Effects of Potential Micro- and Macro-nutrients in Combatting COVID-19

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Abstract

Purpose of Review Gain insight on the effect of some recently studied nutrients and nutritional markers on the COVID-19 disease course.

Recent Findings In vitro studies indicate that SCFAs do not interfere with SARS-CoV-2 infectivity. Observational studies indicate that eating processed or red meat three or more times per week had overall higher risk of pneumonia. Studies suggest that markers of regular outdoor physical activity (high HDL, lack of vitamin D deficiency, lack of obesity, etc.) prevent severe complications of COVID-19.

Summary Although no definitive nutrients were found to significantly alter the COVID-19 disease course, some therapeutic candidates such as calcium, vitamin D, and albumin were surmised. Other nutrients that modulate serum lipid levels, cytokine levels, and albumin levels may hold promise for prevention of morbid or fatal outcomes related to COVID-19, as does the reduction of red or processed meat consumption.

Keywords COVID-19 · Inflammation · Pneumonia · Micronutrients · Cytokine storm · Lipotoxicity · Cholesterol · Vitamin D · Calcium · Albumin

Introduction

Since the start of the COVID-19 pandemic, the World Health Organization (WHO) and Centers for Disease Control (CDC) estimate that by the end of August 2021, there will have been more than 4.48 million deaths worldwide and more than 635,000 deaths in the USA from the SARS-CoV-2 infection [1]. The true level of transmission and calculation of mortality rate is frequently underestimated. Approximately, 80% of the population remains undetected due to asymptomatic status or failure to present to health care facilities due to mild symptoms [3]. Several reports from within the U.S and worldwide cohort groups have identified groups with high-risk characteristics that contribute to a poor prognosis. In patients infected with SARS-CoV-2, disease severity and outcomes are related to the components of the inflammatory cascade and although the exact molecular mechanism is not known, empiric treatments have targeted components of this signaling cascade to reduce morbidity and mortality [2].

The COVID-19 world-wide pandemic has led to huge financial implications with the closure of major businesses and travel. The healthcare system was burdened beyond capacity with a lack of resources and a sudden surge in unemployment left many Americans without employer-sponsored insurance [4]. The viability of a number of hospitals and office-based practices were threatened, leading to the closure of several private practices nationwide. In the first few months of the pandemic, office-based practices had reductions of 60% in volume with a loss of more than 1 million jobs in the health care system [4]. The American Hospitals Association estimated a loss of over $323 billion at the end of the first year due to the pandemic [4]. However, with recurrent surges, utilization of novel therapies, and development and distribution of the COVID-
19 vaccine, the true financial costs of COVID-19 on American healthcare continue to grow.

It is prudent for any healthcare provider to consider the impact of widely available nutrients on altering the infectious disease course when making recommendations to at-risk patients or populations during a pandemic. This information is especially valuable for populations who might not have access to affordable healthcare, novel investigational therapies, or sufficient biomedical equipment.

Inflammatory Response to SARS-CoV-2 Infection

In the process for controlling and resolving the infection by the SARS-CoV-2, an induction of a complex immune response occurs that involves all the immune system components. Once the presence of the virus is recognized by the innate system, the immune response is initiated by production of pro-inflammatory cytokines which activates the specific adaptive response. That response includes natural T-cell killers and the production of specific antibodies by B-cells. These cytokines also amplify the inflammatory response by attracting macrophages and neutrophils, but the imbalance appears to be related to a severe COVID-19 disease course.

The severe inflammatory response seen in COVID-19 is usually characterized by lymphopenia and malfunction of lymphocytes, monocytes, and granulocytes. This increases the possibility of a subsequent superinfection by other micro-organisms and ultimately multi-organ failure [5].

Risk Factors and the Natural History of COVID-19-Related Inflammation/ARDS

The infection by SARS-CoV-2 is characterized by multiple manifestations, ranging from completely asymptomatic to mild common cold-type-related symptoms, which represents most patients (about 80% with myalgia, prolonged fever, diarrhea, and neurological symptoms like anosmia and hypogeusia), to moderate (15%), and severe (5%) disease characterized by acute respiratory and multiorgan failure which can lead to death. The infection can affect any age group or sex, but most commonly affect patients who are of advanced age, immunocompromised, obese, and/or have respiratory and cardiovascular comorbidities; this group of patients carries the greatest mortality rate.

Pathophysiology

The infection is acquired when an infected individual expels micro-droplets of respiratory secretions full of viral particles which can be sustained in the air or deposited in fomites, until they contact the respiratory tract of a susceptible individual. When the virus contacts the bronchial epithelium, its port of entry is the type-II ACE2 + pneumocytes receptor whose expression becomes inhibited and allows the angiotensin II free to bind the AT1aR receptor, generating acute lung damage and its manifestation, severe acute respiratory syndrome (SARS) [5]. The main characteristic of acute respiratory distress syndrome (ARDS) seen in SARS is the peripheral depletion of T-cells, which appears to be a crucial factor in crosstalk between immune homeostasis and microbial overload, and can be used as a prognosis factor related to disease progression and severity.

Inflammatory Cytokines

Another characteristic seen in COVID-19 infection is an unbalanced or excessive immune response known as cytokine release syndrome, which is related to shock state, ARDS, multiorgan organ failure, and potentially death in patients with severe COVID-19. During this cytokine storm, the production of all pro-inflammatory elements can be elevated: IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1α, IFN-γ, and TNF-α; but the most commonly elevated in severe cases are IL-1β, IL-6, and IL-10. There is a correlation between the elevation of these inflammatory cytokines and acute lung injury and mortality, which can represent a prognosis factor and a therapeutic option for patients with severe disease [6].

The cytokine storm is a complex process where, after SARS-CoV-2 is recognized by the innate immune system, CD4 + T cells are activated into T helper (Th) 1 cells which release GM-CSF and induces CD14 + CD16 + monocytes with high IL-6 levels to favor local inflammation and stimulates CD14 + IL-1β + monocytes which increase IL-1β production. The sustaining of the cytokine cascades is related to Th17 which produces IL-17 to recruit more monocytes, macrophages, and neutrophils to the site of infection [6].
Lipotoxicity and Lipid Mediators of Inflammation

Cholesterol homeostasis is integral in maintaining cellular wellness due to its function in maintaining membrane integrity and modulating its fluidity and segregation. It plays an important role in regulating immune function and equilibrating the inflammatory process. As SARS-CoV-2 is a single-stranded RNA virus surrounded by a lipid envelope, it initially requires a lipid attachment to the membrane of the targeted cell to then proceed with fusion and endocytosis. Lipid raft microdomains serve as a deck for virus entrance and delivery of viral genome and can facilitate this pathological process when the concentration of the lipid rafts receptors is increased. Membrane composition and homeostasis influence the susceptibility of developing viral infections and it has been proposed that elevated plasma cholesterol levels can play an important role in infection by SARS-CoV-2, likewise low cholesterol levels can reduce its infectivity. Studies in vitro have shown that depletion of membrane-bound cholesterol ACE2-expressing cells reduces the SARS-CoV-2 binding capacity for the spike protein by 50% [7*].

Cholesterol and fatty acid homeostasis also modulate viral infectivity by enhancing viral fusion when the Cholesterol/fatty acid ratio in the cellular membrane is elevated and by inhibiting its entrance with the appropriate presence of 25- and 27-hydroxycholesterol. In cases of moderate and severe COVID-19 infection, there have been reports of patient serum levels lower than 50% of normal for hydroxycholesterols, lanosterol, lathosterol, and desmosterol, all precursors of cholesterol. HDL particles, known to adapt to acute inflammatory conditions such as during the cytokine storm, can have an antiviral effect independent of their lipid envelope [7*]. Critically low HDL serum levels have been reported in severe COVID-19 patients. Although there is a clear relationship between the composition of lipid rafts and the infectivity and severity of SARS-CoV-2 infection, more research should be made in this area to avoid unsupported pathological and clinical implications.

Meat Consumption

Pneumonia is the most common high-risk complication of COVID-19 [35]. Macronutrient consumption might contribute to propensity of acquiring pneumonia. The UK Biobank study collected information on meat intake at baseline for 474,985 middle-aged adults and linked it to hospital admissions and mortality data. Participants who reported consuming red or processed meat three or more times per week had, on average, higher risk of pneumonia (HR 1.31, 1.18–1.44). Of note, these participants were more likely to smoke and consume alcohol and more poultry meat and consume less fruit and vegetables, fiber, and fish compared to the participants who consumed meat less than three times per week [30•]. Increased BMI observed to be associated with red and processed meat consumption might have caused residual confounding. However, another study found that higher intake of red meat was associated with a higher risk of death due to respiratory disease, including pneumonia [30].

Prebiotics and Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) such as butyrate have been demonstrated to mediate host-microbiota interaction in regard to regulating mucosal permeability and immune response. Starch, arabinoxylan-rich whole grains, and brans from cereals serve as substrates that stimulate the colonic microbial production of butyrate [32]. Because SARS-CoV-2 infection was shown to change microbiota and SCFA production, Pascoa et al. investigated in vitro the impact of SCFAs in the infection of human intestinal biopsies and intestinal epithelial cells by SARS-CoV-2. No change in entry or replication or release of SARS-CoV-2 in intestinal cells was found [34•]. Other studies have shown that butyrate increases cellular infection by H1N1 influenza A virus, reovirus, and human immunodeficiency virus 1 (HIV-1) due to suppression of specific antiviral interferon-stimulated genes [34]. Despite the lack of evidence that SCFAs interfere with SARS-CoV-2 infectivity or the suggestion that SCFAs might allow for increased viral loads, there may be other mechanisms by which prebiotics or SCFAs mitigate the harmful complications of COVID-19 related to inflammation and thrombosis.

Vitamin D

Vitamin D is a fat-soluble vitamin which has been linked to numerous immunological effects including supporting the induction of antimicrobial peptides, inducing autophagy, and aiding the synthesis of reactive nitrogen and oxygen intermediates [8–11]. Vitamin D deficiency has been shown to be associated with increased incidence of respiratory infections [12•]. In the context of COVID-19, multiple studies have proposed that vitamin D is protective from acquiring the infection and that vitamin D supplementation might be effective in reducing disease transmission [12]. Other studies have also proposed that vitamin D deficiency is associated with increased severity of COVID-19 infection [13, 14]. While the majority of these studies are underpowered and suffer from methodological
weaknesses, the evidence still suggests that vitamin D supplementation is a safe, cheap intervention which may be reasonable for use by patients at high-risk of COVID-19 infection [15]; however, it is possible that the health benefits attributed to sufficient levels of vitamin D might be associated with sufficient time spent on outdoor physical activity.

**Calcium**

While hypocalcemia is common in critically ill patients [16] and is often attributed to factors such as vitamin D deficiency, hypoproteinemia, hypomagnesemia, and drug interaction [16], the association of hypocalcemia with increased severity of COVID-19 infection cannot be overlooked. Hypocalcemia has been linked with worse outcomes in various diseases [16, 17], most recently COVID-19 [18–20]. While calcium might seem like an irrelevant bystander, its effects can be massive through different biochemical pathways; most recently, studies have suggested that serum calcium can exert its anti-inflammatory effects by neutralizing free fatty acids in the serum of sick patients, ameliorating lipotoxicity effects, and preventing end-organ failure [21–23]. Based on previous studies indicating calcium supplementation was able to reduce systemic inflammatory response, CRP levels, and local complications [25], the aforementioned studies have proposed that calcium supplementation should be tested as a therapeutic intervention to prevent the transformation from mild to severe COVID-19 infection.

**Albumin**

Serum albumin is a major plasma protein and indicator of morbidity and mortality, and recovery from acute and chronic disease [36, 37]. It is integral in maintaining intravascular oncotic pressure, carrying hydrophobic substances, participating in acid–base balance, and preventing platelet aggregation [25]. It is often misused as a surrogate marker of nutritional status in hospitalized patients [26]. Hypoalbuminemia has been associated with worse outcomes in hospitalized patients in various diseases including almost all organ systems [27]. Hypoalbuminemia has multiple proposed etiologies including underproduction due to malnutrition or decreased hepatic synthesis in liver disease or under the influence of inflammatory mediators, increased consumption during inflammatory and catabolic states and albumin loss in urine or through vascular leak. Severe COVID-19 is associated with reduced serum albumin, a finding seen in multiple studies since the onset of the pandemic [29]. Albumin supplementation has been a recurrent source of controversy over the past few decades with conflicting evidence. Its use has mostly been dependent on clinicians’ anecdotal evidence and personal opinion. Recently, studies have suggested that a temporal factor might be in play in the supplementation of serum albumin [21] with early supplementation resulting in a superior effect over late supplementation. While the controversy over albumin supplementation continues, albumin supplementation appears to be a safe and affordable intervention to be tested either by direct supplementation or by optimizing nutritional support to induce hepatic synthesis of albumin.

**Ongoing Studies**

Currently, there are human clinical trials ongoing looking at the effects of fish oil, olive oil, EPA/DHA, omega-3 fatty acids, Mediterranean diet, exercise, wine, and plant extract supplements on platelet-activating factor (PAF), its catabolic enzymes, and its effect on platelet aggregation. In hopes that micronutrient platelet aggregating factor inhibitors stem the harmful effects of COVID-19-related inflammation and thrombosis, investigators are continuing to study the effects of vitamin C, vitamin D, vitamin B12, zinc, fish oil, quercetin, honey, and others on COVID-19 [31].

**Conclusion**

As the search for effective treatments for COVID-19 continues, specific micronutrients and macronutrients may influence the severity of infectivity, symptoms, and outcomes related to this disease. While the data may show some promise for modulation of albumin, cholesterol, and circulating inflammatory cytokines by consuming more or less of a specific micro- or macro-nutrient, the available evidence is observational and may simply support the fact that obesity is an independent risk factor for poor outcomes when ill with COVID-19. Further research including prospective human clinical trials is needed to determine the most effective dietary recommendations for the prevention and treatment of COVID-19 and its complications.
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