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Nutrition in COVID-19 recovery

Ishrana u oporavku od COVID-19

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covid-19; ishrana, procena; ishrana, poremećaji; nutritivni status; covid-19, post-akutni sindrom.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared at the end of 2019, causing a worldwide pandemic. Most people experienced asymptomatic or mild-to-moderate acute coronavirus disease 2019 (COVID-19) symptoms; however, it was estimated that around 15% of people progressed to a more severe form of the disease requiring hospitalization, and approximately 5% became critically ill [1]. Although the acute phase of the disease has been well described so far, less data is available on the long-term outcomes [2]. Variable terms and definitions are still used to describe prolonged recovery or condition after acute SARS-CoV-2 infection with infection sequelae, such as "post-COVID-19 condition" or "long COVID condition". Long COVID represents a complex condition with different prolonged symptoms. According to the definition given by the World Health Organization (WHO), post-COVID-19 condition, also known as long COVID, occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19. Symptoms last at least two months and cannot be explained by an "alternative diagnosis" [3]. Michelen et al. [4] conducted the most comprehensive review of evidence on long COVID to date. Their findings suggest that this multiorgan syndrome is characterized by fatigue, weakness, malaise, breathlessness, and concentration impairment, among other less frequent symptoms. Symptoms of long-lasting COVID-19 sequelae and complications have been reported worldwide. A study from Italy showed that 87% of inpatients, who recovered from COVID-19, had at least one of the symptoms, even after 60 days [5]. A study in the United States found the prevalence of residual symptoms in 35% of patients treated for COVID-19 on an outpatient basis within 14–21 days after a positive test [6]. Lopez et al. [7] reported that 80% of patients with COVID-19 had long-term symptoms, including an estimate for at least one symptom.

While the focus during the COVID-19 pandemic was on the prevention and treatment of SARS-CoV-2 infection, today, significant attention must be paid to the health status of those who have recovered from COVID-19 or are still recovering from it. Many symptoms and conditions of long COVID, such as fatigue syndrome, sarcopenia, malnutrition, and gut microbiota alteration, are closely related to nutrition. On the other hand, the role of nutrition in the immune system's functioning is well documented today [8, 9]. In this context, it is essential to investigate and better understand the role of nutrition in the prevention of the severe form of the disease and improvement of the SARS-CoV-2 infection recovery. In this article, we present symptoms and conditions in patients with post-COVID-19 conditions closely related to nutrition, and we consider possible nutritional interventions for better outcomes.

Malnutrition

Data from different studies confirm the high prevalence of malnutrition in patients with COVID-19 [10, 11]. A Chinese study reported a prevalence of 52.7% of malnutrition in elderly patients (mean age 68.5 years) with COVID-19 [12]. The Nutricov study describes 37.5% of malnourished COVID-19 patients with pneumonia, with a mean age of 59.5 years, based on Global Leadership Initiative on Malnutrition (GLIM) criteria (weight loss, low body mass index-BMI, and reduced muscle mass) for malnutrition [10]. Malnutrition is a factor that can slow or prevent recovery [2, 13]. Insufficient

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consumption of energy, protein, and certain micronutrients can lead to reduced immune response and increased sensitivity to infections. Sufficient intake of vitamins D, C, A, E, B_6, and B_{12} and minerals zinc, iron, copper, and selenium are necessary to maintain immune function [2, 14–16]. Keeping in mind that some nutrients are crucial in the activation and functional expression of immune cells, it is important to prevent the lack of these nutrients in order to maintain a functional immune system. Screening for malnutrition is important for all COVID-19 patients, but special attention is needed for patients with multiple long-term conditions and people over 65 years of age [17].

Obesity

A different study on SARS-CoV-2 infected patients showed that obesity was strongly associated with negative outcomes [18-21]. Higher in-hospital mortality and the need for mechanical ventilation were documented even in younger patients (18–45 years) with obesity [18]. Simonnet et al. [19] reported that 90% of obese patients (BMI $\geq$ 35 kg/m^2) in the intensive care unit needed mechanical ventilation and that obesity was a strong risk factor for a bad outcome in patients with COVID-19. Earlier studies also support the fact that obesity is a risk factor for more severe clinical outcomes in viral diseases. Such was the case with the study conducted during the 2009 H1N1 pandemic [20]. Furthermore, an Italian study [21] discovered that obese patients required more time to recover from SARS-CoV-2 shedding. Obese people with COVID-19 have higher C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) levels.

Sarcopenia

Sarcopenia occurs during COVID-19, also more often in elderly patients, affecting hospital prognosis and post-COVID-19 recovery. The degree of muscle mass loss and muscle function impairment is influenced by the health status before the infection, the degree of inflammation, anorexia, diminished food intake, lack of physical activity, cardiovascular status, intestinal microbiota [22], and medications such as steroids [23]. A study in the Netherlands found a prevalence of malnutrition in 35% of patients with COVID-19 after hospital admission [24]. About 20% of those hospitalized patients showed an acute weight loss of more than 5 kg. About 73% of all patients were at high risk of sarcopenia. Malnutrition is a proven predictor of sarcopenia [24–26].

Fatigue syndrome

Fatigue is a common symptom in post-COVID-19 patients. An Italian study [5], in which 143 patients (mean age 56.5) were monitored about 60 days after the appearance of the first COVID-19 symptom, showed the frequency of fatigue in 53.1% of respondents. Many other studies have shown a high prevalence of chronic fatigue after acute COVID-19 [27–29]. Fatigue occurs as a "physical" symptom, such as loss of energy and feeling powerless, and a "mental" symptom known as "brain fog". On the other hand, low physical or mental activity prolongs and worsens fatigue and other symptoms [29, 30]. The fatigue significantly affects the ability to perform daily activities and further complicates recovery after the acute phase of COVID-19 [30]. Fatigue that lasts for six months or more is called chronic fatigue [31].

Gut microbiota impairment

The gut microbiota has a number of functions that affect human health. Intestinal bacteria play a role in the digestion and metabolism of fatty acids, producing short-chain fatty acids, vitamins, and amino acids [32, 33]. In addition to the above, their role in the immune response is well recognized. Intestinal bacteria prevent colonization by pathogenic bacteria by maintaining the integrity of the intestinal barrier and producing antimicrobial proteins and lactic acid, which negatively affect the growth of pathogens [32–34]. Intestinal microbiota affects the function of immune cells, development of dendritic cells and T cells, synthesis of the cytokine interleukin (IL)-10, and has an impact on the inflammatory response [14, 35, 36]. Studies in mice have shown that disturbances in the intestinal microbiota lead to impaired immune response and exacerbation of respiratory infections, whether bacterial or viral [37, 38]. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor located in the alveolar epithelial cells and thus enters the cell and causes lung inflammation [14]. ACE2s are also expressed on enterocytes, which indicates a link between gut microbiota and the immune response to SARS-CoV-2 infection [14, 39].

Due to the proven role of intestinal microbiota in immune function, many studies have investigated the effect of different probiotics on immune response and infection in humans [34, 40].

The role of micronutrients and the consequences of their deficiency

Vitamins and trace elements and their role as immunomodulators were the subject of great interest during the COVID-19 pandemic. Vitamin D has multiple roles in the immune response, modulating the production of proinflammatory and anti-inflammatory cytokines and inducing antimicrobial peptides at mucosal surfaces [41–43]. A deficiency in vitamin D is linked to a higher risk for infection of the respiratory tract [43]. Vitamin D prevents excessive inflammatory responses in the lungs and strengthens innate defense mechanisms against respiratory pathogens [44]. A pilot study [45] in hospitalized patients with COVID-19 found micronutrient deficits, primarily vitamin D deficiency, in 76% of patients and selenium deficiency in 42% of those examined. Vitamin A plays a role in the proliferation and differentiation of regulatory T cells and participates in the regulation of some inflammatory mediators [36].

Vitamin C has antioxidant, anti-inflammatory, and immunomodulatory effects; this makes it desirable in the treatment of post-COVID-19 [46]. It is considered that vitamin C strengthens the immune system in various ways, for instance,

by increasing the activity of immune cells as well as other immune agents [47]. It was found that the elderly, diabetics, hypertensives, and patients with chronic obstructive pulmonary disease, who have a higher risk of severe COVID-19 infection, also have lower levels of vitamin C in their blood [46].

It has been shown that vitamin B_9 and other vitamins of the B group normalize homocysteine concentrations in the blood and thus play a protective role in patients suffering from COVID-19 [48, 49]. Zinc plays an important role in the innate and adaptive immune system and the production of inflammatory mediators. Zinc also has an antioxidant effect, and studies have shown that it can prevent the multiplication of viruses [50, 51]; on the other hand, zinc deficiency is associated with a higher risk of complications from COVID-19, hospitalization, and a severe clinical outcome of the disease [52]. Zinc inhibits coronavirus and arterivirus RNA polymerase activity *in vitro*, and zinc ionophores block the replication of these viruses in cell culture [53]. Because of their greater susceptibility to infections due to micronutrient deficiency, these patients can be expected to suffer from more severe and long-lasting forms of the disease.

The role of omega-3 fatty acids is well known, and it includes reducing the risk of cardiovascular diseases and blood clots, maintaining the normal function of the blood vessel wall, lowering the level of triglycerides, and slowing down the production of inflammatory mediators. In recovery from COVID-19, omega-3 fatty acids help reduce excessive inflammation [54].

Nutrition intervention for post-COVID-19

The goal of nutritional therapy in post-COVID-19 patients should be to provide an adequate intake of energy, macro and micronutrients, focusing on correcting nutritional deficiencies, as well as enabling full physical and mental health recovery. Many COVID-19 symptoms and conditions, including post-COVID-19, can result in eating disorders and changes in nutritional status. These symptoms and conditions include the following: smell and taste impairment, loss of appetite, difficulty swallowing, nausea, diarrhea, vomiting, fatigue, and isolation during the infection that limits movement and physical activity, which often leads to anxiety and depression [4, 8, 9, 19, 54]. Research in Poland showed that, during the lockdown, about three-fourths of respondents consumed meat and vegetables once a day, and almost half avoided going shopping [55]. Some studies reported more frequent consumption of unhealthy foods [56]. There was a trend toward increased intake of canned food, flour-made food, and rice [22].

The Chinese authors suggest that the nutritional status of each infected patient should be assessed before starting general treatment [48]. The first step in nutritional management for COVID-19 patients is to identify those at risk of malnutrition, particularly those with comorbidity and older adults, who are thought to be at high risk of poor outcomes [57, 58]. According to the Academy of Nutrition and Dietetics, nutritional screening in long COVID patients includes nutritional history, anthropometric measurements, biochemical parameters, physical examination, and personal and family history. In addition to the basic anthropometric parameters of height, weight, and body mass index, it is necessary to obtain information about body composition (fat mass and fat-free mass) [1, 58]. Anamnestic data should include information on dysphagia, changes in taste and smell, fatigue, and muscle weakness [1]. In patients diagnosed with malnutrition, it is necessary to improve their nutritional status [58].

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines provide recommendations for an energy intake of 27 kcal/kg/day for patients with polymorbidity over 65 years of age and 30 kcal/kg/day for severely malnourished patients with polymorbidity as well as for elderly patients, individually adapted, depending on their nutritional status, physical activity, and disease state [58–60]. Patients who are malnourished may be advised to eat several smaller meals during the day, not to drink liquids during meals, and, if necessary, to take low-volume nutritional supplements to increase energy intake [1, 58]. In obese patients with post-COVID-19, weight reduction is recommended to reduce the risk of obesity-related complications [1].

Recommendations for protein intake are 1 g/kg/day in the elderly, also adapted to nutritional status, physical activity, and disease status, and > 1 g/kg/day in polymorbid inpatients to improve recovery and prevent weight loss [58–60]. In post-COVID-19 patients, protein intake should be higher to prevent loss of muscle mass or improve symptoms of sarcopenia. High-quality protein from animal and plant sources is recommended to provide all the essential amino acids important for the anti-inflammatory response and immunomodulation [1, 61]. Nutritional therapy for restoring muscle mass and improving muscle strength is an important aspect of treatment for patients with post-COVID-19 syndrome. Data from a systematic review and meta-analysis indicate the possibility of using protein supplementation with resistance training in order to restore muscle mass and strength in post-COVID-19 elderly people who have sarcopenia. The use of the amino acid leucine in a balanced diet or as a supplement for muscle restoration in post-COVID-19 patients has shown effectiveness [61, 62].

Fat and carbohydrate intake are recommended according to energy intake in the ratio of 30 : 70 to 50 : 50 in ventilated patients [60]. Adequate intake of omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid can interfere with viral replication and help reduce prostaglandin production as well. On the other hand, lipids (phospholipids, glycolipids, and sphingolipids) can block the activation of platelets, which can prevent thrombotic complications in patients with COVID-19 [61, 63].

The consumption of carbohydrates with a high glycemic index can lead to the synthesis of free radicals and an increase in the level of inflammatory cytokines, which is a characteristic of respiratory infections. Because of all of the above, giving priority to the intake of carbohydrates with a lower glycemic index is recommended [61, 64]. Fiber consumption has been shown to have numerous health benefits. A recommended fiber intake of 25–35 g/day helps reduce systemic and intestinal inflammation. Consuming fiber-rich foods lowers the levels of inflammatory mediators (CRP,

Table 1

Summary table of symptoms and conditions in post-COVID-19 related to nutrition and recommended nutritional intervention

Post-COVID-19 conditions closely related to nutrition	Nutritional interventions
Malnutrition	Adequate intake of energy and macro and micronutrients. Energy intake of 27 kcal/kg/day for patients with polymorbidity over 65 years of age; 30 kcal/kg/day for severely malnourished patients with polymorbidity and elderly patients, individually adapted, depending on their nutritional status, physical activity, and disease state. Protein intake of 1 g/kg/day in the elderly, adapted to nutritional status, physical activity, and disease status, and > 1 g/kg/day in polymorbid inpatients to improve recovery and prevent weight loss. Protein intake should be higher to prevent loss of muscle mass or improve symptoms of sarcopenia. Fat and carbohydrate intake are recommended according to energy intake in the ratio of 30 : 70. Intake of carbohydrates with a lower glycemic index. Fiber intake of 25–35 g/day.
Undernutrition	Advice to eat several smaller meals during the day, not to drink liquids during meals, and, if necessary, to take low-volume nutritional supplements to increase energy intake.
Obesity	Weight reduction is recommended.
Sarcopenia	Protein supplementation with resistance training in order to restore muscle mass and strength in post-COVID-19 elderly people who have sarcopenia. The use of the amino acid leucine in a balanced diet or as a supplement for muscle restoration in post-COVID-19 patients has shown effectiveness.
Fatigue syndrome	Taking antioxidants and essential fatty acids as supplements or in a balanced diet.
Inflammation, impaired immune response	Mediterranean diet: rich in fiber, bioactive compounds such as omega-3 fatty acids, antioxidants, whole grains, fruits, vegetables, virgin olive oil, high-quality proteins from eggs, dairy products, and fish; low in meat, saturated fatty acids, and refined carbohydrates. Plant-based dietary patterns.
Gut microbiota impairment/imbalance of gut microbiota	Intake of probiotics. Probiotics, especially some species of *Lactobacillus* and *Bifidobacteria*, have the potential to modify the microbiota and the immune response, contributing to the protection and improved outcomes of airway viral infection.
Micronutrient deficiency	Supplements of vitamins and minerals are recommended for those with micronutrient deficiency who cannot get enough micronutrients from food. Adequate intake of vitamins D, A, B6, B12, and C, and minerals zinc, selenium, and iron must be provided for better clinical outcomes of infection.

TNF-α, and IL-6) while increasing the levels of short-chain fatty acids [54, 61].

Special attention should be paid to adequate intake of vitamins D, A, B_6, B_{12}, and C and minerals zinc, selenium, and iron, as well as omega-3 fatty acids [48, 58] for better clinical outcomes in viral infection, including COVID-19. Antioxidants and essential fatty acids as supplements or in a balanced diet can help mitigate chronic fatigue syndrome in post-COVID-19 cases. Supplements are recommended for malnourished patients or those with nutritional deficits who cannot get enough macro and micronutrients from food [1].

Positive changes in the intestinal microflora can be supported by the intake of polyphenols and probiotics [1, 65]. Although probiotics are mostly mentioned because of their

beneficial effect on immunity during viral intestinal infections, they also play an important role in the immune response when it comes to upper and lower respiratory tract infections and sepsis. In patients suffering from COVID-19, probiotics help restore the altered intestinal flora. By having a favorable effect on the body's immune response, they also help protect against severe complications of COVID-19, such as acute respiratory distress syndrome and multiorgan dysfunction syndrome. Studies have shown the clinical benefits of using *Lactobacillus* and *Bifidobacterium* in patients on mechanical ventilation in intensive care, showing a lower incidence of upper respiratory tract infections and respiratory-related pneumonia [66].

Adequate hydration should be met in patients with COVID-19 as well as those with post-COVID-19 syndrome. The Dietary Reference Intake for water of 2.7 L/day in adult women and 3.7 L/day in men, respectively [67], may be increased, depending on the patient's condition. It is necessary to keep track of the patient's hydration level.

There is increasing evidence suggesting that diet can affect inflammation and the immune system. Studies conducted in different populations [68–70] have shown a link between the Mediterranean diet and a lower risk of COVID-19 as well as better outcomes in patients with COVID-19. Mediterranean diet (rich in fiber, bioactive compounds such as omega-3 fatty acids, antioxidants, whole grains, fruits, vegetables, virgin olive oil, high-quality proteins from eggs, dairy products, and fish, and low in meat, saturated fatty acids, and refined carbohydrates) can be recommended for patients with COVID-19, including those with post-COVID-19 syndrome [1, 71].

Considering that psychological well-being is often impaired in post-COVID-19, including the appearance of anxiety, depression, and impaired cognitive functions, a diet rich in fruits and vegetables has its advantages. Specifically, studies have shown that an increased intake of fruits and vegetables in the diet reduces the risk of depression [72, 73]. A case-control population-based study that investigated the relationship between COVID-19 and diet determined a 73% lower risk for a moderate to severe form of the disease in subjects with a plant-based diet compared to those with other diet patterns [74]. It should be kept in mind that the study was conducted on a small sample, and the dietary survey was based on self-reporting. Studies conducted before the COVID-19 pandemic have shown that a plant-based diet can be beneficial for some conditions that can occur in COVID-19 patients, including fatigue, muscle pain, depression, and headaches [75–76]. Plant-based dietary patterns reduce inflammatory biomarkers and positively affect immune status [77]. Table 1 shows the summary of symptoms and conditions in post-COVID-19 related to nutrition and recommended nutritional intervention.

Conclusion

Nutritional recommendations for patients during recovery from COVID-19 will depend on the patient's condition, disease-related symptoms, and comorbidities and require an individual approach. In this sense, it is necessary to increase awareness of the importance of nutrition and make access to healthy food one of the priorities, especially for members of sensitive groups, such as the elderly, people with comorbidities, etc., in order to reduce the prolonged effects of COVID-19. Information on dietary recommendations for post-COVID-19 patients available in the literature is often obtained from studies related to the treatment of conditions similar to the post-COVID-19 syndrome.

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