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O papel da suplementação oral com imunonutrientes na resposta inflamatória nos pacientes com COVID-19

The role of oral supplementation with immunonutrients in the inflammatory response in patients with COVID-19

El papel de la suplementación oral con inmunonutrientes en la respuesta inflamatoria en pacientes con COVID-19

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Resumo

Introdução: O coronavírus relacionado ao SARS-CoV-2 se espalhou por quase todos os países, causando a COVID-19. A gravidade da COVID-19 é baseada na inflamação causada pela tempestade de citocinas. Marcadores inflamatórios sugerem uma explicação molecular para a ocorrência de doenças graves e representam um possível tratamento. Objetivo: Esta revisão tem como objetivo analisar a plausibilidade do uso da suplementação oral com imunonutrientes. Discussão: A imunonutrição estuda as interações entre nutrição, sistema imunológico, infecção e inflamação dos tecidos. Arginina é um aminoácido fundamental em processos de estresse metabólico. Sua deficiência implica na capacidade de resposta imune.

Os ácidos graxos ω-3 demonstraram melhorar a complacência pulmonar, oxigenação, tempo de ventilação mecânica e de unidade de terapia intensiva em pacientes com síndrome de angústia respiratória aguda. Essencial para imunidade mediada por células e função de linfócitos T, os nucleotídeos dietéticos têm demonstrado melhorar a citotoxicidade das células natural killer. Considerando que a relação inversamente proporcional entre a presença de IL-6 e TNF-α e a função das células T é bem estabelecida em pacientes com COVID-19, isso reforça a ideia de que o controle de liberação desses biomarcadores pode ser uma forma de tratar essa doença. Conclusão: Nesse cenário, esta revisão levanta a possibilidade de uso da imunonutrição para melhorar a resposta imune dos indivíduos afetados pela COVID-19.

Palavras-chave: Nutriente; Sistema imunológico; Citocinas; Infecção; Coronavírus.

Abstract

Introduction: The SARS-CoV-2 related coronavirus has spread to almost every country, causing the COVID-19. The severity of COVID-19 is based on the inflammation caused by the cytokine storm. Inflammatory markers suggest a molecular explanation for the occurrence of severe disease and represent a possible treatment. Objective: This review aims to analyse the plausibility of using oral supplementation with immunonutrients. Discussion: Immunonutrition studies the interactions between nutrition, the immune system, infection, and inflammation of tissues. Arginine is a fundamental amino acid in processes of metabolic stress. Its deficiency implies in the capacity of immune response. ω-3 fatty acids demonstrated improved lung compliance, oxygenation, mechanical ventilation time and intensive care unit stay in patients with acute respiratory distress syndrome. Essential for cell-mediated immunity and T lymphocyte function, dietary nucleotides have been shown to improve the cytotoxicity of natural killer cells. Considering that the inversely proportional relationship between presence of IL-6 and TNF-α and the function of T cells is well established in patients with COVID-19, this reinforces the idea that the release control of these biomarkers can be a way to treat this disease. Conclusion: In this scenario, this review raises the possibility of using immunonutrition to improve immune response of individuals affected by COVID-19.

Keywords: Nutrient; Immune system; Cytokines; Infection; Coronavirus.

Resumen

Introduccion: El coronavirus relacionado con Sars-CoV-2 se ha extendido a casi todos los países, causando COVID-19. La gravedad de COVID-19 se basa en la inflamación causada por la tormenta de citoquinas. Los marcadores inflamatorios sugieren una explicación

molecular para la aparición de enfermedades graves y representan un posible tratamiento. Objetivo: Esta revisión tiene como objetivo analizar la verosimilitud del uso de suplementos orales con inmunonutrientes. Discussion: La inmunonutrición estudia las interacciones entre nutrición, sistema inmunológico, infección e inflamación tisular. La arginina es un aminoácido fundamental en los procesos de estrés metabólico. Su deficiencia implica capacidad de respuesta inmune. Se ha demostrado que los ácidos grasos de la serie 3 mejoran el cumplimiento pulmonar, la oxigenación, el tiempo de ventilación mecánica y la unidad de cuidados intensivos en pacientes con síndrome de dificultad respiratoria aguda. Esencial para la inmunidad mediada por células y la función de linfocitos T, se ha demostrado que los nucleótidos dietéticos mejoran la citotoxicidad de las células asesinas naturales. Teniendo en cuenta que la relación inversamente proporcional entre la presencia de LA-6 y la función de células TnF y T-cell está bien establecida en pacientes con COVID-19, esto refuerza la idea de que el control de la liberación de estos biomarcadores puede ser una manera de tratar esta enfermedad. Conclusion: En este escenario, esta revisión plantea la posibilidad de utilizar la inmunonutrición para mejorar la respuesta inmune de las personas afectadas por COVID-19.
Palabras clave: Nutriente; Sistema inmunológico; Citoquinas; Infección; Coronavirus.

1. Introduction

Recently, an outbreak of viral pneumonia affected several patients in the city of Wuhan, China (Rothan & Byrareddy, 2020). A new coronavirus was isolated from the respiratory tract of these individuals, the coronavirus related to severe acute respiratory syndrome 2 (SARS-CoV-2) (Huang et al., 2020). Since then, the new virus has spread to almost every country in the world, causing Coronavirus Disease 2019 or COVID-19.

Patients who contracted COVID-19 have a change in leukocyte count, respiratory disorders and an increase in cytokines and inflammatory substances in plasma (Rothan & Byrareddy, 2020). Among the elevated pro-inflammatory substances in the bloodstream, Th1 (IL1-β), IL1RA, IL7, IL8, IL9, Th2 (IL10), basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα and VEGFA can be mentioned. The patients admitted to the Intensive Care Unit (ICU) presented higher serum levels of these inflammatory markers, demonstrating their direct relationship with severity (Huang et al., 2020; Zhong, Tang, Ye, & Dong, 2020).

Patients infected with SARS-CoV-2 who evolve with pneumonia may develop Acute Respiratory Distress Syndrome (ARDS). Given the understanding that ARDS, caused by

SARS-CoV-2, is the result of the inflammatory response, this can be modulated by using different nutritional substrates. It is also important to mention that the inflammatory response is, in turn, based on the oxidative damage of proteases and oxygen free radicals released by leukocytes and the excess of inflammatory mediators produced with their immunosuppressive effects (Grau-Carmona et al., 2011). This potential modulation of the immune system through intervention with specific nutrients is called immunonutrition. The most widely used substrates for this purpose are arginine, glutamine, branched-chain amino acids, omega-3 fatty acids and nucleotides (Calder, 2003).

Considering that ARDS caused by COVID-19 is the result of an inflammatory reaction, this review aims to analyse the biological plausibility of using oral supplementation with immunonutrients (omega-3 fatty acids, nucleotides and arginine) in patients affected by COVID-19 infection to reduce pro-inflammatory substances and, consequently, avoid ARDS in these patients.

2. Methodology

This study is a literature review research, summarizing multiple studies on the subject. To review the biological plausibility of using oral supplementation with immunonutrients in patients affected by COVID-19, an Internet literature search was conducted on the following health electronic databases: PubMed, Scielo and Google Scholar using the terms ‘COVID-19’, ‘SARS-CoV-2’, ‘immunonutrition’, ‘immune system’, ‘cytokines’, ‘coronavirus’ and ‘inflammatory biomarkers’, limited to the English, Portuguese and Spanish language, from December through May, 2020. This time frame was selected to reflect the detection of the new pandemic disease.

This is a qualitative study that involves collecting and analyzing non-numerical data to understand concepts, opinions, or experiences (Pereira et al., 2018) on the attempt to modulate the inflammatory response of COVID-19.

3. General Aspects Of SARS-COV-2 And COVID-19

3.1 Definition of SARS-CoV-2 and COVID-19

Coronaviruses are viruses of the *Coronaviridae* family, order *Nidovirales*, characterized for being enveloped and consisted of RNA as their genetic material. They often infect humans and other mammals (Huang et al., 2020). Most coronavirus infections are mild, but two recent epidemics caused by it around the world have drawn attention.

The first, caused by the coronavirus related to severe acute respiratory syndrome (SARS-CoV), affected Asia more intensely, with a mortality rate of 10% (Cheng, Lau, Woo, & Kwok, 2007; Ksiazek et al., 2003). The second, triggered by the coronavirus related to Middle Eastern respiratory syndrome (MERS-CoV), spread through the Middle East region, as the very name of the virus explains, with a mortality rate of 37% (de Groot et al., 2013; Nassar, Bakhrebah, Meo, Alsuabeyl, & Zaher, 2018).

However, in December 2019, some patients were admitted to hospitals in the city of Wuhan, China. Their diagnosis was pneumonia of unknown aetiology (Rothan & Byrareddy, 2020). After laboratory analysis, a new coronavirus was isolated from the respiratory tract of carriers of the disease and initially named 2019-nCoV, now called coronavirus related to severe acute respiratory syndrome 2 (SARS-CoV-2) (Huang et al., 2020). Since then, the new virus has spread to almost every country in the world. It caused the now called Coronavirus Disease 2019, or COVID-19.

3.2. Clinical And Epidemiological Diagnosis Of COVID-19

Initially, the diagnosis of COVID-19 was based on clinical and epidemiological criteria established by the World Health Organization (WHO). The clinical aspects to be considered were the following: dry cough, fever, diarrhoea, vomiting and myalgia. The epidemiological factors consisted in having travelled to Hubei province, working in the health area, presenting an unexpected clinical course of treatment with rapid deterioration of health status, having established close contact with the SARS-CoV-2 infected in the last 14 days (WHO, 2020).

Currently, COVID-19 has spread around the world, becoming a global emergency (Sohrabi et al., 2020). Therefore, the WHO now recommends that all patients suspected of having the disease should be tested by isolating the nucleic acid of SARS-CoV-2 through

molecular detection technique (RT-PCR)(Ahn et al., 2020). Given this fact, we believe that detection through molecular research of the virus is the main way to diagnose the disease.

3.3 Epidemiology of COVID-19

COVID-19 is transmitted through contact between people, and can even be passed by asymptomatic virus carriers or in the incubation period (Hoehl et al., 2020). One of the significant challenges in combating this disease is the evidence that never in human history there has been an infectious pathology which presented recovered patients with continuous positive viral detection (Jin et al., 2020; Lan et al., 2020)

SARS-CoV-2 can cause five basic spectra of infection: asymptomatic people (1.2%); mild to moderate cases (80.9%); severe cases (13.8%); critical cases (4.7%); and deaths (2.3% in all reported cases)(Jin et al., 2020). The most common symptoms are fever (98%), cough (76%) and myalgia or fatigue (44%). Less commonly, there are reports of the presence of airway secretion (28%), headache (8%), haemoptysis (5%) and diarrhoea (3%) (Huang et al., 2020). The average incubation time of the virus was estimated at 5.2 days (95% CI 4.1-7.0) (Q. Li et al., 2020). Biochemical tests showed normal or decreased leukocyte count with lymphopenia. The tomographic pattern of the lungs of these patients showed bilateral involvement with a frosted glass pattern and areas of consolidation (Huang et al., 2020; Zhu et al., 2020).

Indeed, the wide spectrum of manifestations of the disease is remarkable, which causes difficulty in diagnostic suspicion. Thus, laboratory and imaging tests are useful in elucidating cases and monitoring patients.

3.4. Pathophysiology of COVID-19

The human angiotensin-converting enzyme 2 (ACE2) is the functional receptor of SARS-CoV-2 for cell entry (Zhou et al., 2020). It is expressed in the cell membranes of the lungs, heart, kidneys and intestines (Donoghue et al., 2000).

The gene's polymorphism that decodes the angiotensin-converting enzyme 2 (ACE2) is also associated with the appearance of ARDS, a common complication of COVID-19 (Meyer & Christie, 2013). The pathophysiology of ARDS involves three stages, namely: the first phase of the evolution of the lung injury is called the exudative phase. It is characterized by alveolar endothelial damage and a rupture of epithelial barriers mediated by immune cells

with consequent accumulation of protein-rich fluid within the interstice and the alveolar structures themselves. These changes will promote the activation of macrophages that reside in the alveoli, which in turn will secrete cytokines. These pro-inflammatory substances recruit neutrophils and monocytes or macrophages, in addition to activating epithelial cells and T lymphocytes, establishing a sustained inflammation of lung tissue(Aggarwal, King, & D'Alessio, 2014). Endothelial activation and microvascular injury also contribute to ARDS barrier rupture, which is aggravated by mechanical tissue distension.

The second phase of the syndrome is called proliferative, and the survival of the affected patient depends on it. This stage is characterized by the initial process of repairing the lesions. Once the integrity of the epithelium is re-established, the alveolar oedema is reabsorbed, and the provisional matrix reconstructs the architecture and alveolar function (Huppert, Matthay, & Ware, 2019).

Finally, the fibrotic phase of ARDS may not occur in all patients. It is closely associated with prolonged mechanical ventilation time and considerably increases patient mortality (Thompson, Chambers, & Liu, 2017).

Therefore, inflammatory markers suggest a molecular explanation for the occurrence of severe ARDS and still represent a possible treatment for the occurrence of this complication in SARS-CoV-2 infections (Jin et al., 2020). Among the elevated pro-inflammatory substances in the bloodstream are IL1-β, IL1RA, IL7, IL6, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNF-α and VEGFA.

3.5. Role Of IL6, TNF-A And Reactive C Protein In COVID-19

The first report on laboratory changes in COVID-19 indicated changes in the levels of several substances. Changes in D-dimer, Reactive C Protein (PCR), neutrophil count, urea and serum creatinine, and also in inflammatory markers such as IL6 and TNF-α were cited, indicating changes in the immune status of patients affected by the disease (Guo et al., 2020).

Several studies have shown that IL6 plays an essential role in viral diseases, especially in the respiratory tract, by either producing an immune response or exacerbating the pathology and promoting viral survival. This interleukin is produced in response to tissue damage and influences the proliferation of adaptive and innate immune cells, especially at the lung level. It is also able to promote regulation of T cell responses, resolution of inflammation, tissue remodelling, cell migration, phagocytic activity of macrophages, as well as preventing epithelial cell apoptosis of the lungs induced by viral infections (Messina et al.,

2020). Other evidence in the literature suggests that high levels of IL6, through different mechanisms, may interfere with viral *clearance*. This could somehow establish a state of persistent virulence in the hosts (Robb, Regan, Dorward, & Rossi, 2016).

The Tumoral Necrosis Factor (TNF-α) is a cytokine involved in systemic inflammation, released mainly by macrophages. In viral infections of the airways by influenza, for example, the expression of TNF-α in epithelial cells enhances the antiviral immune response (Messina et al., 2020).

CRP is an acute-phase protein with IL6-induced liver production. It serves as a sensitive biomarker of inflammation, infection and tissue damage, increasing rapidly and sensitively during acute inflammatory responses (F. Liu et al., 2020; Pepys & Hirschfield, 2003). A study conducted in Hunan province, China, revealed that this marker was higher in patients with greater severity of illness when compared with those with a moderate illness level, including a positive correlation with the classification of tomography findings (Tan et al., 2020). Other work conducted in China found that increased CPR and IL6 served as a prognosis of evolution to severity (F. Liu et al., 2020).

Finally, in patients with COVID-19, the higher the serum levels of IL6 and TNF-α, the lower the function of the T cells and vice versa (Diao et al., 2020). This reinforces the idea that controlling the release of these cytokines can be a way to treat the disease caused by SARS-CoV-2.

4. General Aspects Of Immunonutrition And COVID-19

4.1. Definition Of Immunonutrition

Immunonutrition is the science that studies the interactions between nutrition and the immune system, infection, inflammation and tissue injury or damage (Zapatera, Prados, Gómez-Martínez, & Marcos, 2015). It refers to the ability of the immune system to modulate through specific interventions that modify dietary nutrients (Calder, 2003). For over 20 years, it has been recognized that immunonutrient supplementation can alter the course of critical illnesses (Beale, Bryg, & Bihari, 1999).

Many specialized formulas with added immunonutrients are available. First, these diets contained a combination of antioxidant vitamins (C, E, beta-carotene), trace elements (selenium, zinc), conditionally essential amino acids (arginine and glutamine) or essential

fatty acids such as ω-3 (eicosapentaenoic and docosahexaenoic acids) and gamma-linolenic acid (Mizock, 2010).

Supplements with immunonutrients have been demonstrated themselves as adjuvants in several treatments, capable of immunomodular inflammatory response in various pathologies, such as in preoperative situations.

4.2. Immunonutrients And Their Functions

4.2.1. Arginine

Arginine is a conditionally essential amino acid in specific processes of metabolic stress, such as trauma and post-operative. The beneficial effects of this nutrient include its secretagogin function of anabolic hormones, support of immune cell activity (especially T lymphocytes), detoxification of ammonia and improvement of healing processes through the metabolism of proline and polyamines (Bansal & Ochoa, 2003).

Arginine deficiency implies the ability of the immune response to cause T cell receptor abnormalities, increasing the chance of infection contraction and impacting on healing processes. In this scenario, supplementing this amino acid helps to reverse the immunosuppressive state (Ochoa, Makarenkova, & Bansal, 2004; Popovic, Zeh III, & Ochoa, 2007). This deficiency is usually present in the early stages of sepsis (Chiarla, Giovannini, & Siegel, 2006). Thus, the patients who benefit from the supplementation of arginine are those undergoing minor surgery or stress events. Critically ill individuals benefit little, if any, from the supplementation of arginine, and there is indeed a high possibility of increased mortality (Mizock, 2010).

Besides the role in the immune system, arginine seems to serve as the primary substrate for the production of Nitric Oxide (NO) through the action of the enzyme Nitric Oxide Synthase (NOS). NO can regulate several essential processes in ARDS pathophysiology, including vascular tonus, platelet aggregation, leukocyte adhesion and mitochondrial oxygen consumption (Ware et al., 2013).

Thus, arginine is shown to be an important amino acid for inflammatory modulation.

4.2.2. Ω-3 Fatty Acids

Ω-3 fatty acids from cold-water fish, especially eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids are the active metabolites of alpha-linolenic acid (ALA). Humans have a limited ability to synthesize EPA and DHA through di*et al*A metabolization (only 8% is converted) (Bistrian & McCowen, 2006). During a severe acute illness process, ALA's ability to convert to EPA and DHA decreases. Therefore, supplementation of these ω-3 fatty acids becomes essential.

EPA and DHA anti-inflammatory mechanisms include: 1) removal of arachidonic acid from the phospholipid nucleus of inflammatory cell membranes, reducing the production of pro-inflammatory substance; 2) inhibition of synthesis of pro-inflammatory eicosanoids by competition with arachidonic acid in cyclooxygenase and lipoxygenase enzymes; 3) reduction of platelet and leukocyte adhesion in the endothelium; 4) inhibition of inflammatory gene expression; 5) reduction of oxidative lesions by stimulation of glutathione production; 6) improvement of anti-inflammatory resolvin synthesis; 7) a protective lung effect mediated by the reduction of the release of inflammatory mediators derived from the intestine in mesenteric lymphatic vessels and the thoracic duct(Glatzle et al., 2007; Mizock & DeMichele, 2004; Serhan, Arita, Hong, & Gotlinger, 2004).

In ARDS, especially, ω-3 fatty acids have been shown to improve lung compliance, oxygenation and mechanical ventilation time and ICU (Singer & Shapiro, 2009). Although the role of supplementation of these lipids in patients with this syndrome is not known, it is believed that they can reduce reactive oxygen specimens and pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8 (García de Acilu et al., 2015).

Omega-3 fatty acids are undoubtedly an important component for regulating the inflammatory response in various pathologies.

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4.2.3. Nucleotides

Food-borne nucleotides are essential for cell-mediated immunity and T lymphocyte function. In humans, administration of nucleotides in the form of polyadenylic and polyuridylic acid as adjuvants have been shown to improve the cytotoxicity of *natural killer* cells (NK) (Singh, Gopalan, & Sibal, 2002).

4.3. Benefits Of Immunonutrition In Clinical Practice

Many clinical trials have been conducted to evaluate the benefits of immunonutrition, especially in critically ill and surgical patients, using various types, doses and combinations of nutrients (Calder, 2003). Four meta-analyses provide an exciting insight into the consistency of the clinical benefits of this therapeutic option. Most of the clinical trials analysed in the studies used combinations of ω-3 fatty acids, arginine and nucleotides, while others evaluated a combination of these nutrients and glutamine (Beale et al., 1999; Heyland et al., 2001; Heys, Walker, Smith, & Eremin, 1999; Pimentel & Fernandes, 2020).

All four studies showed the capacity of immunonutrition to reduce infections and length of hospital stay, but without significant impacts in reducing the mortality rate of these patients. The benefits generated by this nutritional strategy are likely to come from modulating the production of pro-inflammatory substances.

4.4. Immunonutrition and COVID-19

Discussions about public health decisions often neglect nutritional strategies to improve the functioning of the immune system. This occurs even though there is a vast knowledge about the importance of good nutritional status in immunity (Calder, Carr, Gombart, & Eggersdorfer, 2020). The immune response is weakened in malnutrition states and is demonstrated in model experiments as well as human studies (Messina et al., 2020).

The pathophysiology of COVID-19 is based on the inflammation caused by the cytokine storm generated by the host's inflammatory response against the virus. This disorder would be the precursor to the onset of disease complications, such as ARDS (Huang et al., 2020). There has been no study to date that has evaluated the direct effect of immunonutrition on patients affected by SARS-CoV-2. However, two recent studies provide the theoretical rationale that adequate nutritional support with supplementation, especially of ω-3 fatty acids, would be able to keep immune function close to optimal, would help control the impact of infections, and could help limit the emergence of new, more virulent strains of pathogenic viruses (Calder et al., 2020; Messina et al., 2020).

A study of 182 participants affected by COVID-19, conducted in Wuhan, China, showed that 52.7% of the patients were malnourished and 27.5% were at nutritional risk (T. Li et al., 2020). Another survey also conducted in Wuhan, China, with 141 individuals with COVID-19 identified 85.8% of patients as having high nutritional risk. Patients in the risk

group had more extended hospital stays, higher hospital costs, worse severity of illness and a more abrupt weight change than those without risk (G. Liu, Zhang, Mao, Wang, & Hu, 2020).

Faced with such evidence, an Italian study group established a new nutritional supplementation protocol since almost all hospitalized patients present at the time of admission with severe inflammation and anorexia leading to a significant reduction in food intake. They have opted for the systematic supplementation of *Whey* Protein and micronutrients (vitamins, minerals and trace elements) in an attempt to modulate the immune system and inhibit viral replication (Caccialanza et al., 2020).

A recent literature review discussed the possibility of some nutrients strengthening the immune system and oxidative stress. According to the authors, some dietary components such as proteins, especially glutamine and arginine, ω-3 fatty acids and micronutrients, would be essential to maintain an optimal nutritional status. Accordingly, the study encourages the promotion of healthy eating habits as a way to obtain the benefit of these dietary components to mitigate the pro-inflammatory effects of COVID-19 (Iddir et al., 2020).

It is clear how malnutrition can, therefore, interfere with the evolution of the disease. Regarding the specific issues of nutritional support, the peculiarity of COVID-19 is that, suddenly, this disease may require more invasive measures, when nutritional support may become very problematic due to emergency circumstances and the patient's tolerance to food. Therefore, it is advised that different strategies should be considered in this situation, such as the use of specific hyper protein formulas, highly digestible, enriched with ω-3 fatty acids or other anti-inflammatory or immunomodulatory nutrients (Caccialanza et al., 2020).

Finally, improving the outcomes of COVID-19 may have a significant impact on public health. Firstly, the use of immunonutrition has already been shown to reduce hospital costs when applied in some situations (e.g. surgical preparation) (Braga & Gianotti, 2005). Also, decreasing the patient's hospitalization time allows him/her to have a better quality of life after discharge by preventing loss of functionality (Singer, 2019). This would consequently remove the individual's dependence on the public system, maintaining his or her ability to return to daily activities, including work, more quickly.

4.5. Biological Plausibility on Immunonutrition At COVID-19

As explained so far, coronaviruses tend to infect humans. Moreover, SARS-CoV-2 has been spreading to almost every country in the world, causing COVID-19.

This virus has as functional receptor the angiotensin-converting enzyme 2 (ACE2) (Zhou et al., 2020). The polymorphism of the gene that decodes ACE2 is associated with the appearance of ARDS, a common complication of COVID-19 (Meyer & Christie, 2013). This syndrome is characterized by alveolar damage that promotes the activation of macrophages, which in turn secrete cytokines and pro-inflammatory substances (Aggarwal et al., 2014).

Therefore, inflammatory markers are involved in the occurrence of severe ARDS and interventions that act on the production of these markers may represent a treatment for this complication (Jin et al., 2020). Among the high pro-inflammatory substances in the bloodstream, CRP, IL6 and TNF-α can be mentioned.

In patients with COVID-19, there is a well-established inversely proportional relationship between the presence of IL6 and TNF-α and the function of T cells (Diao et al., 2020). Also, increased CRP and IL6 serve as a prognosis of evolution to severity. This reinforces the idea that controlling the release of these biomarkers can be a way to treat the disease caused by SARS-CoV-2.

In this scenario, the possibility of using immunonutrition to fight infection arises. Immunonutrition refers to the ability of the immune system to modulate through specific interventions that modify dietary nutrients (Calder, 2003). Among these nutrients are arginine, ω-3 fatty acids and nucleotides.

Arginine is a conditionally essential amino acid in specific metabolic stress processes (Bansal & Ochoa, 2003). The deficiency of this amino acid implies in the capacity of the immune response to cause abnormalities in the T cell receptors, increasing the chance of infection contraction and impacting the healing processes. Supplementing it would help reverse the immunosuppressive state (Ochoa et al., 2004; Popovic et al., 2007).

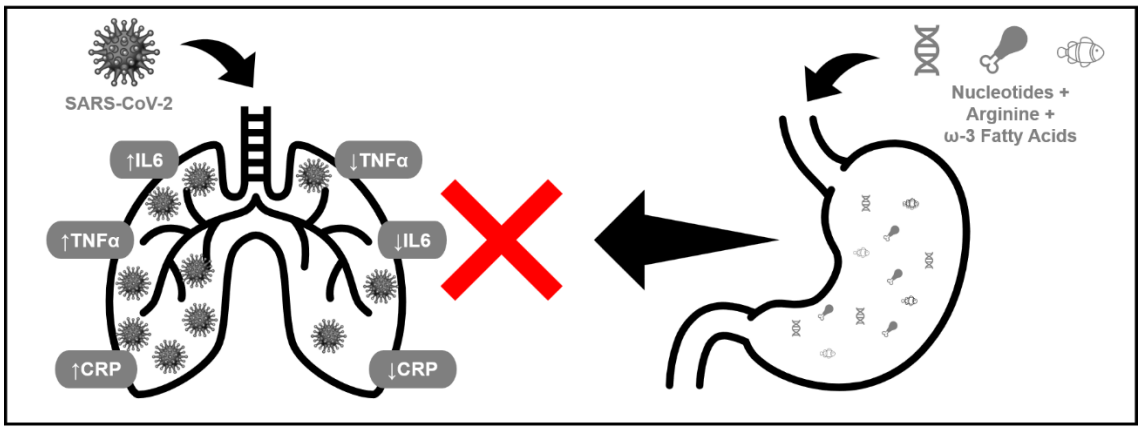
Ω-3 fatty acids have been shown to improve lung compliance, oxygenation and mechanical ventilation time and ICU in ARDS patients (Singer & Shapiro, 2009). Although the role of supplementation of these lipids in this situation is not assured, it is believed that they are capable of reducing reactive oxygen specimens and pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8 (García de Acilu et al., 2015).

Nucleotides are essential for cell-mediated immunity and T lymphocyte function, improving the cytotoxicity of NK cells (Singh et al., 2002).

Finally, considering that COVID-19 can generate ARDS, which in turn results from the release of pro-inflammatory cytokines, including CRP, IL-6 and TNF-α, a modification of the dietary regime in order to modulate this immune response could be advantageous, both to

prevent infection and to care for patients already affected by the disease, improving its results (Messina et al., 2020).

Figure 1- Diagram of biological plausibility: use of immunonutrition X production of pro-inflammatory substances.



Source: Authors.

It is important to observe in Figure 1 an illustrative scheme of the path made by immunonutrients through oral intake and gastric absorption, passing to their serum transport to the target pulmonary cells for diminution of the inflammatory markers production.

5. Conclusion

To sum up, this review raises the possibility of using supplementation with specific immunonutrients such as arginine, ω-3 fatty acids and nucleotides as a way to improve the immune response of individuals already affected by COVID-19.

The dietary components reviewed here are available in oral supplements already commercialized and available in various locations around the world, becoming an alternative in the prevention of severe manifestations of the disease. Finally, we encourage the maintenance of healthy nutritional habits and robust studies that can ratify the theoretical rationale explored in this work.

Clinical trials that can evaluate the use of oral supplements enriched with immunonutrients compared with the use of conventional oral supplements in patients infected with SARS-Cov-2 will be extremely important to verify the real plausibility of this theoretical rationale. Thus, we can make sure that immunonutrients are able to prevent the inflammatory

cascade and the evolution to severity in COVID-19.

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