immune system and the fight against infectious diseases. Malnutrition and obesity, which result from inadequate and unbalanced nutrition, weaken the immune system and reduce the effectiveness of fighting diseases. However, adequate and balanced nutrition, which provides energy and essential nutrients, enhances the development and effectiveness of innate and acquired immunity, making the emergence of infectious diseases less likely and improving the ability to fight disease. Therefore, outbreaks of diseases are increasing, especially in the 21st century, and ensuring that children have adequate and balanced nutrition is crucial to avoiding infectious diseases.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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