Nutritional supplements for immune deficiency

J Luvhimbi, E Bronkhorst

Department of Clinical Pharmacy, Sefako Makgatho Health Sciences University, South Africa
Corresponding author, email: elmien.bronkhorst@smu.ac.za

Abstract

The immune system is an interlinked system of cells, tissues and organs working together to defend the body from pathogens like bacteria, fungi and viruses. Essential nutrients like vitamins and minerals are required to regulate the innate and adaptive immune response. Conditions, such as malnutrition and certain disease states, may require supplementation of different vitamins and minerals to improve the immune system. The use of nutritional supplements can vary depending on the cause of immune deficiency, weather inflammatory or infectious. Getting adequate nutrients in the diet or supplementation is necessary to sustain good immune function and provide resistance against infections. Pharmacists can play a key role in nutritional supplementation according to the four step CARE guide. This article will discuss the use of individual vitamins and nutritional supplements in immune deficiency as well as in other applications.

Keywords: nutrition, immune system, nutritional supplements, pharmacist role

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Introduction

The immune system is a complex, interlinked system of cells, tissues and organs working together to defend the body from pathogens like bacteria, fungi and viruses.[1] When the immune system is weakened, due to inherited defects or other causes such as viral or bacterial infections, malnutrition, autoimmune disease or by use of immunosuppressive drugs, it is referred to as immune deficiency.[2,3]

To ensure that the immune system functions normally, essential nutrients like vitamins and minerals are required. These nutrients regulate innate and adaptive immune response, form an essential part of immune cell structures, help in energy production, and assist to protect against cytotoxicity.[4] Therefore, conditions such as malnutrition or deficiency in macronutrients and micronutrients can decrease the effectiveness of the immune system.[4] This article will discuss the use of nutritional supplements in immune deficiency as well as in other applications.

Figure 1 shows the relationship between nutrition and the immune system.

The use of nutritional supplements can vary depending on the cause of immune deficiency, namely malnutrition, prematurity, steroid-induced malnutrition and those caused by a compromised

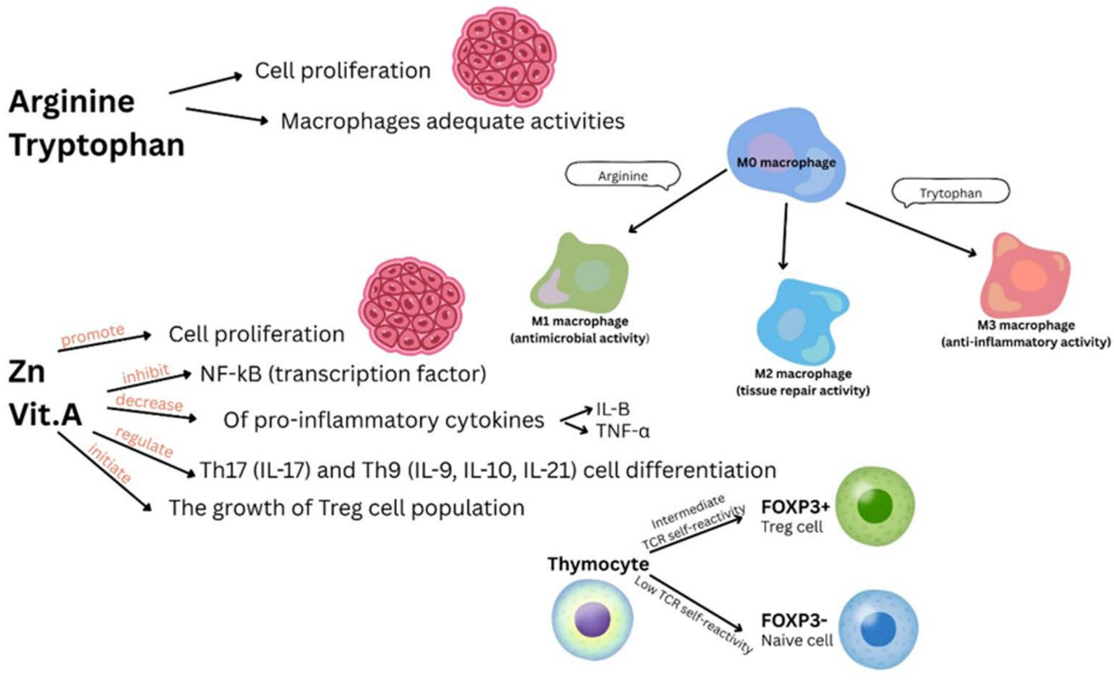

Figure 1: The relationship between nutrition and the immune system

Table I: Infections and associated malnutrition

Disease or cause of immune deficiency	Nutritional supplement	Discussion
Tuberculosis	Vitamin D	Tuberculosis (TB) affects one third of the global population.[10] TB is associated with malnutrition. Active TB patients present with low Vitamin D levels.[13] Supplementation of Vitamin D reduces risk of pulmonary tuberculosis and mortality.[14,15]
Measles	Vitamin A Zinc	Infection is closely linked with malnutrition particularly in children with Vitamin A deficiency. The virus can cause complications like encephalitis, laryngitis, and pneumonia.[11] Vitamin A supplementation has shown 23–30% reduction in measles mortality.[1] The WHO recommends Vitamin A and zinc supplementation for children infected with measles living in areas with Vitamin A deficiency.[16]
Human Immunodeficiency Virus and acquired immunodeficiency syndrome	Folate Vitamin C Iron Vitamin D Nicotinamide	*Children:* HIV and AIDs increases the prevalence of malnutrition in infected children to 40–64%.[12] Children with malnutrition also report deficiencies in folate, Vitamin C and iron, leading to the recommendation to supplement these micronutrients.[17] *Adults:* Antiretroviral therapy may increase Vitamin D metabolism, thus needing supplementation. Nicotinamide shows activity against viruses such as HIV, hepatitis B virus and enteroviruses, as it can reduce viral replication and boost the defence mechanisms of the immune system.[18,19]

Table II: Other causes of immune deficiency

Disease or cause of immune deficiency	Nutritional supplement	Discussion
Neonate and prematurity	Iron Zinc Vitamin D	Newborns, dependent on breastmilk or formulae that limit the diet, makes it difficult to adequately supply the necessary nutrients.[8] Early adequate nutritional support of pre-terms is paramount to limit adverse metabolic outcomes.[20] Preterm infants are supplemented with iron and multivitamins after discharge, but the length and dose of supplementation widely differ.[20]
Young children	Vitamin D Vitamin B12 Zinc	Young children have relatively immature immune systems in the first three years of life.[8] Children aged younger than 5-years present with malnutrition resulting in macro- and micronutrient-deficiency in carbohydrates, fatty acids, Vitamin D and Vitamin B12, which makes them more prone to gastrointestinal and respiratory infections.[21,22,23] In children who can tolerate a normal diet, dietary supplementation with zinc and Vitamin D has been shown to have protective benefits against viral respiratory infections.[24]
Immunocompromised patients ***HIV, Diabetes and Cancer***	Selenium Vitamin C Vitamin E Vitamin B6 Vitamin B12 Vitamin D Zinc Potassium Chromium	Nutritional supplementation is important in immunocompromised patients with HIV, diabetes and cancer.[5,6] Patients with HIV can benefit from adequate nutrition and supplements like selenium and Vitamin C to help facilitate the absorption of antiretroviral medicine and support overall health.[25] In diabetes, immune function is dependent on a balanced diet managing blood glucose levels.[26] Vitamin B6, Vitamin B12, Vitamin C and Vitamin D assist with glucose metabolism, insulin sensitivity, and nerve function. Zinc protects against destruction of beta cells, potassium improves insulin sensitivity, and chromium lowers fasting glucose levels.[27] Maintaining adequate levels of Vitamin D has been shown to reduce the risk of cancers like colorectal, breast and prostate cancer.[6] Selenium decreases the risk of prostate cancer. Anti-cancer effects of Vitamin C and Vitamin E are being investigated.[6]
Steroid-induced secondary immune deficiency	Vitamin D	Long-term steroid use alters Vitamin D metabolism leading to low levels of Vitamin D.[9] Corticosteroids cause a disruption to the microbiome diversity and impair the microbiome's ability to maintain immune homeostasis,[9,28,29] which can impair immune function and increase the risk of infections. Vitamin D supplementation offers benefits like inhibition of renin thereby lowering angiotensin converting enzyme levels,[30] and restores normal cellular metabolism.[31,32]
Inflammatory bowel disease and related autoimmune diseases	Omega-3 Vitamin D Curcumin	The intestinal microbiome is a key contributor to immunity and immune response as an imbalance of this environment can give rise to immune-mediated inflammatory diseases like inflammatory bowel diseases (IBD).[33] Omega-3, Vitamin D and curcumin have shown promising results in the management of inflammatory diseases.[34] *Omega-3 fatty acids* Polyunsaturated fatty acids found in foods like flaxseed and fatty fish, can be used in the management of chronic inflammatory disorders.[21] In Crohn's disease, it may lead to improved maintenance of remission, but the effects remain unclear.[35] In ulcerative colitis, beneficial effects were observed but could not be entirely attributed to Omega-3, as it was used in combination with Vitamin E, Vitamin C and selenium. It is believed that Omega-3 directly blocks the production of pro-inflammatory cytokines.[34] *Vitamin D* Supplementation in Crohn's disease and ulcerative colitis decreases inflammatory markers, reduces need for hospitalisation, and steroid therapy and reduces disease activity.[36] The therapeutic potential of Vitamin D in inflammatory bowel disease is still under exploration due to its role in maintaining the mucosal barrier and functioning of T-cells.[37] *Curcumin* It is a polyphenol found in turmeric roots with strong antioxidant and anti-inflammatory properties.[38] The use of curcumin as adjunctive therapy at high dose (3 g/day) can improve disease activity and induce clinical remission in patients with mild to moderate ulcerative colitis.

Disease or cause of immune deficiency	Nutritional supplement	Discussion
Respiratory infections and common colds	Vitamin C Zinc Nicotinamide Thiamine	Vitamin C has antioxidant effects, believed to reduce oxidative stress during infections. Vitamin C use has been suggested to decrease the duration of common cold symptoms with long term use, while zinc has been noted to reduce the risk of symptom episodes.[39,40] Nicotinamide was effective to control inflammatory storms in Covid-19 patients by targeting interleukin 6 and reduces neutrophil infiltration in in-patients with ventilator- associated lung injury.[41] Thiamine (Vitamin B1) acts as an antioxidant and controls the metabolism of immune cells (namely naïve T-cells, rest macrophages and T-regulatory cells). Thiamine induces the production of antibodies to fight infections, hence effective in reduction of symptom severity as seen during Covid-19.[42]

immune system, as is the case in HIV-infected patients or patients with diabetes mellites, inflammatory bowel diseases and autoimmune diseases.[1,5,6,7,8,9]

Malnutrition and other associated infections

Malnutrition refers to a state where a person is over or undernourished. It is usually accompanied by either states of chronic inflammation (as in obesity known as "hidden hunger" or "obese malnutrition") or increased risk of infections (as in undernourishment). Both these states can impair immune function.[1]

There are several studies that recognise the link between malnutrition and risk of infections, as the immune system is strongly dependent on getting adequate nutrients through diet to sustain good immune function to provide resistance against infections.[1,10,11,12] In this section nutritional supplementation in malnutrition and associated infections will be discussed in Table I and causes of immune deficiency are covered in Table II.

Role of micronutrients in immune function

Vitamin A

Vitamin A regulates the differentiation, maturation, and function of immune cells such as Natural Killer (NK) cells, macrophages, eosinophils and neutrophils, which are responsible for the innate immune system, and destroys invading pathogens.[43] Vitamin A helps to regulate the homing signal for CD4+ and CD8+ cells in the intestinal lamina propria. Therefore, Vitamin A deficiency can result in an imbalance in the microbiota composition and diminishes the activity of macrophages, T-cells, B-cells and reduces antibody titre response of vaccines.[43]

Vitamin B complex

Riboflavin (Vitamin B2) has two effects on the immune system. It helps to boost the proliferation of neutrophils and monocytes, and stimulates the activity of macrophages and neutrophils, which can improve immune function.[4,44]

Nicotinamide (Vitamin B3) is a coenzyme and it also acts as a building block for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are responsible for chronic inflammation.[42] Nicotinamide adenine dinucleotide has immunomodulatory properties, which help to decrease the pro-inflammatory cytokines, Interleukin 1B and 6 and TNF-alpha.[41] Furthermore, nicotinamide is active against viruses such as HIV, hepatitis B virus and enteroviruses, as it reduces viral replication and hence boosts the defence mechanisms of the immune system.[18,19]

Pyridoxine (Vitamin B6) in its active form of pyridoxal 5′-phosphate (PLP) is a cofactor that regulates inflammatory pathways.[42] Vitamin B6 has immunosuppressive effects through the upregulation of interleukin-10, which can deactivate macrophages, monocytes, antigen-presenting cells, and T-cells. This suppressive effect of PLP is helpful in situations whereby the body mounts an excessive T-cell response to an infection.[45]

Folic acid (Vitamin B9) is responsible for deoxyribonucleic acid (DNA) formation, protein synthesis and activation of the adaptive immune response. Folic acid has antiviral activity by inhibiting furin, an essential enzyme needed to fight bacterial and viral infections.[46]

Cobalamin (Vitamin B12) plays a role in erythropoiesis, nervous system function, myelination, cell growth, DNA synthesis and maintains a healthy balance in the immune system.[45,46] Low or inadequate levels of Vitamin B12 and folic acid can lead to immune deficiency by impacting the synthesis of nucleic acids and protein synthesis, which can lead to inhibition of immune cell activity.[45]

Vitamin C

Vitamin C enhances the innate immune system by increasing the migration of neutrophils, proliferation of NK cells and maintains the integral structure of the epithelial barrier by promoting collagen synthesis.[21,22] In the adaptive immune system, Vitamin C promotes T-cell and B-cell differentiation and proliferation.[47] Additional Vitamin C increases the production of antibodies.[48,49] Vitamin C is a potent antioxidant that neutralises reactive oxygen species (ROS), protecting immune cells from oxidative damage during infection and inflammation. It strengthens skin and mucosal barriers by promoting collagen synthesis, helping prevent pathogen entry.[50]

Vitamin D

In terms of the immune function, Vitamin D enhances T-cells, B-cells, and macrophage function and decreases susceptibility to influenza, respiratory infections (pneumonia), hepatitis C, HIV, and other viral infections.[37,51] Additionally, it offers anti-inflammatory effects by inhibiting expressions of pro-inflammatory cytokines.[44]

Vitamin E

Vitamin E is responsible for modulating membrane integrity, signal transduction and oxidative stress in immune cells via the Vitamin E isoforms (α- and Y-tocopherol) which are abundant in their cell membranes. Vitamin E decreases the migration of dendritic cells, interleukin 12 production and leukotrienes, and increases the activity of NK cells.[44]

Zinc

Zinc together with Vitamin A helps maintain the integrity of the skin and mucosal membrane, which is the first line of defence to pathogens.[22] Zinc enhances the cytotoxicity of NK cells, specialised cells which are responsible to target and kill abnormal host cells.[52] In addition to NK cells, there are also macrophages that help defend the body against infections. The presence of zinc can increase the phagocytic activity of macrophages present in the peritoneum against *Escherichia coli* and *Staphylococcus aureus*.[53]

Zinc is an essential part of the adaptive immune system as it is responsible for the growth, differentiation, and activation of T-cells.[22] The type of immune response (whether excessive immune response or autoimmunity) is modulated by the T-regulatory cells, which require zinc to maintain immune tolerance.[54]

Selenium

Selenium is responsible for differentiation and proliferation of T-cells and helps to increase Th cell count. Selenium is essential for the function of selenoproteins, which are a group of proteins that contain the essential trace element selenium that function as redox regulators and cellular antioxidants of the host defence system and help regulate immune response by affecting leukocyte and NK cell function.[22]

New advances around old vitamin supplementation

There are interesting recent studies pertaining to Vitamin C and Vitamin D. The use of high doses of intravenous (IV) Vitamin C in sepsis, ranging from 2–6 g/day or more, is being studied but findings are still controversial, as some studies suggest that IV Vitamin C may result in harm or death.[55,56,57]

Vitamin D's use in vitiligo is currently being investigated as an association with improved symptoms has been demonstrated by several initial studies. These studies have noted reduced skin depigmentation with the use of high oral dose of Vitamin D (35 000 international units [IU] per day) for sixdays.[58,59,60,61]

The role of a pharmacist in nutritional supplementation

Pharmacists can play a key role in nutritional supplementation according to the four step CARE guide proposed by Mai et al. (2020),[62] consisting of "Categorise, Assess, Recommend and Empower".

According to the CARE guide, pharmacists should pay attention to any signs, behaviour or verbalisation by the individuals about a need or want for supplementation and provide tailored counselling and education on supplement selection based on the patient's individual needs. For example, a complaint of being tired would be categorised as someone looking for supplementation for energy restoration while a complaint of a cold would be a need for immune support.[62]

Pharmacists should offer advice on proper use and dosing of supplements to promote safe use, improve compliance, and prevent misuse or overdose. Pharmacists can assess help and identify potential interactions between supplements and medications by asking the patient social care questions relating to lifestyle, dietary habits, existing health conditions, occupation and concurrent medications. Furthermore, the pharmacist can identify drug-nutrient interactions, as is the case with chronic use of, for example, metformin, proton-pump inhibitors, oral contraceptives, corticosteroids and some antihypertensives. Therefore, the involvement of pharmacists in nutritional supplementation is important to achieve optimal patient outcomes, reduce adverse effects and optimise supplement use.

Conclusion

There are various diseases and conditions that may lead to immune deficiency, which is usually associated with a lack in one or more nutrients. Therefore, due to the well-established relationship between nutrition and immune function, nutritional supplementation should be advocated, where possible. Pharmacists play a crucial role in recommending proper dosing of supplements to promote safe use and compliance to achieve optimal patient outcomes.

ORCID

J Luvhimbi https://orcid.org/0009-0009-1244-8068

E Bronkhorst https://orcid.org/0000-0002-6872-5417

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