THE ROLE OF ASSESSMENT AND CORRECTION OF NUTRITIONAL STATUS IN A COMPREHENSIVE APPROACH TO COVID-19 PATIENTS WITH METABOLIC DISORDERS (REVIEW)

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Abstract

The article features the problem of coronavirus disease COVID-19 with emphasis on the nutritional status of the patients. An analytical review of the recent publications related to the aspects of nutritional support for people in outpatient and inpatient treatment for COVID-19 is presented. The article highlights the pathogenetic justification of the relationship between the immune response and metabolic balance of the body, the optimal content of trace elements, vitamins, components of lipid metabolism. The importance of nutrition as a strategy to support human immune function is considered. Methods for determining the adequate energy balance of patients with severe COVID-19 are presented. Groups of foods and key nutrients that may affect the consequences and clinical course of respiratory infections are described. The importance of assessing and optimizing nutritional status to improve the clinical course and consequences of COVID-19 in patients with comorbid pre-existing non-communicable diseases, such as diabetes, cardiovascular disease, obesity with systemic inflammation, is emphasized.

Keywords: *coronavirus disease COVID-19, nutritional status, microelements, vitamins, components of lipid metabolism, diagnosis of malnutrition.*

Coronavirus disease 2019 (COVID-19) is currently a pandemic that has far-reaching consequences for the health of both the individual and the population as a whole and causes serious damage to the society and economy of many countries. Given the great urgency of this problem, identifying the main risk factors for adverse disease and finding possible ways to correct it is one of the priorities of the modern medical community.

To date, a relationship between a number of risk factors, such as diabetes, cardiovascular, cerebrovascular, pulmonary disease, patient age and severe course of the disease, and mortality in patients with COVID-19 has been established. These pathological conditions are mostly characterized by systemic inflammation, which may be a common feature that affects the treatment outcome in patients with new coronavirus disease. An increase of scientific data also proves that the clinical course and consequences of COVID-19 are more unfavorable in those who are overweight or obese [1, 2].

The pathogenetic justification of this phenomenon can be explained by several mechanisms. On the one hand, the presence of obesity affects the immune system by altering the expression of proinflammatory cytokines, which leads to an increase in the cytotoxic response of immunocompetent cells that play a key antiviral role. Thus, according to O'Shea D., Corrigan M., Dunne MR (2013) dendritic cells, which play a crucial role in the relationship between innate and adaptive immunity, in obesity produced twice as much of the immunosuppressive cytokine interleukin-4 (IL-4) and four times more IL-10 than the control group [3]. On the other hand, angiotensin-converting enzyme 2 (ACE2) is known to be a probable receptor for penetration into target cells with extremely high affinity for SARS-CoV2. ACE2 expression in adipose tissue was found to be higher than in the lung, with

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ACE2 receptor expression being the same for adipose tissue in obese and non-obese patients. The difference lies in the mass of adipose tissue and, consequently, more ACE receptors [4].

It should also be noted that obesity is usually associated with the factors of the group of diseases constituting metabolic syndrome, and therefore have a negative impact on the clinical course of COVID-19 and increase the overall risk of mortality [5].

Given the above, the importance of correcting the nutritional status of patients in this cohort and assessing the impact of dietary characteristics on the clinical course of COVID-19 in the acute stage and in the rehabilitation period becomes relevant.

It is now known that almost all nutrients play a critical role in maintaining an "optimal" immune response. Insufficient or excessive consumption of certain substances can have negative effects on the immune status and increase susceptibility to various pathogens [6].

For example, the main functional role of microelements in the cells of the immune system is their participation as cofactors or catalysts for enzymes of free radical oxidation.

Zinc deficiency causes violation of hormonal regulation of growth and puberty in humans and animals, which leads to growth retardation and hypogonadism, reduces psychomotor development, increases susceptibility to infection. Depending on the degree of zinc deficiency, the characteristic features are thymic atrophy and loss of T and B lymphocyte precursors in the bone marrow by 50–70% due to induction of glucocorticoid-dependent apoptosis with subsequent lymphopenia and immunodeficiency [7]. Inhibition of the activity of natural killers, lymphokine-activated killers and mitogen-dependent lymphocyte proliferation is also observed. Such pathophysiological status contributes to the development of autoimmune pathology [8, 9].

Manganese is a component of many enzymes, including manganese-dependent superoxide dismutase, which is involved in lipid peroxidation in the cells of the immune system, as well as in other processes of free radical oxidation. Manganese-dependent superoxide dismutase acts as the main integral scavenger of reactive free radicals with a damaging effect, which are formed in the mitochondrial matrix [10]. Recent studies have shown that manganese-dependent superoxide dismutase, in addition to performing its antioxidant functions, also acts as a fundamental regulator of cell proliferation, a mediator of metabolism and apoptosis. This protein plays an anti-apoptotic role against oxidative stress, ionizing radiation, pro-inflammatory cytokines [11].

Dietary *phosphorus* helps to strengthen the cellular immune system and reduce the humoral immune response. As for magnesium, there are no studies that clearly prove its role in the dysfunction of the immune system, but its important contribution to the process of chronic subclinical inflammation. Individuals who consumed magnesium less than the recommended daily allowance showed a probable increase in the level of C-reactive protein [12].

Vitamins, similar to microelements, regulate the formation of superoxide anion by phagocytes in response to infectious agents, prevent oxidative-dependent tissue damage and increase the activity of natural killers. Thus, reducing the level of vitamin A helps to suppress the humoral immune response to T-dependent antigens, reduces the activity of cytotoxic lymphocytes and increases susceptibility to bacterial infection. At the same time, iodine excess has a suppressive effect on the immune system [13].

Vitamin E deficiency reduces mitogen-dependent lymphocyte proliferation and the activity of natural killers, and its regular intake provides an increase in overall resistance to infectious processes, especially in the elderly and senile [14]. However, there are still no convincing data on the role of vitamin E in prevention and treatment of new coronavirus infection.

Vitamin C mainly affects the non-specific part of the immune system, increasing the synthesis of macrophage proteins, proteins of the complement system and thus enhancing the non-specific resistance of the body and antiviral immunity. A large-scale multicenter clinical study of CITRIS-ALI previously confirmed a reduction in the risk of multiple organ failure and levels of markers of inflammation and vascular damage in patients with acute respiratory distress syndrome (ARDS) of various etiologies with high doses of vitamin C [15].

However, a preliminary study of 167 patients with ARDS due to COVID-19 conducted in the United States did not show a significant improvement with the introduction of 50 mg/kg of ascorbic acid in 5% glucose solution iv every 6 hours for 96 hours [16]. In China, a full-scale clinical study was launched using 24 g of vitamin C per day for 7 days to definitively address the feasibility of including high doses of vitamin C in treatment algorithms for patients with COVID-19 [17].

Vitamin D 3 is one of the most active factors in the regulation of the immune system, influen-

cing the processes of lymphocyte activation and synthesis of anti-inflammatory cytokines. This is mainly due to the inhibition of T-cell proliferation and, as a consequence, the transition from T-helper cells of type 1 (Th1) to T-helpers of type 2 (Th2). It can be argued that decreased Th1 proliferation leads to lower levels of pro-inflammatory cytokines and reduced acquired immune responses, which may be counter-productive to a successful immune response against viruses. Vitamin D also affects the maturation of T cells and can alter the development of inflammatory T-helper mass of cells type 17 (Th17) on the population of anti-inflammatory regulatory T cells (T-regulatory cells), which reduces the level of "provocative" cytokines such as IL-1, IL-6, IL-12, TNF alpha and IL-17 and increase the anti-inflammatory effect of IL-10. Thus, due to its opposite actions on cytokine regulation and T-cell differentiation, vitamin D plays a complex dual role in immunoregulation [18]. Today, in the current COVID-19 pandemic, vitamin D deficiency is considered as one of the potential risk factors and a possible factor in development of the process, which is called cytokine storm [19].

Components of *lipid metabolism* are of great importance in the regulation of immune system functions. Representatives of all classes of lipids have active immunomodulatory potential, especially for phospholipids, sphingolipids and fatty acids. Some researchers have shown that high levels of long-chain polyunsaturated fatty acids (PUFAs), especially omega-3 PUFAs, protect overweight or obese people from developing metabolic syndrome and inflammation from an early age [20]. The importance of lipids is determined by their physiological role: eicosapentaenoic acid (EPA) is required for the synthesis of eicosanoids, docose hexaenoic acid (DHA) is needed to support the vital functions of the immune system. Under inflammation, the DHA and EPA present are enzymatically converted into specialized mediators known as resolvins, protectins, and maresins. These molecules, among others, are responsible for reducing inflammation, including in the airways. Derivatives of omega-6 PUFA, in particular arachidonic acid and its metabolites (prostaglandins, leukotrienes, thromboxanes, prostacyclins), affect the expression of lymphocyte genes, and are direct effectors of many reactions in the cells of the immune system. It is known that deficiency of these essential fatty acids can lead to delayed or incomplete regression of inflammation. This may be important in the context of severe COVID-19 infection, which is manifested by uncontrolled inflammation and cytokine storm manifestations. In animal experiments, the protective effects of specialized mediators formed from EPA and DHA, which are manifested by the elimination of acute lung damage, were demonstrated [21–22]. Currently, a number of studies have also been conducted on the effect of pharmaconutrients, the so-called "immunological nutrition", on the clinical course of severe diseases and acute respiratory viral infections (ARVI). However, the recent Cochrane Review of 10 randomized controlled trials of varying quality involving 1,015 participants found no significant differences in the effects of omega-3 fatty acids and antioxidants on the clinical course of the disease in adults with ARVI according to the number of days of ventilation, duration of stay in the intensive care unit or the level of oxygenation of the blood [23].

Several studies linking the immune system and carbohydrate metabolism disorders are currently known, but insufficient data have yet been obtained on individual pathogenetic components of this process. Obesity and diabetes have been shown to have similar changes in T-cell immunity that may contribute to metabolic disorders. These integral indicators include an increase in the number of CD45 + T cells, a redistribution of leukocytes in the direction of the inflammatory phenotype, and a decrease in the number of suppressive regulatory T cells and protective NK cells. Metabolic changes in obese and diabetic patients may further affect the differentiation and functioning of components of innate and adaptive immunity [24].

Thus, all the main components of food, namely - proteins, fats, carbohydrates, microelements, vitamins, to some extent show immunomodulatory activity, affecting all parts of the immune response, including non-specific protective reactions and native immunity. Both the presence of obesity and the lack of nutrients are important for immune function. Starvation and malnutrition have been shown to suppress immune function and increase susceptibility to infections.

Appropriate assessment of human nutritional status and proper correction are effective tools to improve clinical outcomes, reduce complications, hospitalize and stay in the intensive care unit of patients with COVID-19 in various situations, including polymorbidity, obesity and old age.

Patients at risk of adverse effects should be evaluated for malnutrition using the MUST (Malnutrition Universal Screening Tool) or NRS-

2002 (Nutritional risk screening) criteria. GLIM (Global Leadership Initiative on Malnutrition) criteria can also be used to diagnose malnutrition. GLIM criteria provide a two-step approach to the diagnosis of malnutrition:

First level – risk assessment using proven screening tools such as MUST or NRS-2002.

Second Level – assessment of the malnutrition severity.

Human energy needs can be estimated by indirect calorimetry in the case of availability and guaranteed sterility of the measuring system, or, alternatively, by calculation. According to the ESPEN recommendations, it is recommended to consume 20–30 kcal/ kg/ day, for patients who are in a serious condition or have concomitant diseases – 27–30 kcal/ kg/ day. Clinical observations confirm the need for adequate energy balance in patients with severe COVID-19.

The daily requirement for protein is in the range from 1.2 to 2.0 g/kg. Muscle atrophy may develop in severe patients due to increased protein catabolism. In turn, increasing protein intake can reduce mortality. It is important to provide patients with foods with high energy value, high protein content and optimal bioavailability of nutrients.

Consumption of fats and carbohydrates should meet the energy needs, taking into account the per-centage of energy coming from fats and carbo-hydrates 30:70 (patients without respiratory failure) and 50:50 (patients who need respiratory support).

Optimal nutritional support for adequate immune function may require the consumption of some micronutrients above the recommended level, because infections and other stressors can worsen nutrient status.

In particular, during an infectious disease in humans, the level of vitamin C in the systemic circulation is reduced. To restore its normal level in the blood, it is necessary to prescribe a higher intake of this vitamin. According to some studies in viral pneumonia, the addition of vitamin C to patients ≥200 mg/ day restores depleted plasma and cellular levels of vitamin C and reduces respiratory symptoms and reduces the duration of hospitalization.

The addition of micronutrients and omega-3 PUFAs is a safe, effective and inexpensive way to eliminate nutritional deficiencies, ensure optimal immune function, and therefore reduce the risk and consequences of infections. Multivitamins and mineral supplements, which provide the basic needs for micronutrients, are recommended in addition to an optimally balanced diet.

To sum up, nutrition is an important determinant of a person's immune status. Disorders of cellular immunity, phagocyte function, complement system, cytokine production and immunoglobulin A secretion are directly related to protein-energy deficiency. Thus, assessment and correction of nutritional status should be considered as an integral part of a comprehensive approach to the management of patients with COVID-19 at all stages of the disease in order to personalize and enhance treatment.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

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