



Revisión

Hypothesis regarding the connections between severe COVID-19 in children and nutrition: a narrative review

Hipótesis sobre las conexiones entre COVID-19 severo en niños y nutrición: una revisión narrativa

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Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). Compared with adults, children with SARS-CoV-2 infection may have fewer and less severe symptoms. Gastrointestinal symptoms are commonly reported in children, sometimes as the only manifestation of the disease, and most often manifest as anorexia, diarrhea, nausea and vomiting, or abdominal pain. Although most children have asymptomatic or mild disease, 10 % of those infected may experience serious or critical disease, or even death. Multisystem inflammatory syndrome is a rare but serious condition recently reported in children with COVID-19. Studies indicate that children with obesity are at higher risk of developing severe COVID-19, and inflammation associated with obesity could be one of the factors that worsens COVID-19 symptoms due to an increased inflammatory response involving molecules such as interleukin 6, tumor necrosis factor alpha, and monocyte chemoattractant protein. On the other hand, evidence has been reported of a higher protein expression of ACE2 in the visceral adipose tissue of obese and malnourished humans, and this could be associated with complications and severity of COVID-19. Therefore, regulation of the intake of macronutrients or micronutrients could be used as a strategy to reduce the consequences of COVID-19. Diet in general and bioactive compounds could play an important role in the prevention of the inflammatory cascade. The micronutrients with the most evidence suggesting a role in immune support are vitamins C and D, zinc, and polyphenols.

Keywords:

Pediatrics. SARS-CoV-2. Inflammation. Nutrition. Oxidative stress. COVID-19.

Resumen

La enfermedad por coronavirus 2019 (COVID-19) está causada por el virus "síndrome respiratorio agudo severo-coronavirus 2" (SARS-CoV-2). En comparación con los adultos, los niños con infección por SARS-CoV-2 pueden tener menos síntomas y estos pueden ser menos graves. Los síntomas gastrointestinales se informan comúnmente en los niños, a veces como única manifestación de la enfermedad. Los más comunes son anorexia, diarrea, náuseas y vómitos, y dolor abdominal. Aunque la mayoría de los niños tienen un cuadro leve o asintomático, el 10 % de los infectados pueden experimentar un cuadro grave o crítico, e incluso la muerte. El síndrome inflamatorio multisistémico es una afección poco común, pero grave, que se documentó recientemente en niños con COVID-19. Los estudios indican que los niños con obesidad tienen mayor riesgo de desarrollar COVID-19 grave, y la inflamación asociada con la obesidad podría ser uno de los factores que empeoran los síntomas de la COVID-19 debido a una respuesta inflamatoria aumentada en donde se ven involucradas moléculas como la interleucina 6, el factor de necrosis tumoral alfa y la proteína quimioatrayente de monocitos. Por otro lado, se ha encontrado evidencia de una mayor expresión proteica de ACE2 en el tejido adiposo visceral de los seres humanos obesos y desnutridos, y esto podría estar asociado a las complicaciones y la severidad de la COVID-19. Por tanto, la regulación de la ingesta de macronutrientes o micronutrientes podría utilizarse como estrategia para reducir las consecuencias de la enfermedad. La dieta en general y los compuestos bioactivos podrían desempeñar un papel importante en la prevención de la cascada inflamatoria. Los micronutrientes con mayor evidencia indicativa de que desempeñan un papel en el apoyo inmunológico son las vitaminas C y D, el zinc y los polifenoles.

Palabras clave:

Pediatría. SARS-CoV-2. Inflamación. Nutrición. Estrés oxidativo. COVID-19.

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INTRODUCTION

Obesity or excess ectopic fat deposition is associated with the most important risk factors for developing severe coronavirus disease 2019 (COVID-19) as it reduces the protective cardio-respiratory reserves, promotes poor regulation of the immune system, and mediates progression to a critical state with organ failure (1); this remains true in children (2). It is known that obesity also favors the development of thrombosis in patients, which is relevant given the association between severe COVID-19 and disseminated intravascular coagulation and a high rate of venous thromboembolism. In addition to the cardiometabolic and thrombotic consequences, regardless of whether obesity determines lung function in terms of the immune response, there is a clear association between obesity and a state of chronic inflammation. In addition, it has been described that oxidative stress (OS) may contribute to the pathogenesis of COVID-19 by decreasing antioxidant levels and increasing the levels of pro-oxidant substances such as reactive oxygen species (ROS) in the lung parenchyma (3). On the other hand, the characteristic clinical profile of COVID-19 in children has been reported to start with gastrointestinal manifestations that may affect patient nutrient intake and nutritional status. Another way in which COVID-19 affects the nutritional status of children is the severe presentation of the disease, in which patients go through a critical stage secondary to a rapid progression of the complications of the disease. Critical illness induces intestinal dysfunction and dysbiosis, which extends and accentuates the inflammatory response, causing cellular dysfunction. This has recently been associated with the development of multiple organ failure. At the same time, it causes a loss of macronutrients and micronutrients due to the intense hypermetabolic and hypercatabolic response, leading to increased acute malnutrition, sarcopenia, and muscle weakness, and favoring the development of complications, multiple organ dysfunction, sepsis, and eventually death. Therefore, the aim of this review was to analyze the potential explanations for disease severity in children with COVID-19, as well as potential therapeutic and supportive nutritional strategies.

CORONAVIRUS DISEASE 2019 (COVID-19): PATHOPHYSIOLOGY, CLINICAL CHARACTERISTICS, AND SEVERE MANIFESTATIONS IN CHILDREN

SARS-CoV-2 AND CELL ENTRY

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA virus, approximately 30 kb in length, that is classified as a *Betacoronavirus* in the *Coronavirinae* subfamily. SARS-CoV-2 shares 79 % and 50 % of its genome sequence with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively (4). The genome encodes 9,860 amino acids and 27 proteins, including the spike (S) protein, a transmembrane trimetric gly-

coprotein projecting from the viral surface that determines viral tropism. The protein comprises two functional subunits, S1 and S2, which are responsible for viral attachment to the host receptor and viral fusion to the host membrane, respectively. SARS-CoV-2, like other coronaviruses, uses angiotensin-converting enzyme 2 (ACE2) as a functional receptor for cell entry, and has a higher affinity for ACE2 when compared to SARS-CoV (5).

ACE2 is an enzyme in the renin-angiotensin system (RAS), which involves a mosaic of factors that regulates arterial blood pressure and electrolyte balance (6). The presence of a local RAS has been described in several tissues; hence, ACE2 is in the cell membranes of tissues such as the lungs, ileum, colon, stomach, gallbladder, kidney, testes, arteries, heart, and others (7). The main function of ACE2 is to hydrolyze the peptide angiotensin II, which is a potent vasoconstrictor, to generate angiotensin-(1-7), a vasodilator (6). Differential expression of ACE2 may explain the differences in clinical manifestations between children and adults. In this respect, a recent study mentioned that children have higher levels of circulating ACE2 than adults (8), and since the S protein of SARS-CoV-2 has a high affinity for ACE2, the circulating ACE2 may neutralize the virus and prevent viral arrival at the target cells, and the spread of the infection. It is important to study whether the circulating levels of ACE2 are altered in children with severe COVID-19 and if a nutritional approach might improve the levels of ACE2 in the plasma, with the aim of reducing the severity of the infection.

CLINICAL MANIFESTATIONS IN CHILDREN

Pediatric coronavirus disease-19 (COVID-19) infection is relatively mild when compared to adults. As of June 19th, more than 8 million laboratory-confirmed COVID-19 cases and 450,000 deaths have been reported globally (9). Children represent 1-5 % of all patients diagnosed with COVID-19 and less than 3 % of hospital admissions. Compared with adults, children may experience fewer and less severe symptoms of the infection (10). The most common manifestations in symptomatic children are fever (41-56 %), cough (30-54 %), sore throat (6-46 %), and rhinorrhea (7-19 %) (11). Moreover, gastrointestinal symptoms have been commonly reported in this age group, sometimes as the only manifestation prior to the onset of respiratory symptoms (11). The most frequent gastrointestinal symptoms reported are anorexia (35 %), diarrhea (7-13 %), nausea and vomiting (6-11 %), and abdominal pain (6 %) (11). Other possible gastrointestinal manifestations of the disease in children are liver dysfunction or abnormal liver biochemical tests and ileitis (11).

These broad gastrointestinal manifestations may be caused by the direct invasion of SARS-CoV-2 into the intestine and liver cells that express ACE2 (7). Live viruses and viral RNA have been recovered from stool specimens in children, with longer RNA shedding than in respiratory samples. This demonstrates the presence of SARS-CoV-2 in the gastrointestinal tract and raises the possibility of fecal-oral transmission (12). However, liver disease may also be caused by the inflammatory response to the infection or multiple organ dysfunction in severe cases.

SEVERE DISEASE IN CHILDREN

Although most children have asymptomatic or mild illness, 10 % of those infected may develop serious or even critical illness leading to death (10). It is suggested that children with underlying conditions are at greater risk for more severe disease; however, these clinical observations are based on limited data and have insufficient evidence to support them (13). Some comorbidities suggested as risk factors for increased disease severity in children are chronic lung disease, severe immunocompromised status, cardiovascular disease, and obesity (13). Nevertheless, in children receiving immunosuppressive or immunomodulatory medication for cancer, renal disease, or inflammatory bowel disease, the proportion of patients with severe COVID-19 was low (14), probably due to modulation of the inflammatory response to the virus.

More recently, a multisystem inflammatory syndrome in children (MIS-C), as defined by the Centers for Disease Control and Prevention, has been reported as an uncommon but serious condition temporally associated with SARS-CoV-2 infection. MIS-C mainly occurs in older children and adolescents who have no apparent previous comorbidities (15-17). This syndrome is probably triggered by SARS-CoV-2, as some children have tested positive for viral infection by polymerase chain reaction (PCR) or serology (16,17). The high rate of IgG identification suggests a postviral or delayed immunological response to the virus (15-18). Children with this syndrome have elevated levels of the following inflammatory markers: C-reactive protein, procalcitonin, D-dimer, fibrinogen, ferritin, and interleukin 6. The levels of these inflammatory markers are presumed to correlate with the severity of disease (15,17). Clinically, patients may present manifestations resembling those of Kawasaki's disease: persistent fever, skin rash, bilateral conjunctival injection, oral mucosal changes, cervical lymphadenopathy, and peripheral extremity changes (15,17). However, gastrointestinal symptoms (abdominal pain, vomiting and diarrhea) are more common and are reported in 53-100 % of cases (15,17). Gastrointestinal manifestations precede the other symptoms, and respiratory symptoms may not be present (19,20). This reinforces the previous observation that GI symptoms are more common in patients with severe COVID-19 (21). Multiorgan damage, as seen in patients with MIS-C, includes myocarditis or myocardial injury, acute kidney injury, and shock (15-17,19,20). SARS-CoV-2 may directly cause these lesions, as these organs also express ACE2. However, organ dysfunction is seen after acute infection; therefore, the hyperinflammatory response and OS may be the leading causes of organ damage (22).

Table I summarizes the different characteristics associated with MIS-C in the reported cases (15-20,23-27). Notably, in a cohort of eight patients with MIS-C from London, 80 % of the patients were over the 75th percentile in terms of weight, suggesting that overweight and obesity are comorbidities associated with the syndrome (18). In 21 patients from France, 5 (24 %) met these criteria (17). Moreover, in another publication, 44 children with MIS-C were on average above the 75th percentile, and 39 % were above the 85th percentile (23). This suggests that overweight and obesity may be related to the severity of COVID-19 in children, as is seen in adults (28). Therefore, we reviewed the possible

mechanisms underlying the development of severe COVID-19 in children, including MIS-C, and the role of nutrition.

INFLAMMATORY RESPONSE IN CHILDREN WITH SEVERE COVID-19 AND OBESITY OR UNDERNUTRITION

Obesity is defined as an abnormal or excessive fat accumulation that presents a risk to health (29). Studies indicate that children with obesity are at greater risk of developing severe COVID-19 (23), and the inflammation associated with obesity could be one of the factors that may worsen the symptoms of COVID-19 in children, as seen in adults. The expansion of adipose tissue occurs via hyperplasia, which is defined as an increase in the number of adipocytes, or hypertrophy, which is an increase in the size of adipocytes. The latter is related to hypoxia, fibrosis, and inflammation. Adipose tissue releases free fatty acids that activate Toll-like receptor 4 (TLR4) in macrophages, increasing the inflammatory response. Additionally, in obesity, polarization to M1 macrophages occurs in adipose tissue, and these macrophages release inflammatory molecules such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α) and monocyte chemoattractant protein 1 (MCP1) (30). Therefore, obesity is considered a chronic low-grade inflammatory state, and this basal inflammation could lead to an exacerbated response to the virus and the development of severe COVID-19.

There is limited evidence about the levels of ACE2 in obese individuals. Studies in mice have shown that obesity increases the amount of ACE2 in lung epithelial cells (31), as well as ACE2 activity and protein levels in the adipose tissue (32). Interestingly, less information is available for humans. One study showed a tendency towards increased protein expression of ACE2 in the visceral adipose tissue of obese and malnourished humans; the same tendency was observed for other members of the RAS, such as angiotensinogen, ACE, and AT1 receptor (33). On the other hand, it is worthwhile to mention the opposite pole of obesity, when there is an energy deficit intake, such as an undernutrition status. In this condition, inflammation could worsen the symptoms of COVID-19 since protein-energy malnutrition has been strongly associated with inflammation. Additionally, the visceral adipose tissue of malnourished patients had elevated inflammatory markers such as IL-6 and TNF- α , similar to an obese condition (33). Nonetheless, more studies are needed to establish whether obesity or an undernutrition state may affect the amount of ACE2 in humans, and whether modulation of ACE2 and inflammation by nutrients could serve as a very attractive approach to the prevention of severe COVID-19.

ENDOTHELIAL DAMAGE IN CHILDREN WITH SEVERE COVID-19

Chronic cardiovascular diseases are related to the development of severe COVID-19, and a higher risk of thrombosis has also been described (34); therefore, endothelial cells have gained attention as a target to prevent complications of COVID-19.

Table I. Characteristics associated in children with the multisystem inflammatory syndrome temporarily associated with SARS-CoV-2

No. (%)											
Whittaker et al. (15)	Miller et al. (23)	Belhadj et al. (16)	Toubiana et al. (17)	Grimaud et al. (19)	Cheung et al. (24)	Verdoni et al. (25)	Riphagen et al. (18)	Chiotos et al. (26)	Licciardi et al. (20)	Jones et al. (27)	
Country	USA	France and Switzerland	France	France	USA	Italy	England	USA	Italy	USA	
Sample size	44	35	21	20	17	10	8	6	2	1	
Median age (range), yrs	7.3 (7 mo-20 yrs)	10 (2-16)	7.9 (3.7-16.6)	10 (2.9-15)	8 (1.8-16)	7.2 (2.9-16)	8 (4-14)	7.5 (5-14)	9.5 (7-12)	6 mo	
Male	20 (45)	18 (51)	9 (43)	10 (50)	8 (47)	7 (70)	5 (63)	1 (17)	2 (100)	1 (100)	
History of COVID- 19 contact	NR	13 (37) ^g	10 (48) ^g	NR	11 (65)	5 (50)	4 (50)	NR	NR	0	
Comorbidities ^a	NR	4 (11)	0	0	3 (18)	1 (10)	2 (25)	0	1 (50)	0	
Asthma	3 (5)	3 (8.5)			3 (18)	0	0		0		
BMI > 85 th centile or overweight	16 (36)	6 (17)	5 (24) ^h	NR	NR	NR	5 (63)	2 (33)	NR	NR	
<i>Kawasaki-like symptoms</i>											
Fever	44 (100)	35 (100)	21 (100)	20 (100)	17 (100)	10 (100)	8 (100)	7 (100)	2 (100)	1 (100)	
Rash or skin changes	31 (70)	20 (57)	16 (76)	10 (50)	12 (71)	8 (80)	4 (50)	2 (33)	2 (100)	1 (100)	
Conjunctival injection	23 (52)	31 (89)	17 (81)	6 (30)	11 (65)	8 (80)	5 (63)	2 (33)	2 (100)	1 (100)	
Lips or oral mucosal changes	23 (52)	19 (54)	16 (76)	5 (25)	9 (53)	6 (60)	NR	3 (50)	2 (100)	1 (100)	
Cervical lymphadenopathy	NR	21 (60)	12 (57)	2 (10)	6 (35)	1 (10)	NR	0	NR	0	
Peripheral extremity changes	NR	NR	10 (48)	NR	NR	5 (50)	NR	2 (33)	2 (100)	1 (100)	
Respiratory symptoms ^b	NR	12 (34)	9 (43)	0	7 (41)	NR	NR	4 (67)	0	1 (100)	
Gastrointestinal symptoms ^c	37 (84)	29 (83)	21 (100)	20 (100)	15 (88)	6 (60)	7 (88)	6 (100)	2 (100)	0	
Abdominal pain	33 (75)			20 (100)		NR	6 (75)	5 (83)	2 (100)		
Diarrhea	18 (41)			NR		6 (60)	7 (88)	4 (67)	2 (100)		
Vomiting	25 (57)			20 (100)		NR	4 (50)	5 (83)	2 (100)		
Neurological symptoms ^d	13 (29)	11 (31)	6 (29)	NR	8 (47)	4 (40)	2 (25)	3 (50)	0	0	
Myocarditis or myocardial injury ^e	22 (50)	35 (100)	16 (76)	20 (100)	11 (65)	5 (50)	7 (88)	4 (67)	2 (100)	0	
Vasoactive or inotropic support	22 (50)	28 (80)	15 (71)	19 (95)	10	2 (20)	8 (100)	5 (83)	1 (50)	0	
Coronary aneurysm (z-score ≥ 2.5)	NR	0	0	0	1	2 (20)	1 (12)	1 (17)	0	0	
Invasive mechanical ventilation ^f	1 (2)	22 (62)	11 (52)	8 (40)	0	0	5 (63)	3 (50)	0	0	
Acute kidney injury	7 (16)	NR	11 (52)	14 (70)	NR	NR	1 (12)	4 (67)	NR	0	
Death	0	0	0	0	0	0	1 (12)	0	0	0	
<i>Positive microbiologic testing</i>											
SARS-CoV-2 respiratory PCR	15 (34)	12 (34)	8 (38)	10 (50)	8	2 (20)	2	3 (50)	0	1 (100)	
SARS-CoV-2 serology	31 (70)	30 (86)	19 (90)	15 (75)	9	8 (80)	NR	5 (83)	2 (100)	NR	
Other viruses	0	NR	1 (5)	NR	3	0	1 (12)	NR	NR	0	

SARS-CoV-2: severe acute respiratory syndrome by coronavirus 2; COVID-19: coronavirus disease 2019; No (%): number of patients displaying clinical features (percentage); mo: months; yrs: years; BMI: body mass index; PCR: polymerase chain reaction; NR: not reported; USA: United States of America. ^aComorbidities not including overweight or obesity. ^bRespiratory symptoms: cough, coryza or dyspnea. ^cGastrointestinal symptoms: abdominalpain, diarrhea or vomiting. ^dNeurological symptoms: headache, vision changes, meningeal irritation, cranial nerve palsy, confusion or altered mental status. ^eMyocardial injury: diminished ventricular function on echocardiogram or biochemical evidence of myocardial dysfunction. ^fInvasive mechanical ventilation for cardiovascular compromise or respiratory support. ^gHistory of COVID-19 contact or contact with a family member displaying viral-like symptoms. ^hBMI > 75th centile.

The available information shows that SARS-CoV-2 can infect human blood vessels *in vitro* (35). Since ACE2 is expressed in the endothelial cells that line the blood vessels in multiple organs, SARS-CoV-2 has the capacity to enter those blood vessels and activate an inflammatory response. Recently, an article suggested that SARS-CoV-2 facilitates the development of endotheliitis in several organs in adults. Histological analysis showed the recruitment of inflammatory cells, which can lead to endothelial dysfunction and apoptosis. This could in part explain the impaired microcirculatory function and ischemia found in COVID-19 patients. If we consider that patients with cardiovascular diseases are prone to endothelial dysfunction (36), it is understandable that SARS-CoV-2 infection worsens the inflammatory condition and contributes to the poor prognosis. It is still unknown why children with chronic ailments such as chronic pulmonary disease and obesity are prone to developing MIS-C (37), but a hypothesis is that the presence of a local RAS in endothelial cells and vascular smooth muscle cells (VSMCs) means that ACE2 is embedded in those cell membranes; hence, if SARS-CoV-2 is able to enter and replicate in those endothelial cells, it is plausible that when the virus leaves those cells, it will be able to infect the neighboring cells, the VSMCs. This could increase local inflammation and worsen vasculitis (Fig. 1).

OXIDATIVE STRESS IN CHILDREN WITH SEVERE COVID-19

OS is defined as an imbalance between ROS and antioxidants, leading to cell damage (38). This imbalance is related to the devel-

opment of complications generated by obesity, inflammation, and the immune response. In addition, some viral infections are also known to contribute to increased OS, and have been associated with impaired immune responses (22). All of these factors are known to play major roles in the severity of COVID-19. OS increases the pathological inflammatory response, which is crucial for viral replication and the subsequent development of the disease associated with the virus. The association of severe cases of COVID-19 in children with an elevated BMI may be directly related to a predisposition to OS generation (39). In fact, there are associations between OS, inflammation, and the pathogenesis of SARS-CoV infection (22).

MIS-C, which is temporarily associated with SARS-CoV-2 infection, is similar to Kawasaki's disease, which is characterized by systemic vasculitis caused by inflammation of the blood vessels and subsequent damage to the coronary arteries (40). During the inflammatory process, cells release a number of ROS at the site of inflammation, leading to an exacerbation of OS (41). In addition, ROS can initiate an intracellular signaling cascade that increases the expression of pro-inflammatory genes through the activation of transcription nuclear factor B (NF- κ B), resulting in an exacerbated inflammatory response of the host by inducing the expression of genes such as TNF- α and IL-6, and upregulating inflammatory molecules such as vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and other genes that are overexpressed in SARS-CoV-2-infected patients (10).

These excessive ROS levels not only generate OS but also promote the generation of oxidative damage through the oxidation of various biomolecules such as lipids, proteins, and DNA. Oxidative

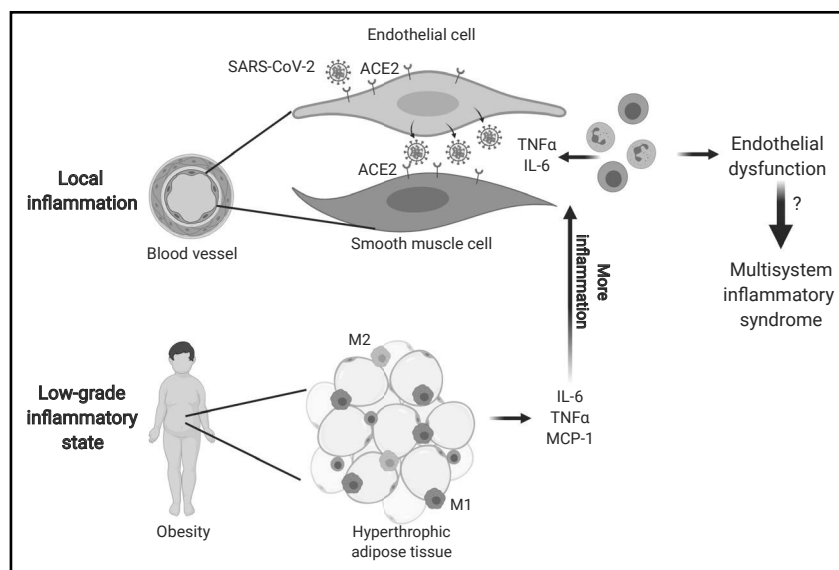


Figure 1.

Hypothesis on the pathogenesis of endothelial damage and vasculitis during obesity and SARS-CoV-2 infection. Blood vessels are constituted by an internal layer known as endothelium, and their neighboring cells are vascular smooth muscle cells (VSMC); both express a local RAS including ACE2. SARS-CoV-2 could infect endothelial cells, multiply, and infect smooth muscle cells, generating inflammation. A pre-existent condition such as obesity with hypertrophic adipose tissue, which releases inflammatory molecules, could worsen the local inflammatory response leading to the vasculitis that is present in the multisystem inflammatory syndrome of children. M1: macrophages M1; M2: macrophages M2; IL-6: interleukin 6; TNF- α : tumor necrosis factor alpha; MCP-1: monocyte chemoattractant protein 1.

damage to proteins and lipids causes alterations and dysfunction in cell signaling; several morphological and functional modifications are promoted by ROS, such as the oxidation of thiols and the downregulation of glycoproteins involved in processes such as cell adhesion, angiogenesis, inflammation, and apoptosis (42). During the infection process, the production of ROS is exacerbated because the activation of the immune system also involves the activity of pro-oxidant hemoproteins such as NADPH oxidase and myeloperoxidase. These enzymes are capable of participating in oxidative reactions leading to the formation of the oxidized protein 3-NitroTyr, which is associated with acute and chronic vascular and pulmonary diseases (43). In addition, excessively high ROS levels promote the oxidation of low-density lipoproteins, which in turn promotes a pro-inflammatory environment, inhibits endothelial nitric oxide synthase, promotes the retention of macrophages in the arterial wall, stimulates the proliferation of vascular smooth muscle cells, and disrupts endothelial function (44). This is very important because these alterations likely play important roles in disturbances in the redox homeostasis of red blood cells, resulting in anemia and the formation of blood clots, which may be associated with the inflammation of blood vessels seen in children with SARS-CoV-2 infection (20). Oxidative damage is increased in obese children due to reductions in the activity of enzymes in the endogenous antioxidant system, and in the levels of endogenous antioxidants such as glutathione (45). Thus, these data suggest that in children, chronic inflammation and OS are essential factors in the development of complications in the setting of SARS-CoV-2 infection. Therefore, regulation of the intake of macronutrients or micronutrients, including bioactive compounds with antioxidant or anti-inflammatory properties, could be used as a strategy to reduce the consequences of the severe inflammatory syndrome present in children during the late phase of SARS-CoV-2 infection.

IMPACT OF NUTRITION WITH REGARD TO REDUCING INFLAMMATION, OS, AND/OR ENDOTHELIAL DAMAGE

Can food and the bioactive compounds therein have an impact on reducing inflammation, OS, and/or the immune response? There is evidence to suggest that isolated nutrients, diet in general, and bioactive compounds could play important roles in the prevention of the inflammatory cascade due to their anti-inflammatory and antioxidant activities (46,47). Although there are conflicting data, the available evidence indicates that supplementation with multiple micronutrients that have immune support functions can modulate immune activity and reduce the risk of infection. The micronutrients and bioactive compounds with the strongest evidence suggesting their role in immune support, anti-inflammatory effects, and a reduction of ROS are vitamins C and D, zinc, and polyphenols. However, it is important to mention that it is necessary to satisfy the complex needs of the patient, including the synergy between macronutrients and micronutrients. Below, we focus on these bioactive nutrients/compounds with specific reference to the evidence regarding the factors underlying respiratory disease.

VITAMIN D

Evidence in children regarding vitamin D supplementation indicates that it reduces the incidence of influenza infection and other acute respiratory infections. This can be attributed to the fact that calcitriol (the active form of vitamin D) stimulates the expression of some antimicrobial peptides in epithelial cells, such as those that line the respiratory tract, protecting the lungs from infection (48). There is also evidence related to signals modulating the inflammatory response by modulating the activity of NF- κ B through the upregulation of the NF- κ B inhibitor protein (IB); in this way, the production of molecules that amplify the inflammatory response, such as IL-6, IL-1, and TNF- α , is inhibited, influencing the production of enzymes such as iNOS, COX-2, and PLA2, that determine the production of free ROS resulting in tissue damage (49).

One of the comorbidities suggested as a risk factor for increased severity of disease in children with chronic lung disease is obesity. Moreover, there is an association between obesity and vitamin D deficiency, and it has been proposed that fat-soluble hormones, including vitamin D, are sequestered in adipose tissue. This results in decreased bioavailability (50) and insufficient serum concentrations of vitamin D, which could compromise the regulation of pathways that promote the innate immune response while suppressing the adaptive immune response (51).

VITAMIN C

Vitamin C is involved in the function of the epithelial barrier, which protects against pathogens, and the cellular functions of the innate and adaptive immune systems; in addition, it protects against OS (52). In particular, it has been documented that vitamin C may protect against lung infections due to its immunomodulatory function and activation of inflammatory mediators. In addition, during infection, vitamin C levels may be depleted, suggesting that vitamin C supplementation could attenuate infections (53).

A systematic review of randomized clinical trials that included studies with children aged 3 months to 18 years evaluated whether the administration of vitamin C had an impact on upper respiratory tract infections (URTIs), which are generally caused by a viral infection; they found that the duration of URTIs decreased by 1.6 days; however, there was no difference in the incidence of URTIs; no serious adverse events were reported (54).

POLYPHENOLS

Polyphenols are compounds that form one or more hydroxyl groups in one or more aromatic rings, and are found naturally in fruits, vegetables, grains, and roots. Polyphenols have antioxidant activity, which may depend on the structure of their functional groups; for example, the number of hydroxyl groups strongly influences various mechanisms of antioxidant activity, such as radical scavenging and the capacity to chelate metal ions. This antioxidant activity is related to the ability of polyphenols to eliminate a wide range of ROS.

Curcumin is a bioactive polyphenol found in the spice turmeric, and it has been documented that it has various biological functions, such as antioxidative and anti-inflammatory activities, in different organs, including the adipose tissue. A recent study found that curcumin could bind the target SARS-CoV-2 receptors, ACE2, and could therefore compete with the virus; this activity could be used to prevent infection (55). Curcumin has also been reported to inhibit influenza virus infection by activating the nuclear antioxidant erythroid factor 2-related factor 2 (Nrf2) pathway, and inhibiting virus-induced inflammatory pathways (56).

This bioactive compound has been evaluated in children and adolescents (7-18 years) with persistent asthma in a randomized clinical trial. In the trial, powdered *Curcuma longa* root (30 mg/kg/day) was administered for 6 months, and they observed that after 3 and 6 months of supplementation, children had less frequent nighttime awakenings, less frequent use of short-acting beta-adrenergic agonists (SA β AA), and better disease control. These results were due to anti-inflammatory and antioxidant effects, which alleviated bronchial hyperreactivity (57).

The synergy of the administration of these micronutrients could produce a better response in a patient; in fact, it is reported that a combination of three bioactive compounds, namely vitamin C,

curcumin, and glycyrrhizic acid, showed a promising control over the production of interferons and regulated the inflammatory response, suggesting that these interventions may be useful for regulating the immune response to SARS-CoV-2 infection (58).

ZINC

Zinc is an essential trace element that plays an important role in the immune function, and the deficiency of this trace element has been associated with increased susceptibility to infectious diseases, specifically viral diseases. It has been observed that in pediatric patients with pneumonia on admission, zinc concentrations are below normal levels. Zinc depletion may be caused by the consumption of zinc by peripheral blood mononuclear cells during the inflammatory response (59). Zinc sulfate supplementation has been evaluated in children < 5 years old (10 mg for children younger than 1 year, 20 mg for children older than 1 year) with pneumonia, and improvements were observed in respiratory rate, oxygen saturation level, and disease duration; in addition, increases were observed in the concentrations of IFN γ and IL-2, resulting in an improvement of clinical symptoms mediated by the cellular immune response (60) (Fig. 2).

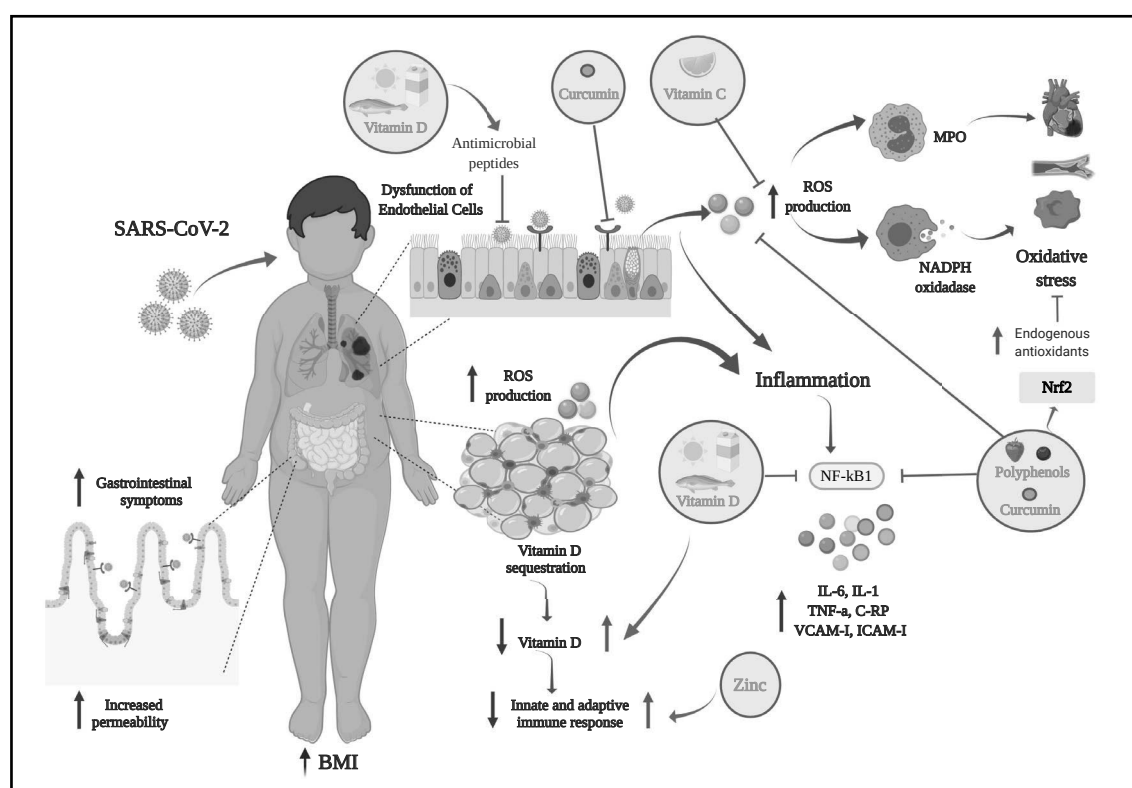


Figure 2.

Hypothesis of a possible interaction between the inflammatory process and oxidative stress in the complications caused by COVID-19 in children with obesity, and the impact of nutrition to reduce their response. ROS: reactive oxygen species; NF-KB: nuclear factor kappa B; IL-6: interleukin 6; IL-1: interleukin 1; TNF- α : tumor necrosis factor alpha; C-RP: C-reactive protein; VCAM-1: vascular cell adhesion molecule 1; ICAM-1: intercellular adhesion molecule 1; MPO: myeloperoxidase; NADPH oxidase: nicotinamide adenine dinucleotide phosphate oxidase; Nrf2: nuclear factor erythroid 2-related factor 2.

CONCLUSION

The pathophysiology of SARS-CoV-2 infection is characterized by aggressive inflammatory responses that are strongly implicated in the damage observed in the airways and organs; therefore, the severity of the disease in children is caused not only by the viral infection itself but also by the host immune response. Given this premise, it is reasonable to consider endothelial dysfunction, mediated by OS and inflammation, as a therapeutic target in COVID-19 patients. Therefore, it is important to discuss the role of nutrition as an adjunct therapeutic measure to decrease the inflammation and OS generated during infection. Additionally, another important factor affecting the severity of COVID-19 is the degree to which the patient is immunocompromised. In terms of nutrition, there is substantial controversy over whether specific nutrients could have an impact on 'improving' the immune system.

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