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A Review of Essential Microelements in the Immune System

Ionut-Iulian Lungu[1], Ioana Babarus[1, *], Liliana Oniciuc[2], Alina Stefanache[1]

[1]Discipline of General and Inorganic Chemistry, Faculty of Pharmacy, University of Medicine and Pharmacy "Grigore T. Popa", Iasi, Romania

[2]Faculty of Chemistry, Alexandru Ioan Cuza University of Iasi, Iasi, Romania

Email address:

ioanababarus@yahoo.com (I. Babarus)

[*]Corresponding author

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Abstract: The immune system is the set of cells and organs that intervene in the body's defense against certain antigens, foreign to the body. This set includes both elements with rapid action and thus belonging to non-specific immunity, and also, elements that provide a slower response, but, with high specificity against each antigen. Nonspecific immunity sums up both cellular and humoral elements, which react quickly on foreign substances and microorganisms. On the other hand, adaptive immunity is based on the existence of lymphocytes, which develop a response, albeit slower, with a high specificity through antibodies secreted by B lymphocytes. Zinc deficiency is the second most widespread micronutrient deficiency. This compound is indispensable for the human body because it is a cofactor for many enzymes including alkaline phosphatase, dismutase superoxide, metalloproteinases. Moreover, zinc is included in the structure of growth and transcription factors and it participates in the cell communication within the immune system. Selenium is an essential trace element, being involved in many biological processes. It is part of a structural component of the amino acid selenocysteine, one of 25 selenoproteins, which are involved in the body's immune defense. Raising the awareness of iron deficiency, recent studies emphasize that it is the most common mineral deficiency worldwide. As it is already well known, iron is particularly important in the transport of oxygen, but its essential roles are not only limited to that. Besides, it is a constituent part of some metalloproteins and a cofactor for many other enzymes. Moreover, iron takes part of ATP synthesis. Therefore, the lack of iron has multiple repercussions on the whole organism, including the immune system.

Keywords: Zinc, Selenium, Iron, Immunity

1. Introduction

The immune system helps to repair damage caused by environmental pollutants and toxins from food (e.g.: glycoalkaloids in potatoes, cyanide-generating compounds in bitter apricot seeds and bamboo shoots, lectins in green beans). Biochemical mechanisms quickly identify any "non-self" molecules and eliminate the threat through neutrophils, natural killer cells (NK) and cytokines. Pathogens and foreign tissues activate slower adaptive immune functions that utilize B and T cells [1]. These immune functions identify specific antigens on the invading microorganism and form antibodies against it, in a manner to be prepared for attack by other immune cells.

Numerous studies have stated that some trace elements (zinc, iron, selenium) are essential for an effective response of immune system. They inhibit viral replication in host cells, exhibiting antiviral activity, while other microelements act as antioxidants [2].

Historically, the importance of micronutrients in the immune system and on infection was based on vitamin C deficiency and the phenomenon of scurvy. In the first recorded controlled clinical trial, published in 1753, James Lind did different diets for patients who were suffering from scurvy. He observed that the most remarkable recovery was for patients who consumed citrus fruit [3]. After this discovery, a series of articles showed that several

micronutrients are essential to the immune system and have synergistic roles based on their complementary mode of action [1].

Nowadays, more and more people know that a balanced nutritional status is crucial for the development, maintenance and expression of the immune response.

A healthy lifestyle and a well-balanced diet contribute to the strengthening of the immune system. Several studies have shown that the lack of quality and quantity of nutrients in the diet affect both innate and adaptive immunity and causes an increase in the morbidity and mortality.

This meta-analysis provides an overview of the importance of micronutrients that are fundamental to immune function and outlines the effect of deficiencies in macronutrients for people who suffering from malnutrition and who become more susceptible to infections and certain pathologies.

2. Material and Methods

We retrieved studies from the PubMed database and systematically reviewed both the mechanisms and biological activity of zinc, selenium and iron with regard to immune system. Mechanisms, doses and factors were also discussed.

3. Results

The immune response is based on an integrated system of cellular and humoral defense mechanisms. These mechanisms are very well regulated by a multitude of factors, secreted by cells, either as stimulators or amplifiers of the immune response, or inhibitors, to stop it, when the "danger" no longer exists, as it has been removed or destroyed [4].

The living organism has the ability to distinguish between what is foreign to it ("non-self"), from what belongs to it, its own structures ("self"), and to put into play a series of defense mechanisms, to fight for the removal, destruction or annihilation of the non-self [5]. If the body does not react by building a rejection response of that agent, it becomes accepted (considered to be its own structure), a phenomenon called immune tolerance [6].

A body's own structure can undergo changes, which makes the host's immune system no longer recognize it as its own structure (self), and thus, there is a contradiction with the notion of non-self [7]. As examples of modified (altered) self-structures, we can mention virally infected cells, malignantly transformed cells. These structures will be recognized as non-self and their presence will trigger the immune response and the generation of specific effectors, such as antibodies, activated cells, effector cells, etc. [8].

Cellular factors play a major role in the rapid, initial defense against infections, as do nonspecific effector cells that then phagocytose and destroy microorganisms [9]. The best known and most important phagocytic cells are granulocytes or polymorphonuclear cells (PMNs): neutrophils, eosinophils, basophils and, among mononuclear cells, macrophages.

Numerous studies report that some trace elements, such as zinc, iron and selenium, have been shown to be essential for an effective response of immune system [1]. Some trace elements inhibit viral replication in host cells, exhibiting antiviral activity, while others act as antioxidants or have the ability not only to regulate the immune response of the host, but also to modify the viral genome. Some have immunomodulatory effects and thus influence the susceptibility, evolution and outcome of a variety of viral infections [10].

Some elements of the immune system such as cell-mediated immunity, antibody responses or natural killer cells may be influenced by deficiencies of trace elements, but also high levels can interfere the activity of these elements [11]. Undoubtedly, a functioning immune system under normal parameters is necessary for the host's ability to prevent or limit infections. Obviously, the optimal level of trace elements and other nutrients for immune function must be included in any diet [12].

There are two types of immunity, the innate and the adaptive ones, that are conditioned by a normal level of zinc. It is essential that it should be included in the diet, because the human body cannot store it [13]. Proper dietary intake of the mineral is essential in maintaining the integrity of the immune system [1]. Regarding the innate immunity, it was discovered that cytotoxicity of natural killer cells, phagocytic activity of neutrophils, the possibility of immune cells to generate oxidants against pathogens and macrophages can be affected by zinc deficiency [14]. The function of adaptive immunity is also influenced by zinc deficiency, particularly the lymphocytes' number and activity [15]. Low levels of zinc cause thymic atrophy, which leads to an imbalance in the subsets of helper T cells [16]. In addition, cytokine production affected by zinc deficiency leads to oxidative stress and inflammation [17].

Even zinc border deficiency, the severity of which is often underestimated, affects different aspects of immunity [18]. The elderly can be frequently exposed to this type of risk, taking into consideration that there is a predisposition of insufficient zinc intake among those over 60 years old and that the plasma zinc concentration decreases physiologically with age [19]. Recent randomized controlled trials, certify that administration of low and moderate doses of zinc (between 10 and 45 mg zinc / day) to healthy elderly people improves the immune function by restoring thymulin activity, increasing the number of cytotoxic T lymphocytes, low number of activated helper T cells which may imply the autoimmunity [20].

Selenium is an important component of the body's antioxidant system. Its role is to protect the body from oxidative stress. Numerous studies confirm that selenium plays an essential role in the functioning of the immune system [21].

Numerous studies have stated that people suffering from malnutrition are more susceptible to infections and certain pathologies due to deficiencies in macronutrients. Recently, it has been confirmed that micronutrients, such as several

vitamins and minerals, also play very important roles in the defense and protection of the immune system to protect against certain infections, inflammation and possibly, cancer [22]. Research states that inadequate selenium levels are due to the incidence, severity or progression of viral infections. When selenium and immunity were examined, it was concluded that the deficiency may lead to the formation of proinflammatory compounds that would influence the risk of certain pathologies such as heart disease and cancer [23]. Recent studies have shown that selenium levels can influence the genetics of a viral pathogen. Thus, the nutrition of trace elements influences not only the host's response to a pathogen, but also the pathogen itself.

Selenium, a trace element that is very important for the optimal functioning of the immune system. It is involved in the functions of the immune system cells. So, an inadequate diet in selenium, leads to various immune deficiencies and diseases, such as atopic asthma, skin cancer, psoriasis, Kashin-Beck disease and myxedematous cretinism [24]. Selenoproteins are vital for activating T cell function. Oxidative stress can affect T cells. Selenium supplementation can boost cellular immunity. Selenium intake has been shown to improve B lymphocyte activation and proliferation and improve T cell function. Selenium prevents oxidative stress that leads to damage the immune system cells and alters platelet aggregation by decreasing the production ratio between thromboxanes and leukotrienes [25, 26].

Selenium has immunomodulatory and antiproliferative properties. It can affect the immune response by altering the expression of cytokines and their receptors. It can also increase the resistance of immune cells to oxidative stress. As part of the enzyme glutathione peroxidase, along with vitamin E, superoxide dismutase, and catalase, selenium forms one of the most important components of the body's antioxidant defense systems [27].

Iron is a vital component in erythropoiesis and it is essential for the proper function of the immune system. Clinical and experimental data show that there is an increased risk of infection related to iron deficiency. Documentation has shown that iron deficiency significantly alters the immune response mediating cells in children as well as in pregnant women [28].

Anemia in children has been reported to be associated with reduced phagocyte activity and decreased levels of immunoglobulins in the blood (IgG4). Iron deficiency affects immune response mediating T cells by decreasing IL-2 production [29]. The number of T lymphocytes, as the *in vitro* proliferative response to mitogenic stimuli, has been shown to be significantly affected among children with low serum concentrations of iron and anemia [30]. Deficiency can increase the risk of infection, so iron is needed for normal immune system function, including bactericidal activity of macrophages, and for T cell development and function. Although iron is necessary for immune system development, iron overload can inhibit some effector immune functions [31].

4. Conclusions

The most beneficial elements with an impact on the immune system are: iron, selenium and zinc. Zinc has a role both in the non-specific immune response and in the specific one. Selenium is important for its antioxidant action, as it prevents oxidative stress that induces damage to immune system cells. Iron is necessary for the normal functioning of the immune system, for the bactericidal activity of macrophages, as well as for the development and functioning of T cells.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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