

REVIEW

UDC 612.015.6:577.164.1:612.017.1

doi: <https://doi.org/10.15407/ubj94.01.005>

PYRIDOXINE, FOLATE, AND COBALAMIN AND THE CONDITION OF THE INNATE AND ACQUIRED IMMUNITY

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Received: 23 September 2021; **Accepted:** 21 January 2022

The immune response to the pathogen depends on the state and coordinated activity of innate and acquired immunity. To date, the positive role of many micronutrients (vitamins and minerals) in maintaining homeostasis of the human immune system has been proven. The aim of the review was to analyze the main manifestations of vitamins B₆, B₉, B₁₂ influence on the state of innate and adaptive immunity. These vitamins play an important role in the synthesis of DNA and RNA, cytokines and immunoglobulins, thus maintaining the proper state of the immune system. The functioning of the main links of specific and nonspecific immunity at the normal vitamin status and at pyridoxine, folate and cobalamin deficiency is compared.

Key words: vitamins B₆, B₉, B₁₂, innate and acquired immunity.

Today, it is definitely known that a complete and balanced diet is one of the determining factors of influence on the harmonious development of the child in general and its systems and organs, particularly the immune system, which determine the child's health condition. Unfortunately, according to the 2020 Global Nutrition Report in the Context of COVID-19, every ninth person in the world is hungry; almost a quarter of all children under five because of malnutrition have stunting or wasting [1]. Economic shock related to the COVID-19 and natural disasters only worsen this situation [1, 2]. According to some studies, malnutrition is the leading cause of the development of immunodeficiency in children of different ages and elderly adults, increasing their susceptibility to infections [3-5]. The other relevant problem is so-called hidden hunger (poor diet) as a form of malnutrition when children and adults experience deficiency of essential vitamins and other micronutrients, which are not synthesized in the organism or are synthesized in insufficient quantities. Such micronutrient deficiencies,

recorded in more than 340 million children below five worldwide, lead to developmental delay, weakening of the immune system, and worsening health [2]. Certain micronutrients have both immunomodulating and antioxidant properties, and upon entering the child's body in sufficient quantities with food and working in synergy with each other, they promote the development of the immune system and effective immune response [6-10]. To date, the positive role of multiple vitamins (A, E, D, C, folic acid, B₁₂, B₆) and minerals (zinc, iron, and selenium) has been proven in supporting the homeostasis of the immune system in children and adults, which determines the immunity to certain infections, the severity of the inflammatory process due to the damaging effect of the negative factor and its consequences [6, 11-13]. Particular emphasis should be given to pyridoxine, folate, and cobalamin, which participate in the folate cycle, are donors of single-carbon units, thus playing a crucial role in the synthesis of nucleic acids and proteins, providing the synthesis of antibodies and cytokines [14, 15]. These vitamins affect the host's

immune response to the pathogen, which depends on the condition and coordinated activity of the innate and acquired immunity [6, 12, 14-16].

This review aimed to determine the main manifestations of vitamins B₆, B₉, B₁₂ impact on the condition of innate and adaptive immunity.

Certain aspects of the functioning of innate and acquired immunity

Throughout the entire life – from birth to death, the human body is exposed to the effect of negative factors, in particular, pathogenic microorganisms and damaging environmental factors [6, 16-19]. The first ones to fight the foreign agents are structures of the innate (nonspecific) immunity, so-called anatomical and physiological barriers of the immune system, such as integrity of skin and mucous membranes; mucus and glycocalyx, lysozyme, fatty acids; the acidity of gastric juice and urine; microbiota; mechanical removal of the pathogen (ciliated airway epithelium, cough, sneezing, vomiting, diarrhea, saliva, tears, sweat) [6, 14, 17]. Upon damaging or impaired function of specific anatomical or physiological barrier, other factors of innate immunity enter the fight, particularly inflammation and phagocytosis [6, 17, 20].

An inflammatory reaction develops at the site of penetration of a foreign agent into the human body, which is aimed at its localization and destruction, as well as the restoration of damaged tissue. During this process in the affected area, mediators of inflammation of the humoral origin (kinins, proteins of the activated complement system, and hemostasis system) and cellular origin (histamine, serotonin, lysosomal enzymes, leukotrienes, cytokines, prostaglandins, reactive oxygen, and nitrogen species) are synthesized; blood flow is also increased that causes vascular permeability, which determines the activity of inflammation [6, 17]. In addition, phagocytes (neutrophils, monocytes, macrophages, dendritic cells) migrate to the damaged site by chemotaxis and phagocytose bacteria, viruses, protozoa, and damaged or dead cells that are lysed by enzymes [6, 17]. Also, phagocytosis stimulates an oxidative explosion, which produces a large number of reactive oxygen species or nitrogen - powerful oxidative bactericidal factors that damage the cellular structures of microorganisms (due to free radical oxidation processes against the pathogen) and contribute to their death and cleansing of the host from the pathogen [6, 18, 21].

If the innate immunity is unable to localize and neutralize the pathogen in the human body for a short time, adaptive immunity is activated [17, 18]. In this case, extracted substances (pathogens, toxins, damaged cells, neutrophils, macrophages, NK cells, mast, and dendritic cells) are moved with the blood plasma flow to the regional lymph nodes, where they are recognized and identified as a foreign body and antibodies are produced due to the interaction of cellular and humoral immunity [6, 14, 17, 18].

Adequate immune response to the pathogen is provided by the collaborative work of innate immunity cells, which form the first line of defense against microorganisms, and highly specific adaptive immunity cells (T- and B-lymphocytes), which complete the elimination of the pathogen from the human organism [20, 21].

Innate immune cells (neutrophils, monocytes, NK cells, mast, and dendritic cells) recognize common pathogen-associated molecular structures of pathogens using surface recognition receptors, such as Toll-like receptors (TLRs). These receptors activate signaling pathways that provide antigen presentation to highly specific adaptive immune cells and cytokine production, as well as subsequent antimicrobial actions of the naive cells, such as degranulation, phagocytosis, and destruction of pathogens [15, 22-24]. Dendritic cells are considered to be the most important antigen-presenting cells [17].

T-helpers (CD4) coordinate the adequate and effective response of highly specific cellular and humoral immunity cells. They send signals about antigens to other immune cells, such as cytotoxic T-lymphocytes (CD8), natural killer cells (NK, CD56), B-lymphocytes (CD19, CD20), activating their activity [6, 17, 25]. There are two types of T-helpers: Th1 and Th2. Induction of Th1 activates CD8, which synthesizes cytokines and lyses pathogens that survive in phagocytes and those that have damaged other human cells. In addition, Th1 produces proinflammatory cytokines (IL-2, IL-12, tumor necrosis factor (TNF- α and β), interferon-gamma (IFN- γ), granulocyte-macrophage colony-stimulating factor), which support inflammatory reactions and stimulate macrophages and CD56, providing the human body with effective cellular immunity from viruses, fungi, protozoa, and intracellular bacteria, as well as from tumor cells. Excessive proliferation of Th1 cells can lead to the development of a cytokine storm (pronounced activity of the inflammatory process) or an autoimmune process [25, 26].

Th2-helper subpopulation cells synthesize IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, granulocyte-macrophage, and granulocyte colony-stimulating factors, promote eosinophil, B-cell activation, and antibody production. Antibodies that are synthesized by plasma cells (transformed by B-lymphocytes) are specific for a particular antigen. By joining the antigen, antibodies change their structure and properties, as a result of which antigen loses its functions (pathogenic effects), and the pathogen is neutralized in the host [17, 25]. In the future, the formed immune complex (antibody + antigen) activates the complement system with immunoglobulins (Ig) M and G, which leads to the formation of a cytolytic (membrane-attacking) complex on the surface of the target cell and its lysis. In addition, antibodies (IgA, IgE, IgG) activate phagocytosis through cytotoxic cells (NK cells, macrophages, neutrophils), which bind to antibodies through the Fc γ RIII receptor, thereby enhancing the cytolysis of the pathogen coated with antibodies specific for its antigens. Also, enhancing phagocytosis contributes to the opsonization of the damaging agents IgG (the most effective opsonins IgG1 and IgG3) through the attachment of the Fc fragment of the IgG molecule to CR1 receptors on phagocytes while binding opsonin C3b (a component of the complement system) with these receptors and the immune complex. [17, 25]. The humoral type of immune response is most important for extracellular microorganisms [17, 18, 25]. It should be noted that excessive proliferation of Th2 cells causes the development of allergic diseases [17, 18].

T-regulatory cells (Tregs) regulate the activity of the immune system. By suppressing other immunocompetent cells (CD4, CD8), they control the immune response to their own and foreign antigens, thereby preventing autoimmune, allergic diseases and the development of cytokine storms during inflammation [17, 25, 27] as, for example, in COVID-19.

In the process of pathogen elimination from the human body, many T- and B-lymphocytes undergo apoptosis, but part of them return to the inactive state and become memory cells, which keep the information (memory) about the eliminated pathogen; thus, immunologic memory is formed [14, 17, 25]. Memory cells monitor the pathogen invasion into the microorganism and, upon repeat encounter with the pathogen, can recognize the antigen and help the immune system produce a much faster and more potent immune response. Within a few hours, memory T

cells are able to multiply and differentiate into Th cells or cytotoxic T cells and B cells into plasma cells [6, 17, 18, 20].

The role of the micronutrients and macronutrients in the optimal functioning of the immune system has been discussed in many papers [4, 6, 20, 22] during the last decade, especially the role of minerals and fat-soluble vitamins [6, 12, 14]. However, despite significant advances in the study of water-soluble vitamins on the regulation of the immune response in recent years, many issues of its impact or the need for supplementation have not yet been fully studied.

Vitamin B₉ (folic acid)

Folic acid, along with vitamins B₆, B₁₂, A, D, E, participates in the activation of defensive functions of immune cells [20]. In particular, during the folate deficiency suffer both innate and adaptive immunity since folic acid plays a crucial role in synthesizing the nucleic acids and proteins, thus ensuring the synthesis of antibodies and cytokines [6, 14, 15, 20]. Besides that, it is also the donor of carbon units for vitamins B₆ and B₁₂ [15, 23]. Folic acid deficiency decreases immunocompetency and resistance to infections [6, 23, 28], affecting cellular immunity by decreasing the level of circulating T-lymphocytes and their proliferation rates in response to the mitogen activation [23], decreasing the activity of NK cells [6, 14, 23, 24], inhibiting of the antibody response [23]. Moreover, the negative status of folic acid increases CD4+ to CD8+ ratio due to the significant decrease in proliferation of CD8+ cells, thus, decreasing cytokine synthesis, phagocytosis, and cellular immunity towards extracellular pathogens and other affected human cells [17, 20, 22, 28].

It is worth noting that folate deficiency, induced in phytohemagglutinin-activated T-lymphocytes, is manifested by the cell cycle arrest in S-phase, induced apoptosis, and the increase in uracil level in DNA (damage by the cytosine deamination) [17, 29], thus decreasing the number of the functional lymphocytes. A decrease in the number of T-lymphocytes and the decrease in NK cell activity, in turn, explain the increased cancerogenesis and increase of DNA and RNA damage during the negative folate status [17, 20, 24, 29]. A decrease in NK cell activity, which affects the innate immunity during vitamin B₉ hypovitaminosis, especially in elderly people, was proved in multiple studies [17, 20].

Vitamin B₆ (pyridoxine hydrochloride)

Vitamin B₆, as well as folic acid, participates in the biosynthesis of nucleic acids and proteins, providing the one-carbon units, which are used in the synthesis of purines and deoxythymidylate, which serve as a basis for the DNA and RNA synthesis [6, 17, 30, 31]. Thereby, vitamin B₆ is essential for synthesizing cytokines and antibodies, which determine the specific and nonspecific immunity. In a number of studies on adults, it was proved that vitamin B₆ hypovitaminosis affects the differentiation, proliferation, and maturation of lymphocytes and, also, production of antibodies and T-cells activity [17, 20, 23, 29].

Furthermore, vitamin B₆ deficiency is accompanied by the decrease in antibody response in delayed-type hypersensitivity reaction and the decrease in NK cell activity. In addition, it is accompanied by the decrease in the synthesis of interleukins IL-1 β (activates macrophages, acts a mediator of acute and chronic inflammation, one of the markers of the autoimmune process) and IL-2 (IL-2 is crucial for practically all immune responses and is the main trigger of the T-cells proliferation), which negatively affects the immune response of the innate and adaptive immunity. [6, 17, 18, 20].

It is worth noting that with vitamin B₆ deficiency, the proliferation of T-helpers is decreased due to inhibition in the differentiation of Th1, which is accompanied by the decrease in cellular and non-specific immunity and synthesis of proinflammatory cytokines. In contrast, the activity of Th2 and the synthesis of anti-inflammatory cytokines are increased, as well as the risk of the development of allergies and autoimmune diseases [17, 20].

Vitamin B₆ takes part in the regulation of the inflammatory process. The seventh study framingham offspring (USA), with 2229 participants, reported an inverse correlation between blood plasma levels of pyridoxal 5'-phosphate – the active form of vitamin B₆ (PLP) with multiple markers of chronic inflammation, including the general inflammation score [32]. Participants with the lowest levels of PLP had the highest levels of chronic inflammation, and participants with the highest levels of PLP had the lowest inflammatory score. Accordingly, it indicates that decreased status of vitamin B₆ in the acute inflammation phase promotes the transition of inflammation into chronic form as a result of insufficiency of innate (decrease in the number of inflammatory

cytokines, phagocytosis) and adaptive (cellular – inhibition of Th1-cells and humoral – decrease of proliferation and activity of antibodies) [18, 32]. A sufficient level of PLP decreases the activity of chronic inflammation since PLP is a cofactor in more than 150 enzymatic reactions [33], and thus it helps to regulate the activity of inflammation affecting the pathways which produce metabolites with immunomodulating effects (kynurenine pathway, metabolism of sphingosine-1-phosphate, transsulfuration pathway and metabolism of serine and glycine) [18, 33, 34].

It should be noted that vitamin B₆ modulates the differentiation and proliferation of lymphocytes, participates in their maturation, and maintains or amplifies NK cells' cytotoxic activity [6, 31, 35].

Vitamin B₁₂ (cyanocobalamin)

Vitamin B₁₂, as well as vitamin B₆ and folic acid, affect DNA and RNA synthesis since it participates in the carbon-1 metabolism and is essential for cell proliferation [6, 14, 17]. Besides, this micronutrient has a crucial role in folic acid metabolism – during vitamin B₁₂ deficiency, an inactive form of folate is produced due to irreversible reaction of 5-methyltetrahydrofolate (5-MTHF) synthesis [18, 23]. Excessive synthesis of 5-MTHF leads to secondary deficiency of vitamin B9 with impairment of thymidine and purine synthesis, which are vital for DNA and RNA synthesis, resulting in decreased secretion of immunoglobulins (IgG, IgA, IgM) and cytokines [7]. These disorders are accompanied by inhibition of immune response to intracellular and extracellular pathogens [14, 17, 23, 30].

Vitamin B₁₂ deficiency causes the decrease in the absolute number of lymphocytes, especially CD8+, and inhibition of their activity and activity of NK cells, abnormal increase in CD4+/CD8+ ratio, therefore affecting the cellular part of acquired immunity and functions of innate protection [6, 7, 30, 36]. It should be noted that intravenous administration of methylcobalamin to adults at a dose of 500 mg/day during two weeks significantly decreased CD4+/CD8+ ratio due to proliferation of CD8+, increased activity of NK cells, which indicates the potential antitumor effect of vitamin B₁₂ and can partially explain the high risk of gastric cancer in anemia caused by vitamin B₁₂ and folic acid deficiency [17].

The studies show that vitamin B₁₂ can act as an immunomodulator of cellular immunity and in-

crease the number of cytotoxic T-cells (CD8+ and NK cells), promoting the elimination of the pathogen from the organism [11, 17, 36].

It should be noted that vitamin B₁₂, vitamin B₆, and folic acid participate in the immune regulation of intestines (vitamin B₆ promotes lymphocyte migration to the intestines, folate is essential for the proper functioning of regulatory T-cells in the small intestine and vitamin B₁₂, as a cofactor, participates in metabolic pathways of the intestinal microbiome [11, 37-39].

Moreover, decreased status of vitamins B₁₂, B₆, B₉ in combination with hypovitaminosis of vitamins C and E causes ruptures and/or oxidative damage of DNA [6, 33, 40-42]. In vitamin B₁₂, B₆, B₉ deficiencies due to phagocytosis disorder oxidative burst is decreased, which leads to the incomplete phagocytosis and inhibition of innate immunity [5, 6, 40-41].

Effects of pyridoxine, folate, and cobalamin on the innate and adaptive immunity during normal vitamin status and their deficiencies are shown in Table 1.

B group vitamins affect the functioning of the immune system, the potency of its adequate response to foreign pathogens, and damaged cells of the body [6, 8, 14, 23]. Inadequate consumption of micronutrients inhibits both nonspecific and specific immunity, affecting the innate antibody reactions. Deficiency of micronutrient intake suppresses both nonspecific and specific immunity, affecting the innate reactions of antibodies, which leads to an impairment of the host's immune response, namely, increases susceptibility to infections [30, 42]. In turn, infections amplify microelements deficiency (due to intoxication, appetite is decreased, and metabolic processes are affected), decreasing intake of nutrients, which further negatively affects the condition of the immune system [44, 45]. Thus, there is a close interdependence between nutrition, immunity, and infections [46]. Deficiency of nutrients, including B vitamins, adversely affects the incidence of infectious diseases in children with immunodeficiency, including those with inborn defects of immunity [43-45]. Inborn impairment of vitamin B₁₂ or folate metabolism can be associated with immune dysfunction, including severe combined immunodeficiency [46].

Conclusion. The analysis of literature sources made it possible to identify the impact of water-soluble vitamins B₆, B₉, B₁₂, which participate in the folate cycle, on the condition of innate and acquired immunity. These micronutrients exhibit a number of synergistic effects on specific and nonspecific immunity. In particular, vitamins B₆, B₉, B₁₂ support or enhance the cytotoxic activity of NK cells, thereby exhibiting an antitumor effect, and also participate in the immune regulation of the intestine, thereby increasing nonspecific immunity. The versatility of the impact on adaptive immunity is expressed in the participation of these vitamins as donors of carbon units in the synthesis of amino acids and proteins, which are necessary for the construction of DNA and RNA, cytokines, and antibodies.

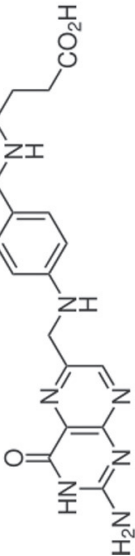
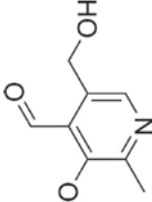
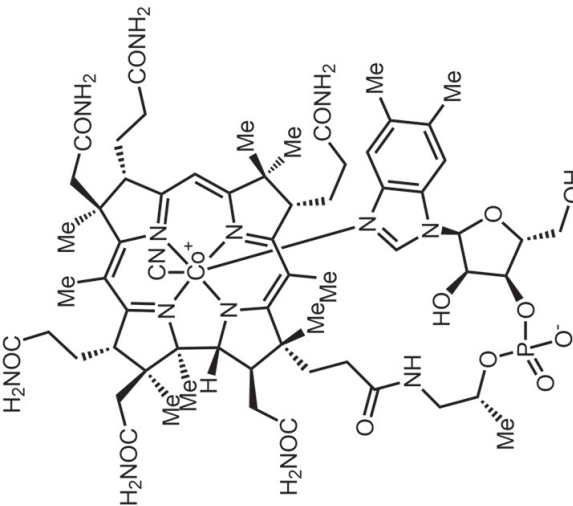
Pyridoxine, folate, and cobalamin influence the immune system, and their optimal levels are essential for ensuring active and adequate immune protection of the organism from intra- and extracellular pathogens. Furthermore, these micronutrients, functioning synergically (synthesis of amino acids and proteins), have a crucial role in synthesizing DNA, RNA, cytokines, and antibodies, thus ensuring the proper functioning of the specific and nonspecific immunity. Therefore, not only direct but also hidden deficiency of these micronutrients can negatively affect the immune system and promote the increased susceptibility to infections, especially if malnutrition is prolonged.

Vitamins B₁₂, B₉, B₆ are the vitamins, which, when taken in optimal amount positively affect the host resistance mechanisms, thus decreasing susceptibility to infectious diseases. Further research is needed to determine the effect of pyridoxine, folate, and cobalamin deficiency on the formation of the immune system in children and to identify clear indications and doses for their supplementation.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. The study was funded by the Ministry of Health of Ukraine from the state budget; the project's title is "Features of vitamin and mineral status in healthy children and children with socially significant diseases".

Table. Effects of vitamins B₆, B₉, B₁₂ on innate and adaptive immunity

Vitamins	Chemical name	Chemical Structure	Impact on immunity	
			Innate immunity	Adaptive immunity
B ₉	Folate		- supports or enhances the cytotoxic activity of NK cells [6, 7, 14]; - exhibits antitumor effect [17, 20, 29]; - participates in the immune regulation of the intestine [28, 37, 38]	- involved in the synthesis of amino acids, DNA, RNA, cytokines, antibodies [6, 14, 17, 30, 31]; - supports Th1-mediated immune response [31]; - stimulates the response of antibodies to antigens [31]; - supports the ratio of CD4/CD8 [7, 17]
B ₆	Pyridoxine, pyridoxal, pyridoxamine		- participates in the regulation of the inflammatory process [32, 34]; - preserves or enhances the cytotoxic activity of NK cells [6, 14, 35]; - participates in the immune regulation of the intestine [28, 37, 38]	- modulates the proliferation, differentiation, maturation and activity of lymphocytes [6, 17, 31]; - supports Th1 immune response, inhibits Th2 activity [6, 17, 20] - participates in the synthesis of amino acids, DNA, RNA, cytokines, antibodies [6, 14, 17, 30, 31]
B ₁₂	Cobalamin, cyano-cobalamin, methyl-cobalamin		- increases the activity and number of NK cells [6, 7, 31]; - exhibits antitumor effect [17]; - participates in the immune regulation of the intestine [28, 37, 38]	- increases the activity and amount of CD8+ [6, 7, 31] - regulates the ratio of CD4+/CD8+ [7,17] - participates in the synthesis of amino acids, DNA, RNA, cytokines, antibodies [6, 14, 23, 31]; - participates in folic acid metabolism [18, 23]; - promotes the growth of the absolute number of lymphocytes [31]

ПІРИДОКСИН, ФОЛАТ І КОБАЛАМІН ТА СТАН ВРОДЖЕНОГО І НАБУТОГО ІМУНІТЕТУ

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Імунна відповідь організму на патоген залежить від стану та злагодженої діяльності вродженого і набутого імунітету. На сьогодні доведено позитивну роль багатьох мікронутрієнтів (вітамінів та мінералів) у підтриманні гомеостазу імунної системи людини. Мета огляду – проаналізувати основні прояви впливу вітамінів B₆, B₉, B₁₂ на стан вродженого та адаптивного імунітету. Ці вітаміни відіграють важливу роль у синтезі ДНК і РНК, цитокінів та імуноглобулінів і тим самим підтримують належний стан імунної системи. У статті порівнюються особливості функціонування основних ланок специфічного і неспецифічного імунітету за нормального вітамінного статусу та за дефіциту піридоксину, фолату і кобаламіну.

Ключові слова: вітаміни B₆, B₉, B₁₂, вроджений і набутий імунітет.

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