

Nutrition and Immunity during Pandemic Viral Infection

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Review Article

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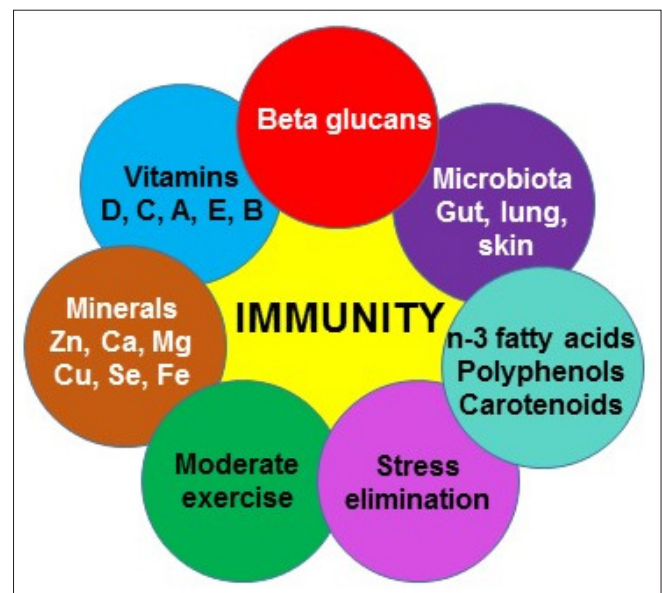
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Abstract

Actual pandemic state of covid-19 infection leads to considerations of the quality of the state of immune system in population and to possible changes of this unfavorable state. In this review, the authors discuss the possibilities of nutritional changes, as the quality of nutrition in global sense is completely unsatisfactory. We assume that optimal supplementation with minerals and vitamins forms the basis for development of adequate immune responses not only to Covid-19 infection, but also to other bacterial and viral infections. It is necessary, however, to use optimal doses of supplements, as either too low or too high dose might decide between the use of a medicine or a poison. We conclude that the major responsibility for optimal approach to supplements lies not only with health professionals, but with the society. It is necessary to repeatedly offer quality information on neglected components influencing the health of the population, including stress, microbiome, adequate physical and psychical strain, and/or optimal diet. Beta glucans and their immunomodulatory activity helps not only in prevention of the whole spectrum of diseases connected with the immune system, but also in treatment of infectious diseases.

In last two decades, the world experienced three epidemics caused by SARS coronaviruses with manifested respiratory syndrome. Covid-19 infection, originating in 2019, is just one of the mutations [1]. The major difference is the fact that when compared to previous epidemics, the SARS-CoV-2 causes much higher number of infected people. By data collected in 221 countries, at the end of 2020 there were more than 10 million infected and more than 1 million deaths. Czech Republic reports extremely high prevalence of this disease, and, when compared to other countries, shows the highest percentage per 100 000 people. More than 1 million cases and over 20, 000 death represents the highest numbers in the whole Europe. In the meantime, some of the countries are opening, but the people are still dying. Significant problems are noticeable globally, not only from the health care point of view, but also economical problems. The major causes are inadequate and practically impossible direct specific treatment [1], delayed and slow vaccination and previous low attention devoted to prevention of infectious diseases. Low interest in inadequate state of immunity in population and low interest on possible solutions is, at least partly, based on geographical location, lifestyle, nutrition and low consideration of possible prevention [3]. Genetic disposition affecting frequency of blood antigen may support a decrease of immune response to α -Gal and result in high sensitivity to infectious diseases caused by pathogens with α -Gal on their surface [4]. Figure 1 summarizes individual components suitable for improvements

of immune responses.



Healthy and balanced diet increases the strength and capacity of the immune system, its cellular components and results in optimal response to pathogens. Ever increasing evidence show the effects of various nutritional components on individual parts of the defense reactions. The relation of blood groups

on anti- α -Gal immunity and incidence of infectious diseases associated with microbiome is well documented [5]. Wide spectrum of vitamins and minerals with antioxidative properties affects not only several functions of the immune system but also the production of anti-microbial proteins, synthesis and release of various cytokines and other mediators. Deficit of minerals and/or vitamins results in lower immunity. Therefore, we believe that it is imperative to precisely define these deficits in individual countries, regions and social groups. Clearly, we need to specify insufficiencies of individual components and offer potential solutions. In this review, we will describe the most important nutritional components and their relation to optimal level of immune reactions.

Vitamin is the most important vitamin out of the whole spectrum of vitamins potentially involved in regulation of immune reactions. Dynamics of serum levels of vitamin D is in humans influenced by season, location, quality as well as quantity of sunshine, age, health and social status of an individual [6-9]. Nutritional effects on vitamin D levels in various countries varies from 5 to 35% of normal values. In European countries were the normal levels (30 to 100 ng/L) found in 10-80% of population [10]. Vitamin D insufficiency is not only involved in induction of numerous autoimmune diseases, chronic disease, inflammatory problems of the gastrointestinal tract, asthma bronchiale, diabetes and multiple sclerosis, but also plays a role in increased mortality [7, 8, 11, 12]. This relation of low levels and development of various diseases results in a push for direct supplementation not only in children, but most of all in senior population, with described strong improvement of general health and measurable reduction of the risk of infectious diseases [2, 3, 7, 11-14]. Epidemiological studies showed increase incidence of vitamin D deficiency in senior population. Besides pathophysiological changes of the skin and increase obesity, these levels also affect level of leptin [15]. Association of leptin polymorphism and leptin-related genes is related to vitamin D levels, which is also involved in immunity against some viral infections [15] including Covid-19 [10, 16]. Important supporting role against uncontrolled inflammatory processes against viral infection is offered by Treg cells. Patients with Covid-19 infection have significantly lower levels of Tregs and vitamin D supplementation can increase their levels. This might result in reduction of clinical manifestation of pneumonia/ARDS, inflammation, thrombosis and additional complications accompanying Covid-19 disease [6, 17]. Supplementation with vitamin D is therefore recommended in population with higher risk of Covid-19 infection [6, 18]. Relation between vitamin D levels and Covid-19 infection were observed even among our patients. Vitamin D can influence elevated inflammatory response and increase healing processes in affected organs, particularly of respiratory tract cells [16].

For more than 6 years, the attention of our clinical laboratory is focused on effects of vitamin D supplementation on immunodeficient patients, both on humoral (IgG4 syndrome) and cellular immune reactions. In addition, vitamin D also plays a robust pleiotropic immunomodulatory role in development

of cystic fibrosis [19]. We repeatedly described significant reduction of seasonal respiratory diseases including SARA 19 in individuals with persistent contamination of infected relative by optimization of vitamin D levels to higher than 40 ng/ml. In individuals with vitamin D levels below 25 ng/ml we found insufficient response to viral infection including Covid-19. None of our vitamin D-supplemented patients with insufficient immune system but vitamin D levels over 40 ng/ml showed clinical manifestation of Covid-19 disease even after clear exposure to Covid-19. All individuals with vitamin D levels below 25 ng/ml showed clinical manifestation of the disease.

Vitamin C is an essential micronutrient for humans with numerous and pleiotropic functions connected with its ability to donate electrons. Major role of vitamin C in immunity is its antioxidant activity and subsequently defense of respiratory apparatus against oxidative stress caused by pathogens [2, 20]. Vitamin C can stimulate phagocytosis, T cell proliferation, interferon induction and lower viral replication [1, 18, 20]. Ability of vitamin C to improve immune response against Covid-19 infection was repeatedly observed [1, 13]. Low levels of vitamin C result in lower resistance to infections, supplementation on the other hand results in stimulation of phagocytosis, activation of lymphocytes and changes in neutrophil chemotaxis [2]. An excellent review describing the relation between vitamin C and immune function proposed the prophylactic prevention of infection by high doses of vitamin C [21]. In addition, vitamin C is necessary for collagen biosynthesis and for sustaining integrity of epithel [18], which helps to reduce some diseases. Supplementation in a blanket manner in children from highly polluted areas of the Czech Republic resulted in strong reduction of respiratory tract diseases.

Vitamin A is necessary for differentiation of epithelial cells, maturation of immune system and support of their functions. A vitamin A deficit leads to lower numbers of NK cells and suppressed phagocytic activity. In addition, vitamin A is responsible for maturation of CD4⁺ T lymphocytes and balance of Th1 and Th2 cells [18]. Depressed levels of vitamin A can increase the risk of penetration of pathogenic bacteria through salivary epithel and its supplementation improves antibody response during vaccination [13].

Vitamin E is involved in maintenance of immune response and supports proliferation of lymphocytes, activity of NK cells and the strength of antibody response during vaccination. Reduction of occurrence of respiratory infections has been repeatedly observed [18]. Insufficient levels of vitamin E result in lower maturation of T lymphocytes and suppressed adaptive immune responses [2].

Vitamin B6 deficit is involved in insufficient maturation of lymphocytes and in depression of their numbers [22]. In addition, it affects thymus and spleen atrophy [18]. Vitamin B12 also influences the numbers and function of lymphocytes [2]. In addition, low levels of this vitamin can result in lower

activity of NK cells and neutrophils [18].

In addition, various minerals are necessary for optimal immune response of the organism. They are involved in maintaining integrity of the secretory system in the gastrointestinal tract, skin, respiratory tract and other barriers. Optimal functions of minerals play role in anti-oxidative activity, anti-microbial activity, differentiation and function of T cells and antibody response.

Trace elements are essential cofactors important for several important proteins [1, 20, 23, 24]. It is necessary to maintain their optimal concentration, as both low and to high levels might be dangerous or even toxic [25]. At the same time, interaction between host and microorganism is dependent on the level of minerals, as trace elements modulate this interaction. In case of disbalance, physiological functions of the organism might be disrupted [6, 12, 17]. In addition to physiological functions, trace elements are also involved in regulation of immune reactions. They play role not only in the quality of various barriers, often playing the role of first defense, but also in the whole spectrum of immune reactions, both nonspecific and specific [1, 13, 18, 20, 23, 24].

Zinc deficiency is known since 1960s. Zinc supplementation needs to be carefully done, so it reduces potential insufficiency and at the same time rule off overdose, which might result in dysbiosis and predisposition to various infections due to the compromised salivary immune response [14, 24, 26]. Zinc supplementation was found to improve antibody response (particularly IgG class), formation of tolerance and induction of production of cytotoxic T cells, cytokines and Tregs [2, 6, 20, 27]. Additional roles are reduction of oxidative stress and regeneration of intracellular killing with induction of macrophage-derived cytokines [14, 24]. Zinc homeostasis-related effects on the activation of key signaling molecules together with epigenetic modification clearly elucidate the role of zinc as a gatekeeper of immune functions [28].

Possible deficit can cause reduction of respiratory tract diseases. It is known that viral infections increase risk of bacterial adherence to respiratory tract epithel [23]. Long-term zinc deficiency can induce persistent inflammatory reactions [6]. Major advantage of zinc supplementation is not only prevention, but also direct effects on respiratory diseases [26]. To keep optimal levels of zinc is beneficial for numerous segments of population, including children, seniors, obese and diabetic patients and people with various immunodeficiencies. However, we not only need to supplement with zinc, we also need to carefully monitor its level, as high doses can result in copper deficiency [24]. The levels of zinc in our patients showed app. 40% with deficient levels, which correlates well with the literature [9, 27].

Optimal levels of copper results in support of various functions of neutrophils, monocytes, macrophages, and NK cells. Low levels of copper can lead to lower proliferation of lymphocytes and reduction of IL-2 production [5]. In immunosuppressed

individuals, copper supplementation resulted in induction of native and adaptive immune reactions and increase of anti-viral immunity including Covid-19 therapy [2, 23, 26].

Selenium is a potent micronutrient important for various facets of mammalian health including immune response. Low levels of selenium result in reduction of NK cell activities and higher risk of microbial infections. In addition, mutation of viral particles with increased virulence has been described [6, 18]. Long-term deficit results in increase oxidative stress and suppressed numbers of monocytes [13]. In addition, selenium was found to have suppressive effects on breast cancer manifested via epigenetic mechanisms [29]. Recent studies found that addition of selenium improved immunodulation caused by beta glucan [30]. Some studies suggested increased risk of Covid-19 infection [24].

Magnesium is the second most abundant cation in cellular systems. Deficit of magnesium is in developed countries quite common and depressed values are commonly found in patients with CVD, diabetes, high blood pressure, obesity, stress and extremely unhealthy nutrition. Long-term deficit results in endothel dysfunction, inflammatory reactions and CD4/CD18 T cell disbalance. It plays a key role as a co-factor for synthesis of immunoglobulins, cell adherence and C3 convertase [for review see 31]. Supplementation can improve the problems with inflammation and decrease the levels on inflammatory proteins.

Calcium acts as a second messenger in most cell types and is extremely important for optimally functioning immune system. Suboptimal levels can cause higher risk of bacterial and viral infections and even higher mortality. Hypocalcemia is closely related with Covid-19 infection [22]. Lower levels of calcium can be found in patients with clinical manifestation of stupor, spasms, delirium and hypotension. Lymphocytes activated by binding of antigen have increased calcium influx [32]. In Covid-19 patients are calcium levels significantly depressed and their improvements result in lower mortality [2]. Similarly, therapeutical use of blockers of calcium channels can reduce mortality [22].

Deficits of iron results in thymus atrophy and reduction of development of naïve T lymphocytes, with subsequent wide range negative effects on immune functions. Proliferation of T lymphocytes is in deficient individuals reduced to 50-60%, with accompanying reduction of NK cell activity and production of T helper cell cytokines. It is clear that it is imperative to maintain optimal levels of iron. Levels that are too high may cause the same problems as levels too low – reduction of immune functions leading to increased risk of respiratory problems [18, 23, 24]. It is well established that iron is necessary for numerous physiological processes. Its high reactivity might induce oxidative stress. This stress can subsequently lead to lower sensitivity of insulin and to lower function of β -cells from pancreas. The levels of ferritin, which is reservoir of iron, can increase and are risk factors for obesity, inflammatory reaction and diabetes II [25].

Ferritin is key indicator of dysregulation of immune functions. Hyperferritemia is one of the inducers of the cytokine storm and the relation of high levels of ferritin with seriousness of Covid-19 disease are currently being evaluated, particularly in diabetic patients [25]. Readers interested in an excellent review summarizing the relation between iron and immunity should read [33].

Beta glucans are natural polysaccharides. Optimal nutritional composition might offer some intake of beta glucan, but current nutritional trend of using industrial type of nutrition constantly lowers the amount of beta glucan in our food. Extensive research of beta glucans and their actions undertaken in last several decades helped to elucidate numerous mechanisms of action and their involvement in improvement of our health, including microbiome, probiotic and prebiotic effects and most of all, immune system [3, 4, 14, 34-37]. Our studies suggested the use of orally-given beta glucan both in prevention and in therapeutical interventions in various types of diseases. An interesting study of Jawhara [14] describes possible use of beta glucan and its fractions for reduction of coagulation. In these studies the individual fractions have activity similar to low molecular heparin. In Covid-19 patients is a high risk of development of diseminal intravascular coagulation. Thrombocytopenia and elevated levels of D-dimer induce higher activation of platelets and higher coagulation. Beta glucan effects might be elevated by addition of adequate dose of vitamin C and D [4, 37]. These studies suggest that beta glucan is one of the most prominent immunomodulators [37]. Development of high quality beta glucan helped our laboratory to offer an unique application with excellent effects both in prevention and in therapy.

Healthy and well-balanced diet can improve immune system and subsequently the reactions of its individual components. Currently, an increasing amount of data showing the role of nutrition on composition and modulation of microbiome has been published. Microorganisms colonize our organs, mouth cavity, respiratory and gastrointestinal tract, and skin. Their composition significantly varies based on ethnicity. Individual composition is formed not only by diet, but also by age, physical conditions, medical treatment and social status of an individual. Abnormal and dysbiotic microbiome is common in older people and in obese individuals [35]. The result is a low level of immune responses as a result of insufficient maturation of immunocytes. The relation between immunity and microbiome is currently a subject of numerous studies, but we still do not fully understand all possible interactions [1, 18, 38]. Microbiome is involved in modulation and regulation of immune system. Its dysbiosis result in increased sensitivity to various diseases including Covid-19 infection [1]. Some studies suggested the use of probiotics with some improvements of the immune responses. Probiotics play a role in regulation of salivary immunocytes and cells present in epithel. Their effects vary based on type of probiotic used. Lactobacillus probiotics elevate anti-viral response including anti-Covid-19 response. In these patients we found significant improvements with improved dysbiosis and changes in Bacteroides and Firmicutes

ratio. In addition, microbiome composition also influences the quality of immune response upon vaccination [1, 14, 23, 24].

Effects of omega-3 fatty acids on immune system are recognized for more than 30 years. Unsaturated fatty acids can change cellular composition of both innate and adaptive branch of immune system. In last few years we observed interest in possible new role of omega-3 fatty acids and their derivatives as signal molecules affecting functions of macrophages, neutrophils, eosinophils, T and B lymphocytes and NK cells. Saturation of omega-3 fatty acids results in reduction of inflammatory diseases, higher production of cytokines, improved formation of antibodies and clear clinical improvements of various diseases [39].

Nutraceuticals and functional food are extremely popular lately. However, low quality of information is often reflected in unsatisfactory nutritional situation. A wide spectrum of various natural extracts such as lutein, resveratrol, isoflavones, green tea extracts etc. is being offered as a possible treatment for cancer, reduction of obesity and/or cardiovascular diseases, but often without any real demonstration of the effects or any mention of possible serious side effects or interactions. Fruit and vegetables as “green medicine” are still rather neglected, despite well-documented positive effects. An old proverb “An apple a day, flu is away” should be used as a motto of modern nutrition.

The relation of stress impulse with the full spectrum of possible inducers is well-established factor in reduction of immune reactions [36, 37, 40, 41]. The mechanisms of action are still unknown, it is sometimes assumed that individual disposition can be responsible. In addition, stress reaction with subsequent depression of immune reactions might be caused by harmful impulses or information. People with significant mental problems can serve as an example [14, 42]. Other dispositions might be connected to difficult work-related conditions or changed environmental conditions [41]. A high frequency of these impulses leads to significant reduction of quality of immune responses, often described in current population. Current Covid-19 pandemia can serve as an example of all points mentioned above [42].

In order to influence pathophysiology of Covid-19 infection and its neuroinductive effects, neuromodulatory approach is necessary [43]. Psychological stress observed during Covid-19 infection results in disbalance of immune system with subsequent depression of number of CD69+ lymphocytes and NK cells. Some studies described significant effects of glucan supplementation on reduction of stress via inhibition of cortisol and improvement of cytokine production [44].

Current time of various lockdowns and home isolations result in serious and long-term lack of physical activity, increased stage of anxiety, depressions and stress. Some degree of physical activity is an easy way to improve these problems [40]. On the other hand, too high physical stress causes high risk of numerous diseases, mostly as a consequence of depressed

salivary immunity, which is often observed in athletes. Optimal response of secretory immunity is an increase of sIgA production, whereas too high activity leads to an increase of cortisol level and thus a decrease of sIgA formation [40, 45]. We observed this situation in professional basketball team. Due to the high physical stress during a tournament, the whole team got infected with Covid-19. We propose to decrease these risks by preventive supplementation with beta glucans, which results in reduction of corticosteroid production, modulation of cytokines and improved salivary immunity [45].

We propose that these nutritional improvements should become an official program of every society interested in the general health and quality of life of its population.

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