REVIEW

Coronavirus Disease 2019 (COVID-19) and Nutritional Status: The Missing Link?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an emerging disease that has reached pandemic status by rapidly spreading worldwide. Elderly individuals and patients with comorbidities such as obesity, diabetes, and hypertension show a higher risk of hospitalization, severe disease, and mortality by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These patients frequently show exacerbated secretion of proinflammatory cytokines associated with an overreaction of the immune system, the so-called cytokine storm. Host nutritional status plays a pivotal role in the outcome of a variety of different infectious diseases. It is known that the immune system is highly affected by malnutrition, leading to decreased immune responses with consequent augmented risk of infection and disease severity. Body composition, especially low lean mass and high adiposity, has consistently been linked to worsened prognosis in many different diseases. In this review, evidence concerning the impact of nutritional status on viral infection outcomes is discussed. *Adv Nutr* 2020;00:1–11.

Keywords: COVID-19, SARS-CoV-2, BMI, obesity, undernutrition, sarcopenia, immune system

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease has rapidly spread across the globe, and as of 1st June 2020, 6 million cases of COVID-19 have been reported worldwide, including >371,000 deaths (1).

Age, diabetes, cardiovascular disease, immunosuppression, and organ failure are risk factors related to illness severity (2). SARS-CoV-2 infection is associated with a broad clinical spectrum, ranging from asymptomatic to the development of serious pneumonia, acute respiratory distress syndrome, and death. Data from 72,314 patients with COVID-19 show that the prevalences of mild, severe, and critical cases were found to be 81%, 14%, and 5%, respectively (2). Fever, cough, fatigue, muscle pain, diarrhea, and pneumonia are the most common manifestations of COVID-19, and may progress to acute respiratory distress syndrome, metabolic acidosis, septic shock, coagulation dysfunction, and organ failure, including liver, kidney, and heart (3–6).

COVID-19 patients usually present lymphocytopenia upon admission, and thrombocytopenia and leukopenia are frequent among those with serious illness (7). Furthermore, augmented concentrations of C-reactive protein and proinflammatory cytokines, such as IL-6, were also associated with severity (7, 8). The body's first reaction against viral infection is the triggering of rapid and synchronized innate immune responses. However, an excessive reaction may cause damage to human tissues (9, 10). It is postulated that hyperinflammatory aggression of the lungs, induced by disproportionate immune activation and coagulopathy, may be involved in disease progression and aggravation.

Nutritional status and diet modulate inflammation and immune function and may be adjusted to impact COVID-19 outcome. Herein, we will discuss the current available evidence concerning the role of nutritional status in COVID-19 patients, as well as the potential relevance of nutritional readjustment in the prevention and management of infection.

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Abbreviations used: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; ICU, intensive care unit; NK, natural killer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Nutritional Status and COVID-19

The unexpected and sudden appearance of new infectious diseases, such as HIV, severe acute respiratory syndrome, chikungunya virus, and now, the COVID-19 pandemic, has emphasized our vulnerability to newly emergent pathogenic agents. Host nutritional status has been accepted as a key factor in the outcome of a variety of different infectious diseases (11).

Obesity

A high prevalence of obesity is described among hospitalized patients with SARS-CoV-2 infection (12–16). In Spanish intensive care units (ICUs), 48% of the first patients admitted with COVID-19 were obese (14). Similarly, among 1482 of US hospitalized patients with COVID-19, 48.3% were obese (17). In the same way, a study from China showed that ∼43% of the hospitalized patients with COVID-19 were obese or overweight at admission (18). Obesity has also been associated with mortality and increased disease severity (12, 13, 15, 19). BMI of patients with cardiovascular disease and SARS-CoV-2 infection in the ICU is higher than that of patients without need for critical care (13). The same study also demonstrated higher overweight/obesity prevalence among nonsurvivors (13). Among the patients who died of COVID-19, obesity prevalence was found to range from 4.60% to 12.10% in Brazil and Italy, respectively (20).

Even though young individuals are at decreased risk of critical COVID-19, if obesity is a concomitant condition, patients are ∼2.0 times more likely to need critical care on admission (21). The association between younger patients with a BMI (kg/m^2) ≥25 and pneumonia at admission was also described, and low-flow supplemental oxygen and mechanical ventilation was necessary in such cases (22).

Thrombotic events potentially aggravate the course of COVID-19 (23), and obese patients are at increased risk (24). Obesity also inflicts detrimental consequences on lung physiology, such as reduced forced expiratory volume and forced vital capacity (25). Invasive mechanical ventilation in patients with COVID-19 has been reported to be positively correlated with obesity, independently of age and comorbidities (15).

Obesity is characterized by an excess of white adipose tissue, which is an extremely active organ with immunologic, endocrine, and metabolic functions (26). Adipose tissue–resident immune cells are important for tissue homeostasis and significant changes in their number and function are observed in obesity. Adipose tissue chronic low-grade inflammation in obesity is attributed to the expansion of effector T cells, including CD4$^+$ helper T (Th) cells and CD8$^+$ cytotoxic T lymphocytes, as well as to macrophage infiltration (27–32). Some studies also describe B-lymphocyte accumulation in animal models of obesity (33, 34), which, through interactions with T cells, increase inflammation (33). The preactivation of specific inflammatory cytokines in the expanded adipose tissue results in reduced antigen response and functional impairment of natural killer (NK) cells, dendritic cells, and macrophages (35, 36). One such immune dysfunction results in a dampened immune response to infections (37–39).

Remarkably increased concentrations of proinflammatory cytokines in patients with severe SARS-CoV-2 infection are considered to be among the most important causes of acute respiratory distress syndrome and multiple-organ failure (40). A balanced pro- and anti-inflammatory response is crucial for body homeostasis (41, 42). The loss or impaired function of one of the regulatory components can favor the "cytokine storm" phenomenon in tissues with exacerbated proinflammatory response, such as the lung and adipose tissue (43). As recently proposed by Ryan and Caplice (44), unbalanced local inflammation is associated with overreaction to viral spread, entry, and viral shedding, leading to amplification and maintenance of the immune response (44). The impaired inflammatory response contributes to the severity of lung lesions found in patients with influenza (45), and may play a key role in COVID-19 progression. We put forward the hypothesis that white adipose tissue acts as a relevant player in the disease, since SARS-CoV-2 enters human cells via angiotensin-converting enzyme 2 (ACE2), which is expressed not only in the lung and heart, kidney, liver, and blood vessels, but also abundantly in the white adipose tissue (46, 47), An additional interesting aspect is that there is adipose anatomical site–associated heterogeneity in the expression of ACE2, which is higher in the visceral depots (48). The enlarged visceral adipose pads in obese patients have been suggested to possibly act as reservoir for viruses, thereby increasing total virus load as a result of an "explosive systemic response of the angiotensin II and angiotensin II type 1 receptor axis" promoted by the tissue, and not perceived by the clinicians, who generally do not envisage white adipose tissue as a vital organ (47).

Obese individuals present additionally, a delayed capacity of IFN production, which allows higher viral RNA replication, consequently increasing the opportunity of the emergence of novel, more virulent viral strains (38, 49). Obesity is also associated with epithelial dysfunction and increased permeability, which could permit rapid virus shedding from the tissue and, consequently, faster spreading (50). Based on these data, it is possible to infer that obesity could have a potential role in the transmission of SARS-CoV-2 (51). In patients with influenza, obesity was related to virus shedding for an extended time (up to 104% longer) than that observed in lean individuals (52), whereas BMI was positively correlated with virus content in exhaled breath (53). Thus, apart from their increased susceptibility to infection, obese individuals could have a role in the augmentation of virus pathogenicity and transmission. Since 52% of the world's population are now obese or overweight (54), practical implications, such as a longer quarantine for obese people, should be considered (45).

It is also important to highlight that obese people may not benefit from a vaccine against SARS-CoV-2 to the same extent as healthy-weight individuals. An association between higher BMI and a greater decline in influenza antibody

titers 1-y post vaccination (55), as well as lower concentrations of vaccine-induced H1N1-specific antibodies in obese mice (56), were reported. Additionally, vaccinated obese individuals show double the risk of developing influenza (and influenza-like illness) compared with normal weight individuals (57). If the same is observed in COVID-19 patients, vaccination may not be an effective method for ensuring protection of the overweight population.

Anthropometric (i.e., BMI, waist and hip circumferences) and metabolic parameters (i.e., plasma glucose and insulin) have been used to evaluate the risk of COVID-19 complications (58). Assessment of insulin resistance, a robust indicator of altered metabolic health, impaired cardiovascular function, and cardiovascular disease–related mortality, is recommended (59) both in primary care, as well as in the evaluation of the potential risk and prognosis in patients with a positive SARS-CoV-2 test result.

It is worth noting that obese patients are at higher risk of the development of comorbidities, such as type 2 diabetes, hypertension, and cardiovascular disease (60). These comorbidities are increasingly associated with disease progression and poor COVID-19 outcome (61). In a meta-analysis with data from 76,993 patients, the prevalence of hypertension, cardiovascular disease, and diabetes in patients with COVID-19 was ∼16%, 12%, and 7%, respectively (62). The incidence of comorbidities was also determined in a meta-analysis of 6 studies: diabetes, hypertension, and cardio-cerebrovascular diseases were found to be 2- to 3-fold more prevalent in ICU/critical patients than in noncritical cases. These results highlight the susceptibility for worsened outcome among individuals with obesity-related comorbidities (63). In addition to increased propensity and worsened outcome in patients with previous cardiovascular metabolic disease, COVID-19 infection can, per se, induce cardiovascular complications, including heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias (64, 65). Diabetic individuals show an increased susceptibility to infectious diseases, especially influenza and pneumonia (65–67), and experience the disease with greater severity when infected with respiratory viruses (68–70).

At present, the reason why individuals with obesity-related comorbidities are at increased risk of severe COVID-19 infection is unrecognized; however, it may be associated with the ACE2 expression in adipose pads and adipose tissue capacity to induce systemic inflammation. ACE inhibitors and angiotensin II type I receptor blockers increase considerably the expression of ACE2, and these drugs are very commonly used for the treatment of patients with diabetes and cardiovascular diseases (71, 72). Thus, the higher ACE2 content could help internalization of the virus by cells, thereby increasing the severity of COVID-19 (73).

Serum concentrations of inflammation-related biomarkers are also considerably higher in patients with diabetes (74). Thus, such patients, when infected, may be at higher risk of developing the "cytokine storm," and consequently of worsened prognosis. In type 2 diabetes there is an imbalance between coagulation and fibrinolysis, leading to increased concentration of clotting factors and relative inhibition of the fibrinolytic system. Additionally, endothelial dysfunction with enhanced platelet aggregation and activation is observed in insulin resistance and type 2 diabetes, favoring the emergence of a hypercoagulable prothrombotic state (75).

Distancing measures aimed at the reduction of social interaction have been adopted in several countries as a measure to reduce the spread of SARS-CoV-2 infection (76). Given the potential risk of developing severe COVID-19, individuals with comorbidities should firmly adhere to protective measures. To decrease the risk of infection and severe disease, diabetic individuals should maintain strict glycemic control. Inadequate glycemic control is associated with several infections, such as pneumonia, endocarditis, and tuberculosis (77). Frequent monitoring of glycemia is even more important for obese individuals with type 2 diabetes, since medication adjustment to maintain blood glucose concentrations may be necessary to adapt to the new caloric requirements of reduced physical activity and energy intake imposed by quarantines (78). In addition, diabetic patients with heart disease or kidney disease may require specific care to stabilize cardiac/renal status (77).

Undernutrition

Undernutrition, a pathologic state in which dietary intake fails to meet the body's energy or nutritional requirements, can arise from inadequate intake of macronutrients or micronutrients, abnormally increased energy expenditure, defective absorption of nutrients, or any combination of these (79). Worldwide, there were an estimated 821 million undernourished individuals in 2017 (80), a condition widely prevalent in developing countries (81). Protein–energy malnutrition, as well as deficiencies in specific single nutrients, are largely related to increased risk of mainly occuring infectious diseases (82–85).

Immune cells show high energy expenditure (86), and energetic and nutritional demand is increased during periods of infection. For example, basal metabolic rate is significantly higher during a fever due to the activation of the immune response (87). Because immune cells have no substantial reserve of nutrients, glucose and amino acid uptake is required for immune system activation (88). Indeed, malnutrition induces a reduction in immune cell number, especially of T cells (81, 85, 89, 90). For instance, lower $CD4^+$ and $CD8^+$ T-cell numbers have been described in malnourished children (91). Moreover, malnutrition induces atrophy of primary lymphoid organs, reducing T- and B-cell numbers, leading to leukopenia (92). This reduced number of immune cells contributes to the impairment of the immune response in malnutrition (93).

Both under- and overnutrition have a great impact on adipose tissue mass, modulating the factors secreted by this tissue, such as hormones and cytokines. During starvation, the activation of immune cells is limited by adipokine signaling, which reduces nutrient consumption, and consequently, the body becomes more susceptible to infection (94). Leptin plays a pivotal role in reporting nutritional status to

immune cells by increasing glucose metabolism in T cells (93). Leptin concentrations are inversely modified in both extremes of body weight, being reduced in malnourished and increased in obese individuals. Experimental studies show that leptin receptor–deficient mice, as well as malnourished animals, present reduced viral clearance, diminished lung IFN-γ concentration, and lower survival during influenza-A pneumonia infection (95). It is known that body adiposity is extremely affected by protein–energy malnutrition, leading to reduced systemic leptin concentrations (96). Therefore, the impaired immune response in malnutrition may be related to poor nutrient intake and dysfunction in leptin signaling, critical factors for the activity and proliferation of immune cells (93). These findings suggest a crucial role of adipose tissue in the maintenance of immune defense in viral infections.

As described previously for obesity, undernutrition may also impact viral replication and pathogenicity. Increased oxidative stress in animal models was associated with virulence and incidence of reproducible genome mutations observed for coxsackievirus and influenza (97). Since this phenomenon was described for 2 distinct viral RNA families, it is possible to infer that malnutrition may affect the outcome of other virus-induced diseases (97).

ACE2, the receptor crucial to the SARS-CoV-2 entry into the host cells, is widely expressed in gastrointestinal cells, such as those of the intestinal epithelium. Therefore, the digestive system may also be affected by SARS-CoV-2 infection, leading to gastrointestinal disorders and impairment of the nutritional status of patients (98). Indeed, anorexia, diarrhea, vomiting, nausea, and mild abdominal pain were reported in COVID-19 patients (7). Anorexia is the most common among the digestive system–related symptoms, and it could be related to inflammation, hypoxia, dysregulated hepatic function, or represent the side effects of therapeutic drugs. Diarrhea is yet another common gastrointestinal symptom, affecting ∼2% to 50% of patients (99). The particular mechanism related to the pathogenesis of diarrhea in patients with COVID-19 is not fully elucidated; however, some possible causes are described: direct aggression to the digestive epithelium by the virus, side effects of antiviral drugs, or dysbiosis of the intestinal microbiota induced by antibiotics (99). Anorexia along with diarrhea could contribute to nutritional imbalance, and consequently to a delay in recovery (100, 101). Moreover, patients with COVID-19 and digestive symptoms were more prone to complications of acute respiratory distress syndrome (7). Clearly, the gastrointestinal symptoms of COVID-19 may be even more harmful in malnourished patients. This aspect could be of even more importance for the elderly, since a reduction in mobility along with a depletion of muscle mass and poor nutrient intake are frequently present in older adults (102).

Aging and Nutrition and COVID-19

Elderly persons are more susceptible to SARS-CoV-2 infection and experience a poorer outcome when compared with younger patients (7, 103, 104). Aging is associated with alterations in both the innate and the adaptive immune response, a process known as immunosenescence (105). Hematopoietic tissue (106, 107), lymphocyte number (108), proliferative and functional capacity of effector lymphocytes (107), and activity of NK cells (109) are all reduced in the elderly. These alterations induce a basal systemic inflammatory state, or "inflammaging" (110), and are associated with an augmented susceptibility to viral infection (111). High morbidity and mortality are observed in elderly patients with infections, especially those of the respiratory tract (112–114). This situation could be prevented through vaccination; however, vaccine efficacy in this population is greatly reduced in comparison to that in younger adults (115–119). Immunosenescence-related alterations, such as reduced concentrations of naive T and B cells, decreased B-cell diversity, and impaired antibody response to new antigens, result in diminished response to vaccination or new infection (108, 120, 121).

Nutritional deficiencies of micro- and/or macronutrients are frequent in older adults, as stated (122). Although there are few data regarding malnutrition in patients with SARS-CoV-2 infection, given the prevalence of severe disease among elderly patients it is likely that a significant proportion of these patients were undernourished at the time of hospitalization (123). In agreement with this hypothesis, the risk of malnutrition and malnutrition in individuals >65 y of age was 27.5% and 52.7%, respectively, in a cross-sectional study in patients with COVID-19 (124). Many reasons may be related to the higher prevalence of compromised nutritional status in older patients with COVID-19. First, a catabolic state induced by the inflammatory response to SARS-CoV-2 infection may induce skeletal muscle wasting. The concentrations of proinflammatory markers, such as C-reactive protein, TNF-α, and ferritin are usually augmented in these patients (125), and the utilization of albumin and even muscle protein may be needed to synthesize the acute-phase proteins (125). This is consistent with the hypoalbuminemia and low calf circumference observed in these patients (126, 127). Second, in addition to respiratory symptoms, gastrointestinal symptoms have been reported as being most prevalent in elderly patients with COVID-19 (7). Thus, digestive tract malfunction can exacerbate the poor nutritional status in older patients with COVID-19. Last, immunosenescence per se may contribute to potentialize all alterations in COVID-19 (128).

Sarcopenia

Sarcopenia is defined by impaired muscle strength, reduced muscle quantity/quality, and poor physical performance (129). The pathogenesis of sarcopenia is associated with proinflammatory cytokines (130, 131), and muscle mass and strength are inversely proportional to IL-6 and TNF-α plasma concentrations in healthy older individuals (131). Loss of muscle mass and function is a usual condition in the elderly, as well as in younger individuals with acute and chronic muscle-wasting diseases, such as cancer, chronic

heart failure, liver cirrhosis, and chronic infection (132). Studies have described that sarcopenia is a predictor of the risk of pneumonia in the elderly (132), and it is associated with mechanical ventilation, hospitalization time, and mortality in ICU patients (130, 132–134).

Sarcopenia may affect normal weight healthy and overweight/obese individuals, being different from weight loss or cachexia (135–137). Augmented fat mass associated with low muscle mass or high fat mass together with low muscle strength are known as sarcopenic obesity (138). Ectopic fat accumulation in skeletal muscle and other tissues is a characteristic of obesity (139). The increased fat content leads to mitochondrial dysfunction and induces the production of reactive oxygen species (134). This microenvironment is related to enhanced secretion of proinflammatory myokines capable of inducing muscle dysfunction (134). In turn, adipose tissue inflammation may be exacerbated by these proinflammatory myokines, supporting the condition of chronic low-grade systemic inflammation. This sets up a vicious cycle supporting inflammation of both skeletal muscle and adipose tissue, hence stimulating and maintaining sarcopenic obesity (134). As obesity has been related to a poor prognosis in patients with COVID-19, it cannot be discarded that sarcopenic obesity is an even more harmful scenario (133).

The sarcopenic phenotype is also associated with decreased physical activity (129). This is extremely relevant in terms of the COVID-19 pandemic, since many people are staying at home and are currently physically inactive (spending a long time sitting or lying down). Prolonged immobility is associated with muscle mass wasting within the first week of bed rest, which is even worse in individuals with the severe form of the disease (140). The duration of hospital stay of COVID-19 patients is, on average, between 11 and 15 d (141); thus, patients may be prone to developing sarcopenia.

Bearing in mind that sarcopenia may play a relevant role in COVID-19 outcome, Krznaric and colleagues (142) recently proposed the utilization of 2 clinical tools to assess nutritional risk and loss of muscle mass and function remotely by incorporating them into telemedicine processes and digital platforms. For a simple, preliminary diagnosis of sarcopenia, the Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls (SARC-F) questionnaire, which evaluates muscle strength, assistance with walking, rise from a chair, climbing stairs, and falls, may be adopted (143). The prescription of personalized nutrition care and support is recommended for patients whose questionnaire results are predictive of sarcopenia and poor outcome (142, 144, 145).

Concluding Remarks

The COVID-19 outbreak has brought a great challenge for all communities and health care systems worldwide. Considering the absence of specific therapeutic treatment and of an effective vaccine, countries are taking strong measures to contain the spread of COVID-19, ranging from increasing social distancing to community-wide quarantine.

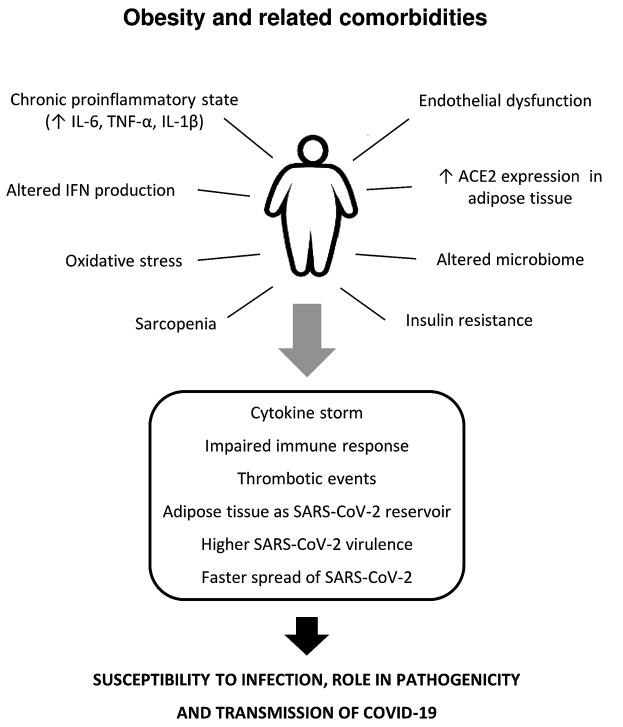

FIGURE 1 Obesity and related comorbidities are associated with physiological alterations leading to higher susceptibility to infection and pathogenicity and transmission of COVID-19. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Changes in dietary habits and lifestyle parameters, due to quarantine and social isolation, may lead to an impaired nutritional status. Obesity and related comorbidities are associated with physiological alterations leading to higher susceptibility to infection and pathogenicity and transmission of COVID-19 (**Figure 1**). Moreover, with no imminent end to the pandemic , people should be encouraged to improve their lifestyle to lessen the risks both in the current and likely subsequent waves of COVID-19. Healthy habits are important not only to ensure optimal immune response but also to prevent and/or treat undernutrition, obesity, and obesity-related comorbidities in COVID-19 patients. Therefore, clear advice on the impact of the nutritional status in COVID-19 outcomes should be provided to alert the population. Finally, it should be emphasized that nutritional status must be considered also in health policies designed to diminish the impact of COVID-19.

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