Biljana Damnjanović[1], Đuro Šijan[4], Ivan Rović[4], Igor Lazić[2], Saša Knežević[2], Jovana Stanisavljević[1,4], Marija Dukić[3], Jelena Vrućinić Kozić[1], Marija Milenković [1,4]

NUTRITIONAL THERAPY OF COVID-19 DISEASE IN INTENSIVE CARE UNITS

Abstract: Since the beginning of 2020, SARS-CoV 2 (Severe Acute Respiratory Syndrome - Corona Virus 2) has been in the focus of scientific circles and beyond. Finding the most efficient therapeutic protocol in prevention and treatment of the new and unknown COVID – 19 (Corona Virus Disease - 2019) disease has been indentified as especially important. SARS-CoV 2 uses various mechanisms to lead patients to malnutrition, which is detected by a higher frequency of admission to hospital treatment, especially on admission to the Intensive Care Unit (ICU). Malnutrition has a negative impact on the course and outcome of the disease. In the pandemic, the number of patients on various types of oxygen therapy and mechanical ventilation increased, and in correlation with that, there has been a greater need for knowledge and education of staff to use different diagnostic and therapeutic modalities and different

[1] Biljana Damnjanović, Emergency center, University Clinical Center of Serbia, Belgrade, damnjangor@gmail.com

Jovana Stanisavljević, Emergency center, University Clinical Center of Serbia, Belgrade, jovanaavramovic@yahoo.com

Jelena Vrućinić Kozić, Emergency center, University Clinical Center of Serbia, Belgrade, jelenavk@yahoo.com

Marija Milenković, Emergency center, University Clinical Center of Serbia, Belgrade, smgk055@gmail.com

[2] Igor Lazić, Neurosurgery Clinic, Clinical Center of Serbia, Belgrade, drsasaknezevic@gmail.com, igorlazic82@yahoo.com

Saša Knežević, Neurosurgery Clinic, Clinical Center of Serbia, Belgrade, drsasaknezevic@gmail.com

[3] Marija Dukić, University Hospital Medical Center Bezanijska kosa, Belgrade, Serbia, mdukic107@gmail.com

[4] Đuro Šijan, Faculty of Medicine, University of Belgrade, Serbia, djuro122@gmail.com

Ivan Rović, Faculty of Medicine, University of Belgrade, Serbia, ivan.rovic.96@gmail.com

Jovana Stanisavljević, Faculty of Medicine, University of Belgrade, Serbia, jovanaavramovic@yahoo.com

Marija Milenković, Faculty of Medicine, University of Belgrade, Serbia, smgk055@gmail.com

approaches in feeding critically ill patients. Nutritional therapy is the basis for maintaining body weight, supporting respiratory function, as well as helping in the overall recovery of patients. Omega 3 fatty acids, vitamins C and D have shown potentially beneficial effects against COVID-19 diseases.

The aim of this paper is to consolidate the current knowledge and recommendations in the field of nutritional therapy in patients with COVID - 19 treated in the Intensive Care Unit.

Key words: *COVID-19*; Intensive care unit; Malnutrition; Nutritional therapy

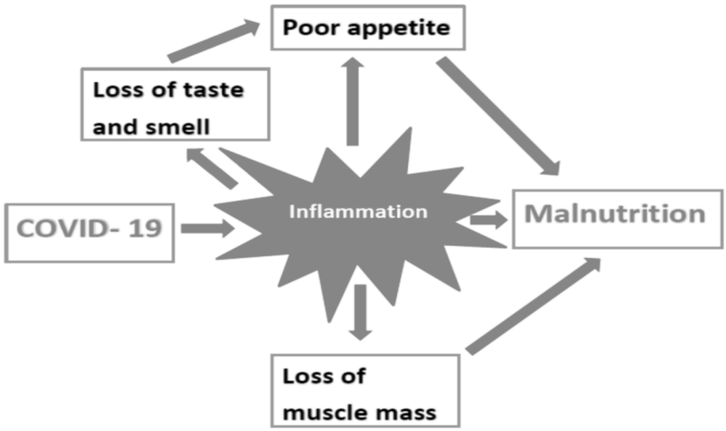
Introduction

Since the beginning of 2020, SARS – CoV – 2 (Severe Acute Respiratory Syndrome - Corona Virus 2) has been the main focus of interest in scientific circles and beyond. Finding the most efficient therapeutic protocol in prevention and treatment of the new and unknown COVID – 19 (Corona Virus Disease - 2019) disease has been indentified as especially important. The basic principles of treatment are the use of antiviral drugs, biological therapy, corticosteroid therapy, anticoagulant therapy, neutralizing monoclonal antibodies, convalescent plasma, oxygen therapy and other methods of maintaining good blood oxygenation (non-invasive and invasive mechanical ventilation), as well as symptomatic and vitamin therapy [1]. In addition to the listed therapeutic modalities, it is necessary to perform adequate nutritional support of patients, physical treatment, psychological support, etc. on a daily basis.

The aim of this paper is to consolidate the current knowledge and recommendations in the field of nutritional therapy in patients with COVID - 19 treated in the Intensive Care Unit (ICU).

COVID-19 and malnutrition

Upper respiratory tract infections are associated with loss of sense of smell primarily due to mechanical obstruction, inflammation, and neurodegeneration of olfactory cells. SARS - CoV 2 infection leads to altered, partial or complete loss of sense of smell and taste, which affects the patient's appetite, reducing it. This loss of smell in COVID-19 disease is thought to be different from other upper respiratory tract infections, primarily due to a lack of severe inflammation and nasal obstruction. It is thought to be based on the expression of ACE2 and TMPRSS2 receptors on neuroepithelial olfactory cells, allowing virus to enter, accumulate and replicate [2]. Systemic inflammation caused by various mechanisms leads to poorer appetite which together with loss of sense of smell and taste leads to reduced food intake. In addition, acute infectious disease leads to inflammatory syndrome and hypermetabolism and loss of muscle mass. Thus, we can conclude that SARS - CoV 2 leads to a vicious circle that leads to malnutrition in different ways [3].



Picture 1. Malnutrition and COVID-19 [3].

A study conducted in Italy, which included 213 hospitalized patients with COVID-19 disease, showed that 54.7% of patients are at risk of malnutrition, while 6.6% had malnutrition according to the Mini Nutritional Assessment score [4]. Allard et al., in their study of 108 patients, proved that 42 (38.9%) of them were diagnosed with malnutrition on admission to the hospital for the treatment of COVID-19 disease [5]. Later on, a study by Bedock et al., which included 112 patients with SARS-CoV2 virus infection, showed that according to GLIM (Global Leadership Initiative on Malnutrition) criteria, 42% of patients were malnourished, 24% moderately and 18% severely. They also proved that the prevalence of malnutrition is significantly higher in patients treated in ICU [6]. Wierdsma et al., proved in their study that every fifth patient admitted for hospital treatment of COVID-19 has severe acute weight loss (> 5 kg), where 85% of patients with detected acute weight loss are admitted to the ICU, and 73% of patients have a higher risk of sarcopenia [7].

In recent months, numerous studies have led to the following conclusions: there is a high incidence of malnutrition in patients with COVID-19 at hospital admission, a negative impact of malnutrition on the prognosis of COVID-19 was proven, as well as a negative impact of COVID-19 on body weight in both hospitalized and non-hospitalized patients [8].

It should be noted that obesity is also a form of malnutrition. Adipose tissue is a major source of macrophages that secrete inflammatory mediators. Leptin, a hormone that increases appetite and speeds up metabolism, is released from adipose tissue, and is structurally similar to IL-6 and IL-12. Also, in obese people, the production of Th1 cells and B lymphocytes is increased. All of this leads to a state of constant low-grade inflammation, which can be unfavorable for infections, and precipitate an ineffective immune response, i.e. hyperproduction of IL-6 and cytokine storm, damage to lung tissue, etc. It is believed that due to the existence of this constant low-grade inflammation, obesity is a risk factor for a more severe form of the disease as well as death in patients with COVID-19 disease [9].

Nutritional therapy of COVID-19 patients

After admission of patients for hospital treatment, especially in elderly patients, those with comorbidities and obese people, it is necessary to perform screening and potential diagnosis of malnutrition. The diagnosis of malnutrition, according to the criteria of the Global Leadership Initiative on Malnutrition, is made through two steps. In the first step, it is necessary to screen for malnutrition through MUST (Malnutrition Universal Screening Tool) or NRS-2002 (Nutrition Risk Screening) criteria, and in the second step, malnutrition is confirmed by the existence of at least one phenotypic and at least one etiologic criterion [10].

Table 1. *Phenotypic and etiologic criteria for diagnosing malnutrition accord to Global Leadership Initiative on Malnutrition*

Phenotypic criteria	Etiologic criteria
Body weight loss (%) >5% within 6 months > 10% beyond 6 months	**Reduced food intake** 50% of energy need > 1 week, or any reduction for > 2 weeks, or any chronic gastrointestinal disorder that adversely impacts food assimilation or absorption
Low BMI (kg/m^2) <20 (< 70 years) < 22 (>70 years)	**Inflammation** Acute disease/injury/chronic diseases
Reduced muscle mass Reduction verified by validated body composition measuring techniques	

BMI- body mass index

As mentioned above, the incidence of malnutrition is high in patients with COVID-19 and it is assumed that malnutrition itself negatively affects the course and outcome of the disease, and therefore it is necessary to introduce adequate nutrition to patients in order to reduce disease complications and strive for a good treatment outcome.

Every introduction of nutrition starts by determining the individual's energy needs. The best, but also the most complex method of determining energy needs is indirect calorimetry, which is a method of calculating a person's need for energy indirectly by calculating energy consumption at rest. Specifically, the degree of energy consumption is calculated by measuring the consumption of O2 and the amount of CO2 in exhaled air [11]. Today, there is an increased tendency towards indirect calorimetry, considering that other types of calculating energy needs can lead to excessive or insufficient intake of nutrients in relation to needs. Excessive nutrient intake in critically ill patients is associated with hyperglycemia, liver steatosis, as well as increased mortality, longer hospital stays and duration of mechanical ventilation, higher risk of infections, organic failure, etc. However, as indirect caorimetry is an extremely expensive and often inaccessible technique, energy needs can also be calculated by measuring the amount of exhaled CO2 (EEVCO2 - energy expenditure based on CO2 measurements). After reading the amount of CO2 (VCO2), the energy needs of the organism are calculated by the following formula EEVCO2 (kcal / day) = VCO2 (ml / min) x 8.19. This method is inferior to indirect calorimetry, but is superior to using formulas that based on body weight [12].

An alternative, more commonly used method of calculating energy needs are calculations with body weight. The European Association for Clinical Nutrition and Metabolism has recommended that the energy intake of critically ill patients should be 25 kcal/kg/day, with the gradual introduction of a full diet within the first 3 days. Also, the protein intake is recommended to be 1.3g/kg/day and the ratio of fats and carbohydrates in the diet is recommended to be 30:70 in patients without respiratory insufficiency and 50:50 in patients who are on some kind of mechanical ventilation. It should be noted that in obese people, energy and protein needs are calculated through ideal body weight [10].

Patients in whom per os diet cannot provide energy and micro- and macronutrient needs, especially in the elderly and polymorbid individuals, it is necessary to introduce oral nutritional supplements. Oral nutritional supplements in patients at risk or recorded malnutrition should provide at least 400 kcal/day and at least 30g of protein [13]. In case that oral nutrition is impossible, enteral nutrition is the second choice of nutritional support, while parenteral nutrition is the last choice of nutritional support when the previous two types are not feasible [10].

Nutritional therapy in Intensive Care Unit

The years of COVID-19 pandemic brought an extraordinary increase in the number of patients who required treatment in the ICU. In the pandemic, the number of patients on various types of oxygen therapy and mechanical ventilation increased, and in correlation with that, there has been a greater need for knowledge and education of staff to use different diagnostic and therapeutic modalities and different approaches in feeding critically ill patients.

As mentioned beforehand, there is a high incidence of patients with malnutrition, especially in ICUs. However, it is estimated that only half of malnourished patients are detected in clinical practice, while sarcopenia is mostly unrecognized [14,15].

Nutritional therapy of patients on HFNC – high flow nasal canuula

High oxygen flow nasal cannula has been shown as effective in the treatment of acute hypoxemic respiratory failure, acute heart failure and pulmonary edema, post-surgical respiratory failure, as a good form of oxygenation in the preintubation and postintubation period, etc. [16]. It has also shown its effectiveness in patients with COVID-19. The diet of patients on HFNC does not differ from the diet of patients with a different type of oxygen therapy modality (low-flow nasal cannula, O2 mask, ...) or patients without it. There are few studies conserning the diet of patients on HFNC.

Leder et al., examined the impact of oral nutrition in infants and adults and concluded that 78% of adults and 34% of infants treated with HFNC were able to eat. The per os diet was successful in all those who started it, so there was no need to introduce enteral nutrition. The use of HFNC alone should not delay per os diet initiation [17]. The European Society of Intensive Medicine (ESCIM) states in its recommendations that the start of the diet should be within 24-48 hours of admission and that HFNC oxygenation is not a contraindication for adequate energy and protein intake [18].

Nutritional therapy of patients on non-invasive mechanical ventilation

Non-invasive mechanical ventilation (NIV), in addition to its use in respiratory failure, chronic obstructive pulmonary disease, cardiogenic pulmonary edema and other conditions, has been shown as effective in the treatment of SARS-CoV 2-induced lung damage. The official ESPEN recommendations for the nutrition of patients with COVID-19 are based on the fact that the nutrition of patients on NIV should be per os, if it is not possible then enteral nutrition should be introduced, and parenteral nutrition should be usad as a last resort.

People who are on NIV can rarely be fed orally. A study conducted in Japan showed that 107 out of 150 people admitted to the ICU due to acute respiratory distress were unable to ingest food per os, which represents more than 70% of hospitalized patients in the ICU. Also, patients who were on NIV and enterally fed had significantly more frequent complications such as vomiting and aspiration pneumonia, while intrahospital mortality did not differ between enterally fed patients and control groups [19]. However, another study involving 1,075 patients admitted to the ICU showed that the incidence of later need for invasive mechanical ventilation and death was twice as high in patients who were fed enterally [20].

Therefore, the approach of enteral feeding patients with NIV has certain side effects, so it is necessary to apply the postulates of modern medicine and individualize the therapy as much as possible, as well as prevent, recognize and treat side effects in time.

Nutritional therapy of patients on invasive mechanical ventilation

The diet of patients on mechanical ventilation with COVID-19 disease does not differ much from the diet of patients with other conditions that require invasive mechanical ventilation. According to ESPEN recommendations, all patients who are likely to stay in the ICU for more than 48 hours should start the diet [21].

Enteral feeding is the first choice of diet. Parenteral nutrition should be started only after using all the possibilities of enteral nutrition, or due to contraindications for the use of enteral nutrition (intestinal insufficiency, severe intestinal inflammation, intestinal obstruction, inability to place a feeding tube, etc.). Enteral nutrition should be started by the nasogastric route. Due to the existence of gastric intolerance (large gastric residual volume) resistant to the use of prokinetics (erythromycin, metoclopramide) in patients who feed by the nasogastric route, it is necessary to switch to a postpyloric diet. In critically ill patients in the ICU, a hypocaloric diet is started with a successive increase in energy intake in the first 3 days, and from the 4th day a full diet is introduced, ie. 25 kcal/kg/day and 1.3 g protein/kg/day. Enteral nutrition should not be initiated in hemodynamically unstable patients as well as in patients with life-threatening hypoxia, hypercapnia, and acidosis [10,21,22].

Parenteral nutrition showed an advantage over enteral nutrition in patients who were on mechanical ventilation and vasopressor therapy (due to the regulation of shock). Mortality within 28 and 90 days, length of hospitalization, time spent on mechanical ventilation, vasopressor therapy, and need for dialysis did not differ between subjects who were fed enterally and parenterally. People fed enterally had significantly greater complications connected with the gastrointestinal tract, such as diarrhea, intestinal ischemia, acute pseudoobstruction of the colon [23].

Prone position as an adjuvant therapy has found a place in the COVID-19 pandemic. Switching patients to a prone position may be effective in reducing mortality in patients with ARDS [Acute Respiratory Distress Syndrome] if performed adequately and in a timely manner [24].

The question is whether the transfer of patients to the prone position can adversely affect enteral nutrition by increasing the gastric residual volume, vomiting, aspiration, and even the incidence of aspiration pneumonia. It is considered that the enteral nutrition of patients who move to the prone position is not associated with higher intolerances and complications [25].

Immunonutrition

Over the years, research has been conducted in the direction of examining nutrients, more precisely their effect on the patient's immune response. The amino acids arginine, glutamine, nucleotides, omega-3 fatty acids (DHA - docosahexaenoic acid, EPA - eicosapentaenoic acid), etc. were tested. Higher intake of DHA and EPA, as well as their higher concentration in the blood, is associated with a lower number of inflammatory cytokines. Also, omega-3 fatty acids increase the activity of cells of the innate and acquired immune system [26,27].

It is believed that omega-3 fatty acids can affect the course and outcome of COVID-19 disease by various mechanisms. Omega-3 fatty acids reduce the secretion of proinflammatory cytokines IL-1β, IL-6, TNF-α and thus reduce the risk of cytokine storm. On the other hand, EPA and DHA show an antiviral effect, primarily by enhancing the phagocytic activity of cells of the innate immune system - neutrophils and macrophages. In addition, omega 3 fatty acids potentially increase IFN, which has an inhibitory effect on viral replication [28]. Omega 3 fatty acids can also lead to inhibition of the COX enzyme (cyclooxygenase) and prostaglandin synthesis, which are also proinflammatory in nature [29].

Formulas for parenteral nutrition enriched with omega 3 fatty acids have shown a significant advantage over formulas that are not enriched with DHA and EPA. A significantly lower risk of infection by 40% and sepsis by 56% during hospitalization was observed in patients receiving parenteral preparations enriched with omega-3 fatty acids. Also, these people were hospitalized on average 2 days less, and had approximately 2 days shorter stay in the ICU [30].

Vitamins C and D vs. COVID-19

With the onset of the pandemic and the daily growth in number of patients, the use of supplements has significantly increased, primarily with the aim of preventing or reducing the symptoms of COVID-19 disease. The question that was immediately asked was whether they can really do that. The use of vitamins C and Zn for 3 months, 3 times a week is not associated with a lower risk of infection, however, the use of vitamin D reduces the risk of infection with SARS-CoV 2 virus by 9% [31]. In addition, lower levels of vitamin D in the blood are associated with a higher risk of developing more severe forms of COVID-19 disease [32]. The beneficial effect of vitamin D in COVID-19 is thought to lie in increased ACE2 expression and regulation of the immune system by various mechanisms. In addition to being a receptor for the entry of SARS-CoV2 virus into the cell, ACE2 plays an important role in preventing the occurrence of complications of respiratory infections. Also, vitamin D could potentially lead to reduced virus replication [33].

Starting with previous knowledge about vitamin C, its important role in innate and acquired immunity, its role as an antioxidant, in maintaining epithelial integrity, improving the differentiation and proliferation of B and T cells as well as in reducing the severity and duration of common colds, it has also found its role in the treatment of COVID-19. In the national protocol for the treatment of patients with COVID-19 disease, in addition to the use of vitamin D, the use of vitamin C is also recommended. Vitamin C has been shown to have a beneficial effect in the early stages of sepsis and ARDS by reducing 28-day mortality [34]. This is supported by a study that examined the effects of vitamin C use in COVID-19 patients treated in ICU. Significantly lower mortality was observed in patients receiving vitamin C [35].

Regardless of the positive effects of previous studies, the extent to which the use of vitamins D and C can potentially be beneficial, one should be careful when using them. Excessive intake of vitamin C can lead to nausea, diarrhea, abdominal cramps, oxalate nephropathy, while the use of vitamin D in high doses can cause vomiting, abdominal pain, loss of appetite, cardiac arrhythmias, kidney damage anywhere from calculus formation to renal failure [36, 37].

Refeeding syndrome

Refeeding syndrome is extremely significant, but often neglected in everyday clinical practice. It occurs due to the initiation of diet in patients with malnutrition or patients who are in starvation. It is primarily characterized by a potentially fatal disbalance of body fluids and electrolytes (hypophosphatemia, hypokalemia, hypomagnesaemia) [38].

The population at risk of developing refeeding syndrome are firstly critically ill patients, then people with psychiatric illnesses, people with malignancy, malabsorption, alcohol and psychoactive substances abuse etc. Uncharacteristic symptoms do not allow us to easily suspect of refeeding syndrome, so the basic diagnostic principles are reflected in checking the electrolyte status of the patient. The most common symptoms and signs of refeeding syndrome are heart rhythm disorders (tachycardia), rapid breathing and edema, but blood pressure disorders, cardiac arrest, pulmonary edema, respiratory arrest, mental status disorders, platelet dysfunction, abdominal pain, diarrhea, constipation, etc. can be found as well. The treatment of refeeding syndrome is replacement of electrolytes and micronutrients, as well as in the reduction of caloric intake in the presence of clinical manifestations [39,40].

Conclusion

In everyday clinical practice, physicians must keep in mind that adequate nutritional support for patients with COVID-19, especially those in intensive care units, is key to maintaining body weight and supporting respiratory function, but also has a significant contribution to the overall recovery of patients.

Conflict of interest: none declared.

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