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MINI REVIEW

Immunonutrition as a potential strategy to prevent and cope with coronavirus disease (COVID-19)

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Abstract

In this article, a brief review of immunonutrition as a feasible alternative to modulating the immune system in defence of the SARS-CoV-2 that causes COVID-19 was presented. Immunonutrition is the nutritional practice that includes the necessary nutrients to modulate the activity of the immune system in health and disease. To date, studies are encouraging because they indicate that a good diet restores or improves the immune system's response to pathogens such as SARS-CoV-2. In addition, applying immunonutrition helps people recover with fewer sequelae after going through a serious infection in hospitalization and/or intensive care unit. Finally, it is suggested that immunonutrition be applied in conjunction with other good lifestyles and strictly following current health recommendations.

1. Introduction

In March 2020, the world declared a new pandemic caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) (ISID, 2021). This virus causes the coronavirus disease or COVID-19 and as is well known, the virus infects people of any age, being more susceptible to people suffering from comorbidities such as obesity, diabetes and hypertension. These comorbidities are related in one way or another to diet. The immune system, being very present in our tissues, and maintaining homeostasis, in some way also participates in the development of these comorbidities (Calder, 2020). But what is the scientific basis for the relationship between COVID-19, diet and the immune system?

Nutrition is a crucial component in our well-being since each of our cells receives nutrients that come from our daily diet. The cells of the immune system are dependent on nutrients for their proper functioning and when a poor diet is observed these cells are damaged, dramatically affecting homeostasis at the systemic level and if eventually, one is infected with a virus, such as SARS-CoV-2, the immune system will not generate an efficient response (Calder, 2020; Derbyshire and Delange, 2020). Taking this into account, the question arises, what do we need to do to have an efficient immune system?

A feasible answer could be immunonutrition, which defines itself as the nutritional practice that helps us to be able to incorporate the set of necessary nutrients that will contribute to modulating the activity of the immune system (Derbyshire and Delange, 2020).

Scientific evidence indicates that immunonutrition is proactively involved before, during and after COVID-19 infection (Kamyari *et al*., 2021). The prognosis of the patient depends on how the patient's immune system responds to the presence of the virus. Failures in the response of the immune system will generate the tissues and organs of the infected patient to not resist the inflammatory catastrophe characterized by the cytokine storm and likewise the proliferation of the virus (Derbyshire and Delange, 2020; de Araújo Morais *et al*., 2021).

This mini-review discussed the fundamentals and importance of immunonutrition as a strategy to deal with COVID-19. In addition, the emphasis on the importance of integrating other approaches and lifestyles to ensure that the patient has fewer sequelae from a serious infection by this severe virus.

2. The immune system and COVID-19

SARS-CoV-2 enters the airways and once it reaches the lungs, it infects the alveolar epithelial cells. Infection

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occurs by the virus binding to the ACE2 receptor (angiotensin-converting enzyme 2) (Bold *et al*., 2020). The entry of the virus into cells triggers an immune response called inflammation in which a wide spectrum of cells are recruited, such as dendritic cells, macrophages and neutrophils (Zabetakis *et al*., 2020). The infection can go unnoticed in asymptomatic cases. However, the disease can evolve and severely compromise other tissues due to uncontrolled inflammation leading to shortness of breath, septic shock, and heart problems (Fernández-Quintela *et al*., 2020).

A patient with COVID-19 presents two main events: a) oxidative stress: The cells of the lungs release free radicals that are harmful to the tissues and can spread to other parts of the body (Calder, 2020); and b) severe inflammation: It occurs because the immune system releases an excessive amount of inflammatory cytokines; a process called "cytokine storm" (Calder, 2020). Both scenarios cause severe tissue damage to the COVID-19 patient, mainly lung tissue, causing "acute respiratory distress syndrome" (ARDS). Therefore, the more oxidative stress and inflammation, the greater the risk that the patient will die (Calder, 2020).

There are different treatments for this disease are their effectiveness depends on many factors, where the health status prior to the virus infection is crucial. The previous health status depends on genetic and environmental factors. Among the environmental factors that contribute to an adequate immune response we have: good nutrition, healthy environments, absence of stress, good quality of sleep, not smoking, and not consuming alcohol or drugs (Kalantar-Zadeh and Moore, 2020). For the purposes of this review, good nutrition practised through immunonutrition will be the main focus.

3. Immunonutrition-immune system-COVID-19

While different pharmacological treatments are being tested, the question arises in the community of nutritionists and dietitians whether certain foods or nutritional regimens can prevent SARS-CoV-2 infection or reduce its aggressiveness (Kalantar-Zadeh and Moore, 2020; Laviano *et al*., 2020; Derbyshire and Delange, 2020). This is based on the fact that the nutritional status of the person is crucial to coping with viral infections. Malnutrition impairs the immune system, increasing the risk of viral infection and disease severity (Silverio *et al*., 2020).

There is scientific evidence that indicates that immunity against COVID-19 is improved by incorporating the following nutrients mainly in the diet: vitamin D, vitamin C, vitamin B, vitamin A, polyunsaturated fatty acids (omega-3), zinc and magnesium (Fernández-Quintela *et al*., 2020). In this context, the term immunonutrition has been proposed, which consists of the consumption or administration of specific nutrients in order to modulate the function of the immune system (Derbyshire and Delange, 2020) (Figure 1).

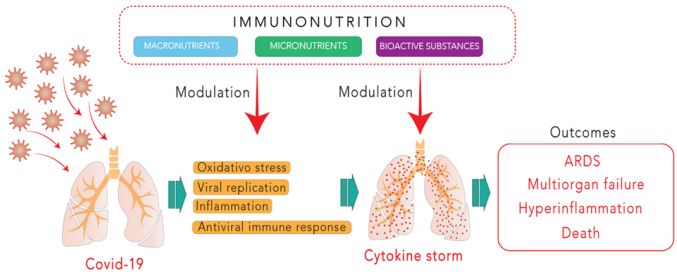

Figure 1. Immunonutrition in coronavirus disease (COVID-19)

Studies show that a healthy diet has a rapid anti-inflammatory effect even in people suffering from obesity (Butler and Barrientos, 2020). A widely recommended diet is the Mediterranean diet, whose effects are systemic, preventing and helping to cope with infectious diseases such as COVID-19 (Angelidi *et al*., 2021). The Mediterranean diet is very diverse because it includes polyunsaturated fats, dietary fibre, proteins, carbohydrates, polyphenols, and other bioactive substances. The wide repertoire of nutrients in the Mediterranean diet ensures the synergism of nutrients with anti-inflammatory, immunomodulatory and antioxidant activity (Zabetakis *et al*., 2020; Angelidi *et al*., 2021).

Next, the scientific evidence of certain nutrients that could potentially modulate the immune response against viruses such as SARS-CoV-2 will be discussed.

3.1 Proteins

Protein deficiency has been associated with impaired immune system activity primarily through altered levels of antibodies or immunoglobulins and impaired gut-associated lymphoid tissue. In this context, it is emphasized that the consumption of proteins of high biological value (eggs, meat, fish and dairy products) is highly relevant for the immune system because it exerts an anti-inflammatory effect. Specifically, some researchers propose that arginine and glutamine are amino acids with good immunomodulatory activity (Iddir *et al*., 2020).

3.2 Vitamin C

It has been widely reported that this micronutrient is crucial for a good immune response. It can be acquired through the consumption of fruits, mainly citrus fruits

(Aman and Masood, 2020). Vitamin C is well known to be a coenzyme of multiple enzymes in the metabolism of all tissues in the body. In particular, the cells of the immune system prioritize using this vitamin because it strengthens them and prepares them for their fight with germs such as viruses, bacteria, fungi and more. This vitamin is said to work against COVID-19 due to its antioxidant and anti-inflammatory activity (Gasmi *et al*., 2020; Derbyshire and Delange, 2020). Vitamin C would be participating in the following phases: a) before infection: enhancing the immune response. That is, "training" our immune cells that would go to the battlefield to face the virus; b) during infection: Vitamin C contributes to the production of the biological arsenal of the immune system to be able to neutralize the infection.

Likewise, this vitamin participates in ameliorating excessive inflammation so as not to cause collateral damage to the tissues. Supplementation with vitamin C in addition to other standard treatments has shown beneficial effects. In critical patients, the intravenous injection of high doses of vitamin C has been tested, however, these studies are not conclusive yet (Zhang *et al*., 2021). Currently, there are clinical trials underway to elucidate whether the use of high doses of vitamin C intravenously could be beneficial in critically ill patients (Carr *et al*., 2021); and c) after infection: In patients who have been cured of severe infection, vitamin C helps tissues to regenerate easily. This is based on the fact that vitamin C is crucial for the synthesis of collagen, a protein that is important for the integrity of tissues.

3.3 Vitamin D

This fat-soluble vitamin is another nutrient with a solid reputation as an immunomodulator (Gasmi *et al*., 2020; Untersmayr and Kallay, 2020). It is obtained from three main sources, exposure to sunlight, the consumption of foods rich in vitamin D and supplementation. In either case, the inactive vitamin D reaches the liver and is converted into 25-hydroxyvitamin D, then passes to the kidney, transforming into an active form 1,25-dihydroxyvitamin D or calcitriol. Immune cells can utilize vitamin D due to the presence of vitamin D receptors. Additionally, some cells of innate and adaptive immunity can take 25-hydroxyvitamin and independently convert them to the active form (Calder, 2020; Untersmayr and Kallay, 2020). There are currently millions of people with vitamin D deficiency, particularly in areas with little sunlight (Bold *et al*., 2020). Pereira *et al*. (2020) reported that vitamin D deficiency is positively associated with COVID-19 severity. Based on this, measures should be taken at the public policy level so that the population maintains adequate levels of vitamin D in the blood and thus prevent complications from COVID-19 in countries most affected by this disease (Yisak *et al*., 2021); this can be achieved through diet or supplementation (Gasmi *et al*., 2020).

3.4 Zinc

It is another essential nutrient that is required in trace amounts and, like other micronutrients, contributes to the function of many enzymes and transcription factors involved in the function of the immune system (Chasapis *et al*., 2020; Derbyshire and Delange, 2020). Zinc has direct or indirect activity on certain types of viruses. For example, pyrrolidine dithiocarbamate (zinc ionophore) inhibits the enzyme responsible for replicating the genetic material of SARS-CoV-2 (Chasapis *et al*., 2020). Zinc deficiency contributes to an increased risk of inflammatory diseases, infections, and viral pneumonia, particularly in people with a developing or altered immune system (Gasmi et al., 2020). Based on that, it can be suggested that zinc supplementation would be beneficial for the prophylaxis and treatment of COVID-19, however, more solid evidence is required to test these hypotheses (Kumar e*t al*., 2020).

3.5 Bioactive substances

One of these substances that have recently gained prestige is quercetin, a flavonoid that *in vitro* studies has been shown to have antiviral activity (Keflie *et al*., 2020). Some studies indicate that the co-administration of this substance and vitamin C has synergistic activity improving the antiviral immune response. Despite these *in vitro* effects, great caution is advised when trying to recommend products that claim to have these substances (Colunga-Biancatelli *et al*., 2020). None of these substances should be offered as a "cure" for COVID-19 disease because they have not passed rigorous clinical trials (except vitamin C) on their effectiveness and safety.

4. Poor diet-immune system and COVID-19

It is well documented that a poor diet alters the function of the immune system, increasing the susceptibility to suffering from severe infection (de Araújo Morais *et al*., 2021). Unlike a Mediterranean diet, a Western diet chronically activates innate immunity and disrupts the functions of adaptive immunity. This is based on the fact that the consumption of high amounts of saturated fat activates signalling pathways related to inflammation (Zabetakis *et al*., 2020). Experiments in mice show that when the diet is high in saturated fat, there is a greater macrophage infiltration into the alveoli; an unfavourable situation in the case of COVID patients

(Butler and Barrientos, 2020). Adopting a Western diet predisposes to the development of comorbidities such as type 2 diabetes, obesity, cardiovascular diseases and more. These, as is well known, increase the risk of infection and severity of COVID-19 (Zabetakis *et al*., 2020).

5. Comorbidities and COVID-19

A person may be suffering from single or multiple comorbidities when diagnosed with COVID-19 and it is well known that comorbidities increase the risk of hospitalization, enrolment in intensive care unit and even death (Laviano *et al*., 2020). Comorbidities compromise the proper functioning of the immune system and are also generally the product of poor lifestyles, including a poor diet. Obesity and diabetes are risk factors for the person to suffer from severe COVID-19 (Silverio *et al*., 2020). The prevalence of these comorbidities is mainly due to the preference for diets high in saturated fats, refined carbohydrates and a low preference for unsaturated fatty acids, antioxidants and fibre; characteristic of a western diet (Butler and Barrientos, 2020).

Next, the elaboration on the rationale for how these comorbidities affect the immune system in its fight against COVID-19.

5.1 Obesity

There is a high prevalence of obesity among COVID -19 patients. In a Spanish ICU, 48% of the first to be hospitalized were obese (Silverio *et al*., 2020). Obesity is a chronic disease that significantly compromises the immune system. The excess of white adipose tissue in these patients promotes the release of substances that promote inflammation and cause the patient to be in a state of low-grade chronic systemic inflammation (Silverio *et al*., 2020; Di Renzo *et al*., 2020). An inflammatory environment is negative and is a requirement for the appearance of diseases (Fernández-Quintela *et al*., 2020). When SARS-CoV-2 enters the respiratory tract, the virus encounters an “altered” and “reactive” immune system. This “exaggerated” inflammation causes the immune system to destroy lung tissues, increasing the severity of severe pneumonia that occurs in patients with COVID-19 (Zabetakis *et al*., 2020; de Araújo Morais *et al*., 2021).

Another mechanism by which obesity can alter immune function is through the indirect alteration of iron metabolism. Chronic low-grade systemic inflammation increases the release of the hormone hepcidin in the liver. This hormone decreases iron metabolism and if this micronutrient is not available, the function of the immune system is also dramatically compromised (Stoffel *et al*., 2020).

Therefore, urgent measures must be taken to tackle the problem of obesity. Large-scale measures such as quarantines alter eating habits, which somehow increase the incidence of this metabolic disorder (Matsungo and Chopera, 2020). Immunonutrition in obese patients must be addressed to avoid severe complications and aftermaths (Di Renzo *et al*., 2020).

5.2 Diabetes

In diabetes, carbohydrate metabolism is compromised and has different etiologies. The state of hyperglycemia alters several signalling pathways of the immune system and this is impaired the innate and adaptive immune response. The United States Centers for Disease Control and Prevention reported that people with type 1 and type 2 diabetes are at high risk of acquiring severe COVID-19 due to metabolic disturbances and immunosuppression (Grabia *et al*., 2020). Grabia *et al*. (2020) report that during the pandemic, patients with type 1 or 2 diabetes showed an improvement in their eating habits, a situation that could contribute to improving the metabolic and immune alterations that occur in the disease.

6. General considerations

The scientific community is currently designing effective vaccines and drugs to combat COVID-19. Still, a great challenge is to modulate the immune response by reducing inflammation without altering the correct functioning of the innate and adaptive responses (Derbyshire and Delange, 2020). In this context, the focus should not only be on drug design but also on immunonutrition (Fernández-Quintela *et al*., 2020; Soares and Müller, 2020; Kamyari *et al*., 2021) which requires the mandatory participation of clinical nutritionist professionals (Cawood *et al*., 2020). Furthermore, the cost of supplementation would make the immunonutrition approach feasible in order to prevent and strategically cope with the disease (Derbyshire and Delange, 2020). What would be on standby is to evaluate the correct dosages and combinations of nutrients for this type of infection (Derbyshire and Delange, 2020).

It is important to mention that nutritional therapy is also carried out in the intensive care unit (ICU). Given this, it is necessary to continue conducting studies on the effectiveness and safety of enteral nutrition during the ICU stay (Martindale *et al*., 2020). Another aspect to consider is that access to fresh, safe and cheap food must be a priority in public policies to have a long-term effect

on multiple diseases, including COVID-19. In addition, considering the arrival of vaccines, various studies emphasize that obese people should be intervened with healthy diets because the effectiveness of vaccines is reduced in these patients (Butler and Barrientos, 2020). It is strongly suggested that the practice of immunonutrition should not be considered as a cure or treatment, it must be complemented with other healthy lifestyles to achieve sustained effects on the immune system.

Conflict of interest

The authors declare no conflict of interest.

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