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Obesity as a Potential Risk Factor for COVID-19 in Children

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Abstract

In 2019, a new infectious disease, severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2), arose in Wuhan, China, and soon affected individuals worldwide. Early in the pandemic, there was minimal information about the severity of symptoms and whether the disease would affect children the same as adults. Currently, there is a higher transmission rate of SARS-CoV-2 among adults; however, new studies have demonstrated that pediatric patients with comorbidities are more likely to present severe symptoms. Different studies have demonstrated an association between an increase in the number of Angiotensin-converting enzyme 2 (ACE 2) receptors in adipose tissue and SARS-CoV-2. SARS-CoV-2 enters the cells by binding to ACE 2 receptors and therefore activates the renin-angiotensin-aldosterone system (RAAS), which leads to COVID-19 progression. Specific comorbidities, for example, obesity, can influence the severity of symptoms presented by pediatric patients and treatment complexity. Some of the symptoms seen in patients with COVID-19 include fever, cough, sore throat, sneezing, myalgia, or fatigue. In the worst-case scenario, acute respiratory distress syndrome (ARDS), shock, and multiorgan failure can occur. Studies have revealed that obesity is the third most common factor amongst pediatric patients with SARS-CoV-2 admitted into the intensive care unit. Pediatric patients with obesity present an increased risk for hospitalization because obesity impairs immune function, leads to chronic subclinical inflammation, and contributes to cardiorespiratory diseases. Due to the association between obesity and increased levels of inflammatory cytokines, pediatric patients with obesity who acquire COVID-19 present a higher mortality rate.

Keywords: Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, obesity, pediatrics, COVID-19, comorbidity, Coronavirus, cardiac damage, coagulation activity, inflammatory responses, child, adolescent

Introduction

In late 2019, the worldwide impact of the coronavirus disease 2019 (COVID-19) arose from the newly discovered cause of pneumonia in Wuhan, China. Initiating the COVID-19 pandemic, data was minimal. Despite the dramatically increased burden on the healthcare system worldwide since the identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), particularly the tiny proportion of children with confirmed cases among the general population brought a new hypothesis with the principal thought that children were not likely to be severely affected by SARS-COV-2 and only experienced mild clinical symptoms and favorable outcomes [1].

Children made a minority of infections worldwide. It was not until subsequent studies discovered that a large percentage were asymptomatic that specialists' concerns about whether children could develop severe disease grew [1]. As the pandemic progressed, some children experience a severe clinical presentation, and even the disease burden increase. Therefore, it was necessary to identify high-risk groups of children based on the data available at the moment [2]. The data on pediatric cases of coronavirus disease 2019 (COVID-19) have been reported very limited, and the etiology of epidemiology in children is still unknown. Furthermore, comorbidities such as obesity, diabetes,

heart disease, chronic lung diseases, and immunocompromised status are well known in the general population for the high prevalence of severe COVID-19 [3].

Although, in general, children represent a minority of the severe cases in this coronavirus pandemic, it was vital to define children as high risk for the severe disease to lower the risk of hospitalization and life-threatening complications. In a meta-analysis, it has been identified that children presented mild symptoms in 79%, who tend to have an excellent prognosis (95%CI 65−91%; I2 = 93.5%), whereas only 4% (95%CI 1−9%; I2 = 76.4%) experienced the severe disease [3]. However, it was not until several clinical studies conducted analyzed the relevance of obesity on COVID-19 severity, and there was directly correlated to general ICU admission (RR, 2.46; 95% CI, 1.08–5.63) and identified as a risk factor for severe disease in COVID-19 patients (RR, 1.43; 95% CI, 1.24–1.64) [2]. Unfortunately, during the COVID-19 pandemic, the increase in the rate of obesity called "covibesity" in children increase the prevalence of excess weight (overweight and obesity) from 23.9% in the pre-COVID-19 period to 31.4% in the COVID-19 period [4].

Obesity and COVID

Pediatric patients under 18 years of age account for an estimated 1.7% of severe acute respiratory syndrome coronavirus 2 (SARS-Co V-2) clinical infection in the United States, with estimates ranging from 2.0 to 4.8% globally [5]. Although the rate of transmission among pediatric patients is lower than adults, some implicating risk factors can lead to higher severity of disease course. Obesity is one of the most common comorbidities among hospitalized children with COVID-19 [5]. A retrospective study in Wuhan, China reported a higher body mass index (BMI) correlated with increased mortality risk in COVID-19 patients aged 14-45 years [6].

Obesity in pediatric patients was the third most prevalent demographic factor among children admitted to the ICU, with COVID-19; immunosuppression and cancer being the first and second most prevalent. In addition, as in adults, obese pediatric patients have been shown to have risk factors such as chronic subclinical inflammation, impaired immune response, and underlying cardiorespiratory diseases, making them more prone to hospitalization due to COVID-19 [6].

Angiotensin-converting enzyme 2 (ACE-2) has a dual role in the setting of COVID infection has been underlined: increased expression of ACE-2 may predispose to more massive exposure to the virus but may also avoid the RAAS-mediated lung injury in response to viral infection later [7]. Obesity is associated in humans and experimental animals with an imbalance in the RAAS system, resulting in an overexpression of the ANG II and AT1R axis at the systemic and adipose tissue levels [7]. This statement is reinforced by findings in obese rats showing that without adequate exercise, the deleterious ANG II and AT1R axis predominates despite the increased quantity of ACE-2. Healy et al. experimented and found that high-fat-fed rats showed an increase in expression of ACE-2 in the lungs, which might help explain the extent of severity among obese patients [6]. Furthermore, five obese pediatric patients who have been diagnosed with hypertension and are taking antihypertensive drugs from the angiotensin-converting enzyme inhibitor family or angiotensin receptor blockers have increased expression of ACE-2 receptor, making them more vulnerable to COVID-19 infection [5].

The primary entry route for SARS-CoV2 is through the upper respiratory tract or facial mucosal surfaces. Viral particles can enter cells by binding to ACE-2 receptors, followed by receptor-mediated endocytosis. Destruction of these receptors by the pathogen leads to a disruption in the Renin Angiotensin Aldosterone System (RAAS) and kinin-kallikrein system (KKS), which results in severe inflammatory and circulatory dysfunction [4]. The KKS regulates biological processes such as inflammation, pain and coagulation. Bradykinin regulates tissue plasminogen secretion (tPA); impaired function of KKS can lead to thrombus formation as seen in these patients [4]. In a subset of patients, there is a catastrophic hyperimmune pro-inflammatory response which, in turn, produces multisystem manifestations including prominent vascular permeability, hypercoagulable state, tissue inflammation, and destruction culminating into acute respiratory distress syndrome [7]. This series of events is caused by an increase of CD8+, CD4+, Th1, and Th17 compared to T reg and Th2, which have an anti-inflammatory function. Furthermore, adipose tissue secretes hormones such as leptin which induce the secretion of pro-inflammatory cytokines (IL-6, TNF-alfa and IL-1) by macrophages. This in turn suppress T reg and Th2's activity and promotes response by Th1. Opposite to leptin, adiponectin is another hormone secreted by adipose tissue with anti-inflammatory properties that has been observed in low levels in obese pediatric patients [4].

The severity of COVID in obese patients

The clinical presentation of COVID-19 has a wide range of severity. The severity rate also differs between the adult and pediatric populations, with children and adolescents generally having lower severity of COVID-19. Obesity has been recognized as independent risk factor for severity of COVID-19 infection [4]. Recent studies have confirm the hypothesis of obesity as a risk factor for more severe disease in obese children compared to children without comorbidities with a relative risk of developing severe form of COVID-19 equal to 2.87 [4]. It is not fully understood how obesity increases the severity of COVID-19 in children [4]. Although, the hypotheses include: A lower presence of comorbidities, higher capacity for pulmonary regeneration, and less expression of ACE2. This makes endocytosis for viral particles less efficient [6].

Adipose tissue can increase susceptibility and progression of COVID-19 infection through several mechanisms. ACE-2 functional receptor highly expressed in the adipose tissue activates the IFN-

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alfa pathway, and it could transform the adipose tissue into a potential viral target and reservoir [4].

The chronic inflammation state produced in obese patients with COVID-19 increases the risk of developing coagulopathies due to the negative regulation of anticoagulant proteins. Simultaneously, it produces a positive regulation of procoagulant factor and adhesion molecules. All those responses increase the risk of venous thrombosis in patients with COVID-19 and obesity [8]. The severe disease is associated with acute respiratory distress syndrome (ARDS), shock, and multiorgan failure [3]. Moreover, the severe disease requires ICU admission and mechanical ventilation or death due to the infection. A study describing clinical and epidemiological features in children and adolescents found that obesity and overweight were among the most prevalent comorbidities [2].

Prognosis

Obesity is associated with worsened prognosis in COVID-19 affected children. Obese people are likely to have more significant amounts of inflammatory cytokines, including tumor necrosis factor a (TNFa), IL-6, and IL-1b and C- reactive protein, because of increased pro-inflammatory macrophages and their high visceral fat [8,9]. In addition, pulmonary disorders such as obstructive apnea, Pickwick syndrome, and surfactant dysfunction may be present in obese children, leading to poor prognosis. In addition, obesity increases the risk of invasive mechanical ventilation [8]. Further, procedure difficulties can occur in obese children, like difficulty in venipuncture, and intubation, which might lead to prolonged hypoxia episodes during the procedure, resulting in a bad prognosis [6].

Obesity-related inflammation along with the COVID-19 hyperinflammatory response raises the susceptibility to severe COVID infection in children [9]. Obesity is associated with high mortality in young individuals infected with COVID-19. Underlying mechanisms include intensified inflammatory response, increased damage to the heart, kidney, and elevated coagulation activity. The imbalance of the inmune system in obese children may contribute to the intense and severe systemic inflammatory reaction called “cytokine storm” [8]. Moreover, obesity increases the risk of sepsis and multiorgan failure [8]. All the above factors might contribute to the bad prognosis in obese children with COVID-19 infection [6].

Conclusion

Our opinion article found that obesity is a risk factor that could aggravate COVID-19 in the pediatric population. High body mass index correlates with a higher risk of complications, and children with comorbidities are more likely to present severe symptoms and more hospitalization rates in the pediatric ICU. Considering obesity in the third place of the risk factors, preceded by immunosuppression and cancers as the first and second; evaluation of the symptoms and signs of alarm in the pediatric patients is an essential step in the treatment and clinical management of this disease. Children with obesity have a worsened prognosis and have a higher morbidity and mortality rate by COVID-19.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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