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REVIEW ARTICLE

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The importance of dietary balance at COVID-19: the systematic review

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Abstract

Introduction: COVID-19 disease has been heralded as a global pandemic by the World Health Organization. Dietary therapy and immunity play a decisive role in SARS-CoV-2 infection. In this sense, the lack of regulation and the excessive immune response to the viral stimulus produces an exacerbated pro-inflammatory cytokines (cytokine storm), reaching the state of hyperinflammation. **Objective:** To conduct a systematic review of the main considerations in the management of dietary therapy in the control or prophylaxis of COVID-19. **Methods:** Clinical studies with qualitative and/or quantitative analysis were included, following the rules of the systematic review-PRISMA. **Results:** A total of 370 articles were found involving dietary therapy, immunity, and COVID-19. A total of 107 articles were evaluated in full, and 28 were included and discussed in this study. Underlying systemic inflammation is believed to exacerbate COVID-19 infection. Studies have shown that there is a high risk of mortality in individuals with pre-existing health problems, such as diabetes, hypertension, cardiovascular disease, and obesity. Nutritional status is known to play a significant role in patient outcomes. It is necessary to follow a diet characterized by anti-inflammatory properties to benefit or prevent COVID-19. Adequate supplies of zinc, selenium, and vitamin D are essential for resistance to other viral infections, immune function, and reduced inflammation. There are nutritional triggers to favor immune-strengthening responses, as well as improving the performance of mitosis, meiosis, and all cellular functioning, all of this functioning is directly integrated with the energy balance and nutritional status of the body. Endogenous metabolites and nutrients in the diet can directly influence epigenetic enzymes. **Conclusion:** It is necessary to control the activities of inflammatory mediators through modifiable risk factors, such as diet, exercise, and healthy lifestyle choices to control or prevent the harmful effects of COVID-19.

Keywords: Dietary therapy. Nutrition. Immunity. Nutritional management. COVID-19.

Introduction

COVID-19 disease has been heralded as a global pandemic by the World Health Organization [1]. The appearance of the new coronavirus (SARS-CoV-2) has resulted in the aggravation of comorbidities of various diseases, as well as worsening in patients with nutritional deficiency [2]. It is necessary to understand the mechanisms by which comorbid patients are at greater risk of evolving to severe forms of the disease, even death [3]. In this sense, immunity and nutrition play a decisive role in SARS-CoV-2 infection. In this sense, the lack of regulation and the excessive immune response to the viral stimulus produces an exacerbated pro-inflammatory cytokines (cytokine storm), reaching the state of hyper inflammation [4,5].

Therefore, the vulnerable and immunocompromised in our societies seem to be more susceptible to serious complications from COVID-19. The presence of poor nutritional status and pre-existing non-communicable diseases (NCDs), such as diabetes mellitus, chronic lung diseases, cardiovascular diseases (CVD), obesity, and several other diseases that make the patient immunocompromised. These diseases are characterized by systemic inflammation, which may be

a common feature of these NCDs, affecting patient outcomes against COVID-19. In this sense, the nutritional status and the role of diet and lifestyle are decisive and must be taken into account, as they can directly affect the results of patients with COVID-19 **[6]**.

In this regard, it has been postulated that a healthy nutritional status promotes immune function and can prevent the onset of a serious infection in COVID-19 **[7-10]**. In this context, the optimal immune response depends on an adequate diet and nutrition to keep the infection under control. So, as an example, sufficient protein intake is crucial for optimal antibody production. Also, the low level of micronutrients, such as vitamin A or zinc, was associated with an increased risk of infection, as this deficiency promotes inflammatory processes and oxidative stress. In contrast, dietary constituents with anti-inflammatory and antioxidant actions are highlighted by vitamin C, vitamin E, carotenoids, and polyphenols **[11]**.

In this sense, several of these dietary elements can interact with transcription factors, such as NF-kB and Nrf-2. An important example is vitamin D, which protects tissue against viral cellular infection through the angiotensin-2 converting enzyme (ACE2). Dietary fiber and short-chain fatty acids also showed anti-inflammatory effects **[11]**.

Therefore, the present study performed a systematic review of the main considerations in the management of dietary therapy in the control or prophylaxis of COVID-19.

Methods

Study Design

The present study was followed by a systematic literature review model, according to the PRISMA rules. Access available at: http://www.prisma-statement.org/.

Data sources and research strategy

Clinical studies were included as case reports, retrospective, prospective and randomized trials with qualitative and/or quantitative analysis. Also, some review studies were included. Initially, the keywords were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and later verified and validated by the MeSH system (Medical Subject Headings, the US National Library of Medicine) to achieve consistent search.

Mesh terms

The main MeSH Terms were Dietary therapy. Nutrition. Immunity. Nutritional management. COVID-19. The literature search was conducted through online databases PubMed, Periodicos.com, Google Scholar, Ovid, Scopus,Web of Science and Cochrane Library.

Study quality and risk of bias

The quality of the studies was based on the GRADE instrument, with randomized controlled clinical studies, prospective controlled clinical studies, and studies of systematic review and meta-analysis listed as the studies with the greatest scientific evidence. The risk of bias was analyzed according to the Cochrane instrument.

Results

Literature Review and Discussion

A total of 370 articles were found involving dietary therapy, immunity, and COVID-19. Initially, was held the exclusion of existing title and duplications following the interest described in this work. After this process, the summaries were evaluated and a new exclusion was held. A total of 107 articles were evaluated in full, and 28 were included and discussed in this study (**Figure 1**).

After analyzing the findings selected in the present study, it is believed that the underlying systemic inflammation may exacerbate COVID-19 infection. Studies have shown that there is a high risk of mortality in individuals with pre-existing health problems, such as diabetes, hypertension, cardiovascular disease, and obesity. In this sense, it is necessary to control the activities of inflammatory mediators through modifiable risk factors, such as diet, exercise, and healthy lifestyle choices. In this sense, only the adoption of a consistent and long-term dietary pattern benefits human health. In this regard, there is considerable evidence that food and nutrients affect the functioning of our immune system **[12-14]**.

In this context, nutritional status can have a significant impact on an individual's general health, reducing comorbidities and reduced susceptibility to the development of infections such as COVID-19. However, according to the WHO, there is still no single food or natural remedy with proven scientific evidence to prevent COVID-19 infections **[1]**. Despite this, based on previous studies, it is known that nutritional status plays a significant role in patient outcomes **[15]**. Therefore, it is necessary to follow a diet characterized by anti-inflammatory properties to benefit or prevent COVID-19 **[16-19]**.

In this sense, evidence suggests that dietary patterns and individual nutrients can influence systemic markers of immune functions. Thus, maintaining the nutritional status at this time is significant, given that

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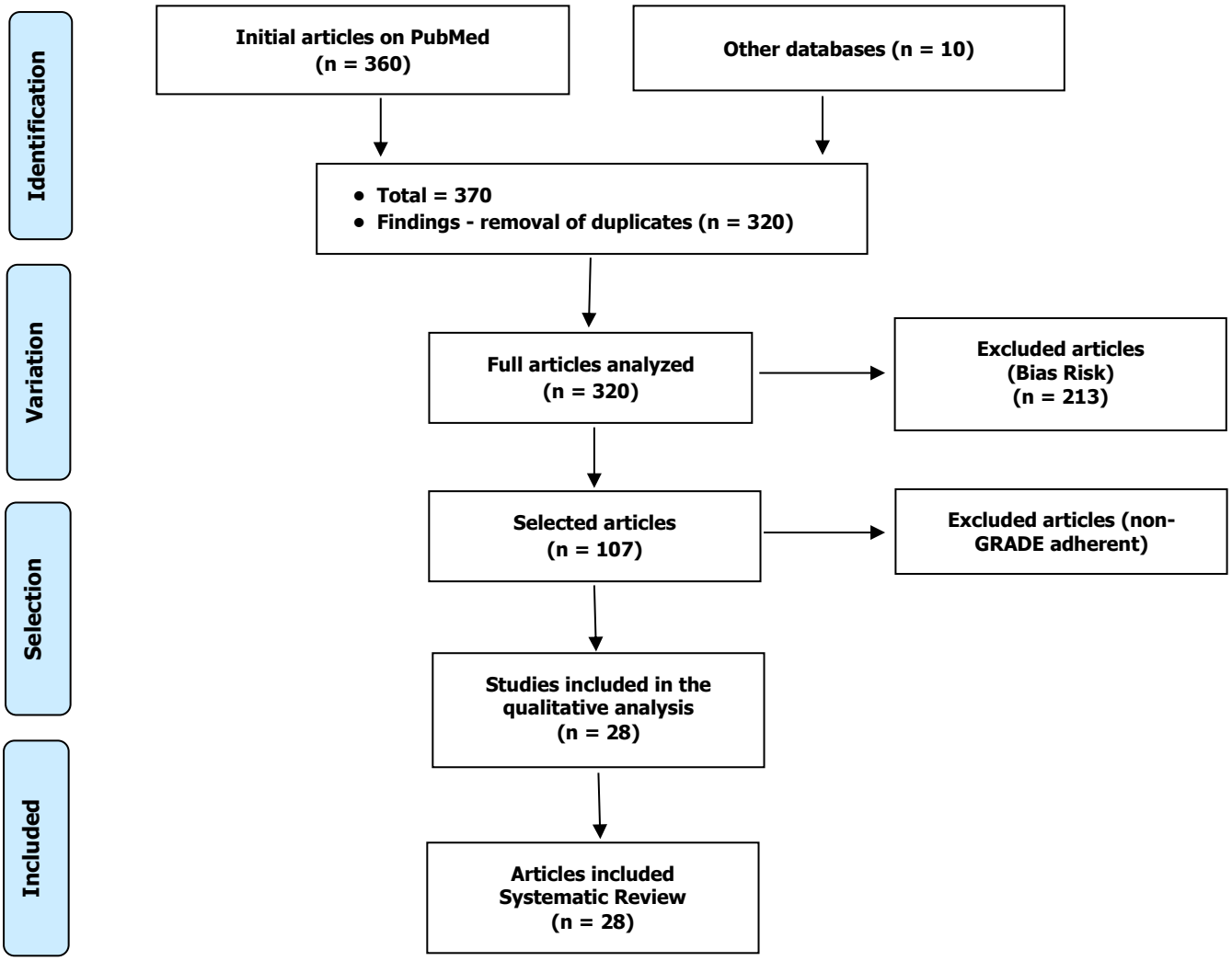
Figure 1. The selection process of scientific articles.



the fight against COVID-19 can last a long time. Also, to maintain a healthy immune system, special attention must be paid to maintaining a healthy diet, lifestyle, and exercise regimen **[20]**.

Also in this scenario, there are nutritional deficiencies of calcium, vitamin C, vitamin D, folate, and zinc among elderly populations **[21]**, making them immunodepression **[22]**. Thus, a healthy and balanced diet can provide the macro and micronutrients, prebiotics, probiotics, and symbiotics needed in the elderly that can restore and maintain immune cell function **[23]**.

Table 1 shows the main macro and micronutrients that are highlighted for the maintenance of a balanced diet and, consequently, for a better immune response. In this context, a review study examined the usefulness of early intervention with micronutrients, with a focus on zinc, selenium, and vitamin D, to alleviate the increase in COVID-19. The results revealed that there is direct evidence for associations between zinc, selenium, and vitamin D, and COVID-19. An adequate supply of zinc, selenium, and vitamin D are essential for resistance to other viral infections, immune function, and reduced inflammation **[24]**.

In this scenario of nutritional triggers to favor immune-strengthening responses, as well as improving the performance of mitosis, meiosis, and all cellular functioning, all this functioning is directly integrated with the energy balance and nutritional status of the body. The metabolic by-products and substrates that regulate epigenetics and signaling pathways are considered to have an instructive rather than an observer role in regulating cell fate decisions. Metabolism encompasses the interactions between diet, microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to sustain life **[25]**.

Furthermore, endogenous metabolites and nutrients in the diet can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate, controlling chromatin accessibility and downstream gene expression patterns. Thus, most substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways such as the tricarboxylic acid cycle,

Table 1. Dietary patterns and COVID-19 **[5,6]**.

Dietary Patterns	*Main considerations at COVID-19*
Mediterranean Diet	A balanced diet rich in foods with anti-inflammatory and immunomodulatory properties, including essential vitamins (C, D, and E) and minerals (zinc, copper, calcium, etc.)
Fruit and Vegetables	It has nutrients with antioxidant properties, vitamins, minerals, and phytochemicals that include phenolic compounds that can exert antioxidant, anti-inflammatory, and other beneficial effects. They are also important sources of fiber for intestinal health.
Fish and Fish Oils	They contain polar lipids that exhibit potent antithrombotic effects. Other bioactive compounds in fish, such as peptides, can also prevent thrombosis, the generation of ROS, and hypertension. Currently, 2-4 g of n-3 fatty acids appear to be physiologically relevant against hypertension, inflammation, and thrombosis.
Vitamin C	Reduced Cold Severity: They have reduced the symptoms of a cold, making it less severe. Reduced duration of cold: Supplements decreased recovery time by 8% in adults and 14% in children, on average.
Vitamin D	Researchers recommend doses of 10,000 IU/d (250 µg/d) of vitamin D3 for several weeks to rapidly increase 25-hydroxyvitamin D concentrations, followed by 5,000 IU/d (125 µg/d) to keep concentrations above 40 -60 ng/mL (100-150 nmol/L), which may be beneficial against COVID-19.
Vitamin E	The RDA for vitamin E for healthy adults according to the NIH DRI is 15 mg/d (maximum tolerable intake level 1000 mg/d). Although vitamin E has been recommended as a potentially beneficial nutrient against COVID-19 infection, there are currently no estimates of a beneficial dosage.
Zinc	Although the RDA for zinc according to the NIH DRI is 8-11 mg/d of zinc for adults (upper tolerable intake level of 40 mg/d), it has been suggested that a zinc intake of 30-50 mg/d can help control RNA viruses such as influenza and coronaviruses.
Copper	Although there was no recommended dietary intake of copper against COVID-19, a copper intake of 7.8 mg/d has been shown to reduce oxidative stress and alter immune function.
Fiber	Studies demonstrate a lower incidence of bacterial translocation across the intestinal barrier with the administration of dietary fiber, suggesting that this nutrient modulates immunity. Recommended fiber sources range from 25 to 38 g/day.

methionine cycle, folate cycle, glycolysis, β-oxidation, and the hexosamine pathway **[25]**.

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact the cellular state by modulating the activity of the signaling pathway. A clear example is through the mechanistic target signaling pathway of rapamycin (mTOR) and, in particular, the mTOR 1 complex (mTORC1), which regulates cell growth only when nutrients and growth factors are present. Depletion of specific nutrients including arginine, leucine, and S-adenosyl methionine prevents growth factor-induced activation of mTORC1 by blocking Rag GTPase-mediated mTORC1 recruitment to the lysosome where it can be activated by Rheb GTPase **[25]**.

Another way nutrients are detected to impact the cellular state is through AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance and in the process regulates cell growth and autophagy. Furthermore, transcription factors can be directly regulated by metabolites. Kynurenine tryptophan is an endogenous agonist for the aryl hydrocarbon receptor and alpha-ketoglutarate (α-KG) which binds and activates IKKβ and initiates NF-κβ signaling **[25]**.

Thus, nutritional health acts directly on the human intestinal microbiota, impacting the metabolism and the immune system for tissue regeneration. Recent discoveries on the role of the "nutrological microbiota" in mechanisms involved in tissue regeneration, in particular skin, liver, bone, and nervous system regeneration **[26]**.

In this aspect, in the inflammatory phase, vitamin A increases the release of cytokines, bromelain, and amino acids to prevent prolonged inflammatory events, vitamin C increases neutrophil migration and lymphocyte activation. In the proliferative phase, vitamin C is needed for collagen synthesis, glucosamine increases the production of hyaluronic acid. Vitamin A, on the other hand, promotes the differentiation of epithelial cells. Zinc is needed for DNA and protein synthesis and cell division. In the remodeling phase, amino acids and proteins play a key role in stabilizing

the wound scar **[27]**.

Finally, reduced age-related muscle repair efficiency contributes to the development of sarcopenia. Nutrients such as amino acids, polyunsaturated fatty acids, polyphenols, and vitamin D can enhance skeletal muscle regeneration by targeting key functions of immune cells, muscle cells, or both **[28]**.

Conclusion

Adopting a consistent and long-term dietary pattern benefits human health. In this regard, there is considerable evidence that food and nutrients affect the functioning of our immune system. It is necessary to control the activities of inflammatory mediators through modifiable risk factors, such as diet, exercise, and healthy lifestyle choices to control or prevent the harmful effects of COVID-19.

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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