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THE IMPACT OF NUTRITION ON THE COVID-19 PANDEMIC

Abstract: *People who eat a well-balanced diet tend to be healthier with stronger immune systems and lower risk of chronic illnesses and infectious diseases. The human immunity has a pivotal role in nutrition acquisition from the pathogens and damaged body tissue during the SARS-CoV-2 virus infection, which may lead to transient overnutrition in the patients, lead to lipotoxicity and further damage in non-adipose tissues, and cause hyperinflammation and cytokine storm in severe cases of COVID-19. Optimal nutrition can improve well-being and might mitigate the risk and morbidity associated with coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The majority of documents encouraged the consumption of fruits, vegetables, and whole grain foods. Thirty-one percent of the guidelines highlighted the importance of minerals and vitamins such as zinc and vitamins C, A, and D to maintain a well-functioning immune system. Thus, in this article, we analyze nutritional recommendations for COVID-19 disease, and clinical trials on vitamins and supplements in the treatment and prevention.*

Keywords: *Immunity, nutrition, pathogen, tissue, SARS-CoV-2 virus infection, lipotoxicity, non-adipose tissues, hyperinflammation, COVID-19, acute respiratory syndrome coronavirus 2.*

Introduction: As we continue to keep an eye on COVID-19 and its new strains, now is a great time to strengthen our immune systems to combat the virus. Those of us that have a better nutritional status can fight the disease better than others. If our immune system is working really well, we don't get infected. In general, nutrition affects our entire body. All body processes require enzymes, and many vitamins and minerals help enzymes work better. A number of micronutrients, including vitamins C and D and zinc, have been shown to play key roles in supporting immune function and in reducing risk of respiratory infection. These nutrients can be obtained from the diet and are available as dietary supplements either alone or as part of multivitamin or multinutrient mixtures. There are many other dietary supplements available including, omega-3 fatty acids ('fish oil'), probiotics and plant isolates like garlic. The use of specific dietary supplements in both prevention and acute treatment of infection with SARS-CoV-2 has been promoted by prominent medical entertainment personalities on television and social media since the beginning of the current coronavirus pandemic.

Evidence of high human-to-human transmissibility of SARS-CoV-2 has made social isolation the best preventive measure to avoid the spread of COVID-19 [1]. This pandemic is substantially affecting lifestyles, healthcare systems, and national and global economies. Social isolation is often an unpleasant experience that may have negative effects on mental health [2]. It has been suggested that, until quarantine ends, self-isolation is likely to cause psychological and emotional symptoms [3], changes in mood and altered sleep or eating patterns [4], worsening of chronic health conditions, weight gain, and increased use of alcohol, tobacco, or illegal drugs.

Optimal nutrition is one of the main determinants of health that can improve well-being and mitigate the harmful health consequences associated with social distancing by helping to prevent or control most chronic diseases (eg, diabetes, hypertension, and excess body weight/obesity); aid in the regulation of sleep and mood; and prevent fatigue [5,6]. Nutritional modulation of the immune system is also important across the age spectrum. During early childhood, breastfeeding can provide protection against infections and respiratory diseases, as breast milk contains antibodies, enzymes, and hormones that can offer health benefits [7]. In older adults, the group at most risk for COVID-19, changes in dietary habits lead to significant alterations in immunity and inflammation, termed immunosenescence and inflammaging [8]. Some nutrients, such as omega-3 polyunsaturated fatty acids and probiotics, have been linked to anti-inflammatory responses and enhanced resistance to upper respiratory tract infection [8]. In individuals infected with SARS-CoV-2, nutritional status is a crucial factor for optimal prognosis and can determine the clinical severity of COVID-19 [9]. Dietary supplementation with selected vitamins (eg, A, B, C, and D), minerals (eg, selenium, zinc, and iron), and omega-3 fatty acids was suggested by Zhang and Liu [10] as a treatment option for COVID-19 patients and as preventive therapy against lung infection. However, the use of micronutrient supplements to prevent infections remains questionable. Since to date there is no vaccine or evidence-based treatment for COVID-19, the optimization of nutrient intake through well-balanced meals and the use of good hygiene practices in food selection, preparation, and conservation is probably the most effective approach for managing the continuous risk of viral infection. This epidemic began with animal-to-human infection, and the direct cause of death is generally due to ensuing severe atypical pneumonia. CoVID-19 has now been declared a pandemic by the World Health Organization, and people in all countries are under quarantine in order to reduce the spread of the virus, which then also lessens the impact on medical resources. Since quarantine is associated to the interruption of the work routine, this could be result in boredom. Boredom has been associated with a greater energy intake, as well as the consumption of higher quantities of fats, carbohydrates, and proteins [11, 12]. Further, during quarantine continuously hearing or reading about the pandemic without a break can be stressful. Consequently, the stress pushes people toward overeating, mostly looking for sugary “comfort foods” [13]. This desire to consume a specific kind of food is defined as “food craving”, which is a multidimensional concept including emotional (intense desire to eat), behavioral (seeking food), cognitive (thoughts about food), and physiological (salivation) processes [14]. Of interest, a gender difference has been reported in food craving, with a higher prevalence in women than in men. Carbohydrate craving encourages serotonin production that in turn has a positive effect on mood. In a sense, carbohydrate-rich foods can be a way of self-medicating anti stress. The effect of carbohydrate craving on low mood is proportional to the glycemic index of foods. This unhealthy nutritional habit could increase the risk of developing obesity that beyond being a chronic state of inflammation, it is often complicated by heart disease, diabetes, and lung disease that have been demonstrated to increase the risk for more serious complications of CoVID-19 [15]. Quarantinerelated stress also results in sleep disturbances that in turn further worsen the stress and increase food intake thus giving rise to a dangerous vicious cycle. Therefore, it is important to consume food containing or promoting the synthesis of serotonin and melatonin at dinner. A considerable variety of plant species including roots, leaves, fruits, and seeds such as almonds, bananas, cherries, and oats contain melatonin and/or serotonin. These foods may also contain tryptophan, which is a precursor of serotonin and melatonin. Protein foods such as milk and milk products are the main sources of the sleep-inducing amino acid tryptophan. Moreover, tryptophan is involved in the regulation of satiety and caloric intake via serotonin that mainly lowers carbohydrate and fat intake, and inhibits neuropeptide Y, the most powerful hypothalamic orexigen peptides [16]. Further, beyond sleep-inducing properties, milk products such as yogurt could also augmented natural killer cell activity and reduce the risk of respiratory infections [17] During quarantine the increased intake of macronutrients could also be accompanied by micronutrients deficiency as occurs in obesity [18], which is commonly associated with impaired immune responses, particularly cell-mediated immunity, phagocyte function, cytokine production, secretory antibody response, antibody affinity, and the complement system, thus making more susceptible to viral infections [19]. Thus, during this time it is important to take care of nutritional habits, following a healthy and balanced nutritional pattern containing a high amount of minerals, antioxidants, and vitamins. Several studies reported that fruits and vegetables supplying micronutrients can boost immune function. This happens because some of these micronutrients such as vitamin E, vitamin C, and betacarotene are antioxidants. Anti-oxidants increase the number of T-cell subsets, enhance lymphocyte response to mitogen, increased interleukin-2 production, potentiated natural killer cell activity, and increased response to influenza virus vaccine compared with placebo [20]. Beta Carotene is most abundant in sweet potatoes, carrots, and green leafy vegetables while sources of vitamins C include red peppers, oranges, strawberries, broccoli, mangoes, lemons, and other fruits and vegetables. The major dietary sources of vitamin E are vegetable oils (soybean, sunflower, corn, wheat germ, and walnut), nuts, seeds, spinach, and broccoli. In addition, quarantine could be associated to a less time spent outdoor, less sun-exposure, and reduced production of vitamin D as a result of lower levels of 7-dehydrocholesterol in the skin. Vitamin D deficiency in winter has been reported to be associated to viral epidemics. Indeed, adequate vitamin D status reduces the risk of developing several chronic diseases such as cancers, cardiovascular disease, diabetes mellitus, and hypertension that significantly higher risk of death from respiratory tract infections than otherwise healthy individuals [21]. Further, vitamin D protects respiratory tract preserving tight junctions, killing enveloped viruses through induction of cathelicidin and defensins, and decreasing production of proinflammatory cytokines by the innate immune system, therefore reducing the risk of a cytokine storm leading to pneumonia. Since the time spent outdoor and consequently the sun exposure is limited, it is encouraged to get more vitamin D from diet. Foods containing vitamin D include fish, liver, egg yolk and foods (e.g., milk, yogurt) with added vitamin D. Another essential trace element that is crucial for the maintenance of immune function is zinc. It has been reported that zinc inhibited severe acute respiratory syndrome (SARS) coronavirus RNA-dependent RNA polymerase (RdRp) template binding and elongation in Vero-E6 cells [22].

Some group scientists [23-26] say that aside from interventional trials involving vitamins and supplements in COVID-19, data have also been published regarding serum levels of vitamins, minerals, and nutrients and their role in COVID-19.89,90 Most of the data involve vitamin D levels. A full review of deficiencies in COVID-19 is beyond the scope of this article, but representative studies are discussed below to better contextualize supplementation in COVID-19. Interested readers can find a more in-depth analysis on this topic in the cited review articles. Several retrospective studies found a relationship between vitamin D levels and COVID-19 positivity rate. Amongst patients aged >70 years old, one study showed that patients positive for COVID-19 had significantly lower median vitamin D levels compared to those negative for COVID-19 (9.3 ng/mL versus 23.1 ng/mL, respectively; p=0.037). Similarly, another study found positive COVID-19 tests were associated with deficient vitamin D status (defined as <20 ng/mL) at the time of testing (relative risk 1.77, 95% CI 1.12–2.81; p=0.02). Moreover, a third study demonstrated an association between low vitamin D levels (defined as <30 ng/mL) and an increased likelihood of COVID-19 infection (p<0.001) [27-29].

Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is expressed on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses. Vitamin D has previously been proposed to have antiviral effects, which led to a theoretical benefit of its use as an adjuvant in treating COVID-19 infections [30]. Several retrospective studies have addressed an observed correlation between low serum vitamin D levels and severity of the course of COVID-19 disease symptoms, which is evaluated later in this paper [31].

Vitamin C, a water-soluble vitamin, plays various roles, including supporting connective tissues through collagen synthesis, wound healing, and enhancing the immune system through its bactericidal properties and antibody boosting [32]. It has previously been proposed as having a theoretical benefit in immune defence against COVID-19 infection, based on its known properties and hypothetical, inconsistent evidence supporting its role in symptom mitigation in the common cold [33]. Additionally, various studies have demonstrated the positive effects of vitamin C against Epstein–Barr virus, enterovirus/rhinovirus-induced acute respiratory distress syndrome, and severe sepsis and in mechanically ventilated patients with acute respiratory distress syndrome in the ICU [34-36]. IV vitamin C was investigated based on variable evidence of its use in critically ill patients and showed no mortality benefit but some symptom management benefit [37].

Magnesium has previously been shown to increase 25-hydroxyvitamin D levels when they are <30 ng/mL at baseline; [38] thus, if vitamin D helps protect against COVID-19, magnesium could in turn also be beneficial. So far, magnesium has only been studied in combination with vitamins B and D. The combination therapy showed significant decreases in oxygen support (including ICU support) ($p=0.006$); however, there were no significant differences in the outcome of oxygen support, excluding any ICU support [39].

Vitamin B12 has been observed to play a fundamental role in gut microbiome [40], which can affect the innate immune response [41]. Some data report that SARS-CoV-2 RNA was found in the stool of patients testing positive for COVID-19, implying that there could be involvement of the gut–lung axis in COVID-19 infections. Additionally, one study demonstrated that the faecal microbiome of patients testing positive for COVID-19 was significantly altered compared to a control group [42]. Similar to magnesium, vitamin B has only been studied in combination with vitamin D and magnesium. As stated above, this combination therapy showed significant decreases in oxygen support (including ICU support) (p=0.006); however, there were no significant differences in the outcome of oxygen support, excluding any ICU support.

Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids. The proposed immune-related mechanism of action of zinc is through enhancement of the innate anti-infective properties of basophils, eosinophils, and neutrophils [43]. Some weak evidence supports the use of zinc in mitigating symptoms of the common cold [44-46]. Additionally, zinc has demonstrated inhibition of RNA polymerase in vitro but this has not been studied in SARS-CoV-2 [47,48]. Zinc supplementation has been minimally studied in COVID-19; however, one trial demonstrates that zinc, both alone and in combination with vitamin C, showed no significant decreases in COVID-19-related symptoms compared to no study intervention [49]. Zinc is crucial for normal development and functioning of cells mediating part of the immune system. She added that studies have shown that increased concentrations of zinc can inhibit the replication of viruses like poliovirus and SARS-coronavirus.

ALA is an anti-inflammatory and antioxidant. It has previously been shown to decrease the levels of serum inflammatory cytokines and inflammatory-related symptoms in patients with acute coronary syndrome, liver transplantation, and kidney–pancreas combined transplantation [50-53]. Only one study investigated the use of ALA in COVID-19, and this study demonstrated no significant differences in the Sequential Organ Failure Assessment (SOFA) score by day 7 of therapy or mortality [54]. SOFA is a validated scoring system used to predict mortality in ICU patients [55].

Such tools may be useful during the COVID-19 pandemic. Probiotics were recommended by only one institution,11 which did not provide a specific amount or examples of food sources. Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.” [56] They can act through diverse mechanisms, including modulation of immune function, production of antimicrobial compounds and organic acids, improvement of gut barrier integrity, formation of enzymes, and interaction with resident microbiota. [57] Studies of probiotic species belonging to the Lactobacillus and Bifidobacterium genera have shown promising results regarding improved immune function. [58] Fermented dairy products might be a good option to improve the gut microbiota, although further studies are needed to better elucidate the modulatory mechanisms of the microorganisms in these foods. Only one agency provided guidance on alcohol consumption. The Food and Agriculture Organization of the United Nations20 recommended that alcohol intake be limited, but no specific amounts were provided. Excessive alcohol consumption is associated with reduced host immunity to viral infections and increased susceptibility to tuberculosis and bacterial and viral pneumonia in humans and animals. [59] On the other hand, some benefits of moderate alcohol consumption have been reported, including reduced risk of cardiovascular disease, alleviation of acute stress, improved mood, and increased relaxation. [60] Current guidelines for moderate intake recommend no more than 1 drink per day for women and no more than 2 drinks per day for men. It should be noted that individuals who do not drink alcohol should not start drinking. Finally, generic terms and phrases such as "healthy diet," "variety of foods in each group," "variety of fresh and unprocessed foods," and "varied diet" were observed in the majority of the documents. These messages might not be clear enough to encourage people to make healthy food choices. Specific recommendations, including examples of food and instructions for food preparation, would improve the public health message.

All documents reported that there are currently no known supplements to prevent COVID-19. Only 2 documents mentioned that it might be possible to use supplements to meet dietary recommendations. Some vitamins and minerals improve immunity; however, the idea that more is better is a misconception. Megadoses of vitamins and minerals can induce toxic and adverse effects [61,62] or interact with medications, leading to enhanced or reduced pharmacological effects [63]. On the other hand, it is important to note that

Dietary Reference Intakes have been established for healthy individuals and are based on a diet providing 2000 kcal/d [64]. Thus, healthcare professionals should individualize dietary plans by considering factors that can increase nutrient requirements, such as specific diseases/conditions, medications, dietary patterns (eg, vegetarianism), and exercise intensity. For this purpose, the range from the Recommended Dietary Allowance to the Tolerable Upper Intake Level can be used to optimize the dietary plan [65]. The Brazilian Association of Clinical Nutrition11 reported that vitamin C supplementation may be useful for individuals at risk of respiratory viral infections. Vitamin C is a recognized antioxidant nutrient that can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and, ultimately, microbial killing [66]. However, a systematic review involving 10 708 participants showed that doses of vitamin C exceeding 1 g/d were not beneficial in reducing the incidence of colds among the overall population [67]. On the other hand, such doses might be effective in reducing the duration of colds by 8% to 18%. In addition, vitamin C may be useful to prevent the development of colds in people exposed to brief periods of intense physical activity or to cold temperatures [68]. Vitamin D is another antioxidant that has been associated with a reduction in pulmonary infections [69,70]. Evidence that vitamin D can prevent or treat influenza is inconclusive [71], but vitamin D status has been associated with the severity of COVID-19. Potential mechanisms include increased secretion of antimicrobial peptides, decreased production of chemokines, inhibition of dendritic cell activation, and altered T-cell activation [72]. None of the documents reviewed here suggested vitamin D supplementation as preventive therapy against COVID-19. However, Rhodes et al31 suggested that countries south of latitude 35 north have low population mortality, which might indicate a role of vitamin D in determining outcomes from COVID-19. When deficiency is detected, oral supplementation with doses between 2000 and 4000 IU/d is indicated.11 Although a higher dose has been recently proposed with the aim of reducing the risk of infection (vitamin D3, 10 000 IU/d for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d) [73], this is still controversial and contradicts other recommendations. Since it is not feasible to recommend biochemical analysis of vitamin D levels during a pandemic, targeting vulnerable populations for vitamin D supplementation can mitigate the health risks associated with COVID-19, especially since vitamin D deficiency has been shown to correlate with hypertension, diabetes mellitus, obesity, and darker skin pigmentation. Although it may be controversial, vitamin D supplementation to prevent deficiency may, at the very least, provide benefits by sustaining bone mass during lockdown. Zinc and selenium are antioxidant micronutrients often considered for supplementation. Zinc is a cofactor of superoxide dismutase, an enzyme present in the mitochondria and cytosol of cells that suppresses oxidative stress. Excess zinc, however, also causes cellular oxidative stress [74]. A narrative review showed ample evidence of the antiviral activity of zinc (10 mg/kg of body weight, up to 600 mg/d total) against a variety of viruses, such as influenza [75]. In addition, zinc is critical in generating both innate and acquired (humoral) antiviral responses. However, the authors concluded that further research is needed on the antiviral mechanisms and clinical benefits of zinc supplementation as a preventative and therapeutic treatment for viral infections. A recent study suggested that the elderly are at risk for zinc deficiency, which increases susceptibility to infections such as pneumonia.

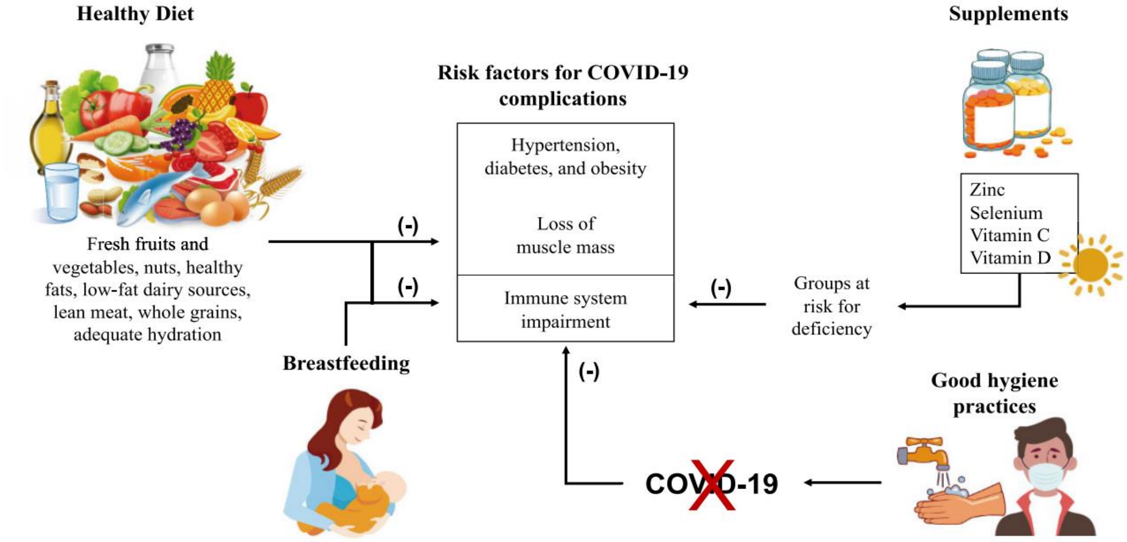

Figure 1. *Rationale for dietary recommendations during the coronavirus disease 2019 (COVID-19) pandemic. Key nutrients that support the immune system can be obtained through dietary components that include fresh foods (eg, fruits and vegetables), fish, lean meat, dairy, water and other non-sugary beverages, and healthy fats. A healthy diet can also decrease the risk of, or help control, hypertension, diabetes, obesity, and muscle atrophy, which are all considered risk factors for COVID-19 complications. There are no known supplements that can prevent COVID-19; however, in populations at risk of deficiency, supplements can mitigate the public health risks associated with COVID-19. Breastfeeding benefits an infant's immune system, protecting against viruses and bacterial infections. The use of personal protection, such as masks, along with good hygiene practices, such as frequent handwashing with soap and water or alcohol-based sanitizers, can prevent COVID-19 transmission and immune system impairment. Symbol: (-): inhibitory effect.*

Zinc supplementation (ie, elemental zinc, 30 mg/d) might be adequate to improve immune function and to reduce the risk of infections in this group [76]. Selenium has been found to increase the activity of glutathione peroxidase, another antioxidant enzyme, and to augment a number of host immune responses, including interferon c production, T-cell proliferation, antigen stimulation, and natural killer cell activity. In fact, an experimental study with mice and influenza virus showed that selenium deficiency led to more severe disease and an increased proinflammatory immune response, resulting in increased pathology in the lungs. Selenium is an important trace element that can be found in nuts, breads, grains, meat, poultry, fish, and eggs and is easily obtainable from dietary sources (see the Dietary recommendations section). In summary, it is preferable to obtain antioxidants from food rather than from supplements. However, supplements are recommended for individuals who have specific challenges in meeting dietary requirements. The key message regarding dietary supplements is that individuals should not rely on supplements to prevent COVID-19. Further studies into the effects of vitamin and mineral supplementation on outcomes related to COVID-19 (eg, disease severity, inflammatory status, hospitalization, death, etc) are warranted. Currently, several clinical trials on vitamin D (n ¼ 21), vitamin C (n ¼ 15), zinc (n ¼ 15), and selenium (n ¼ 1) supplementation are under way (www.clinicaltrials. gov). It is hoped that the results of these studies will lead to a better understanding of the relationship between micronutrients and COVID-19.

Figure 1 describes the rationale behind the dietary guidance and the personal hygiene practices recommended during the COVID-19 pandemic, along with the potential mechanisms linking diet and the prevention of COVID-19 complications. De Faria Coelho-Ravagnani, C., Corgosinho, F. C., Sanches, F. L. F. Z., Prado, C. M. M., Laviano, A., Mota, J. F gave own conclusions in own article [11]: This review summarizes recent scientific literature and existing recommendations from national and international nutrition agencies on an optimal diet, vitamin and mineral supplementation, and good hygiene practices for food preparation during the COVID-19 pandemic. The findings can be used to help dietitians and healthcare professionals better address dietary recommendations during the COVID-19 pandemic. Guidance related to the safe handling of food, from production to consumption, is critical to reduce the risk of viral dissemination. The general recommendation is to consume a diet based predominantly on fresh foods such as fruits, vegetables, whole grains, low-fat dairy sources, and healthy fats (olive oil and fish oil) and to limit intakes of sugary drinks and processed foods high in calories and salt. Dietary supplements (ie, vitamins C and D, zinc, and selenium) should be administered to individuals with, or at risk of, respiratory viral infections or in whom deficiency is detected. Breast milk is the safest and healthiest food for infants, and breastfeeding should be encouraged, even in women diagnosed with COVID-19.

Conclusion: In conclusion, in this article we have discussed nutritional recommendations for COVID-19 disease, nutrition acquisition by human immunity, transient overnutrition and the cytokine storm in severe cases of COVID-19 and dietary recommendations during the COVID-19 pandemic. It should also be noted that this article cited several vitamins and their clinical analysis in relation to COVID-19. The findings of several scientists were analyzed. Hopefully, this article will be an impetus for in-depth research.

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