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COVID-19: Pathophysiology and implications for cystic fibrosis, diabetes and cystic fibrosis-related diabetes

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ABSTRACT

The novel SARS-CoV-2 coronavirus (COVID-19) has become a global health crisis since its initial outbreak in Wuhan, China in December 2019. On January 30, 2020, the WHO recognized the COVID-19 outbreak as a Public Health Emergency, and on March 11, 2020, it was declared a pandemic. Although all age groups have been affected, patients with cystic fibrosis (CF) and patients with type 1 or type 2 diabetes have been categorized as highly vulnerable to SARS-CoV-2 infection. Thus far, studies have found that the incidence of SARS-CoV-2 in the CF population is lower than the general population. We review the underlying protective mechanisms which may reduce inflammation and lung damage in CF patients, thus decreasing their risk of severe COVID-19. While the effect of SARS-CoV-2 in those with *diabetes* related to CF is unknown, other forms of diabetes have been associated with more severe disease. To further understand the potential impact of SARS-CoV-2 in cystic fibrosis-related diabetes, we provide a comprehensive overview of the potential factors contributing to COVID-19 severity in other forms of diabetes, including direct viral effect on the pancreas and indirect effects related to hyperglycemia and immune dysregulation.

Introduction

In 2019, the beginnings of a global pandemic emerged in Wuhan, China and was identified as novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This highly infectious virus triggers a cytokine storm and hyper-inflammation resulting in pneumonia and acute respiratory distress, although it is now evident that the virus affects more than the pulmonary system alone [1,2]. Among those most severely affected by the virus, there is a high prevalence of concomitant conditions including underlying respiratory disease and diabetes. It is therefore reasonable to hypothesize that individuals with cystic fibrosis-related diabetes (CFRD), who have both an underlying respiratory disorder and related insulin dependent diabetes, would be at high risk for morbidity and mortality with SARS-CoV-2 infection.

Approximately 40%–50% of people with cystic fibrosis (CF) will eventually develop CFRD [3]. CF is the most common life-threatening genetic disease in Caucasians and is caused by an autosomal recessive

mutation in the CF transmembrane conductance regulator (*CFTR*) gene [4]. This leads to viscous secretions in multiple organs, including the pancreas, presenting as pancreatic insufficiency in up to 90% of people with CF [5]. Inflammation and destruction of insulin-producing islet beta cells cause pancreatic endocrine dysfunction, resulting in progressive glycemic disturbance and subsequent negative impact on lung function, weight, and mortality [6–8]. It is postulated that the subsequent hyperglycemia may predispose those with CFRD to many of the same risks of severe disease with SARS-CoV-2 as those with type 1 and type 2 diabetes [9,10].

The aim of this manuscript is to characterize the effects of SARS-CoV-2 on individuals with CFRD. Due to limited data regarding the effects of the virus on this specific population, we examine the effects of the virus on those with CF and on those with type 1 and type 2 diabetes. We extrapolate our findings to suggest the likely impact of SARS-CoV-2 on those with CFRD.

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Epidemiology of SARS-CoV-2 in cystic fibrosis

In March 2020, when SARS-CoV-2 was declared a pandemic by the World Health Organization, it was suspected that the virus would have a significant impact on those with pre-existing conditions. It was a concern of the CF community that those with CF were especially vulnerable, and that individuals with CFRD were at even higher risk.

According to the Cystic Fibrosis Foundation (CFF) Patient Registry, the first CF testing for SARS-CoV-2 was performed on February 17, 2020 with the first positive test noted on March 16, 2020. Testing increased steadily throughout the months and by the end of August 2020, over 5500 tests had been performed on patients with CF, with over 270 of those reported as positive.

Contrary to initial suspicions, multiple studies have found that the incidence of SARS-CoV-2 in the CF population is lower than the general population [11,12]. In a retrospective, descriptive, observational study by Mondejar-Lopez et al. completed in Spain between March and May 2020, eight individuals with CF (one post-lung transplant) tested positive for SARS-CoV-2. The accumulated incidence in CF was 32/10,000 versus 49/10,000 in the general population and the general death rate was 5.85/10,000 versus none in the CF population [13]. Another study conducted in Belgium evaluated 149 patients with CF between April and May 2020 and measured their anti-SARS-CoV-2 IgM and IgG levels. A lower seroprevalence was noted in individuals with CF (2.7%) versus the general population (4.9%), suggesting a lower infection rate [14]. An overview study conducted in Italy concluded that the infection rate was indeed lower in the CF population than that of the general population [15,16].

In March 2020, the disease severity of SARS-CoV-2 in CF was yet undetermined and as a result, the Global Harmonization Registry group was mobilized to assess the worldwide impact of the virus on CF. An initial study, completed between February and April 2020, evaluated 40 cases from 8 participating countries and concluded that SARS-CoV-2 in the CF population has a spectrum of severity and outcomes very similar to the general population, and not necessarily worsened by the pre-existing CF [11]. The second round of the study, completed between February and June 2020, involved 19 countries with a cohort of 181 SARS-CoV-2 positive CF cases (0.21% of the CF population of all 19 countries). The second round had a similar conclusion as the initial study regarding severity and outcomes, but it found that a more severe clinical course may be associated with CFRD, increased age, decreased lung function and a history of transplant.

Specifically regarding CFRD, the second Global Harmony Registry study revealed that of the 181 cases, 56 (31%) had CFRD while 90 (50%) did not. However, 35 (19%) were unknown, suggesting the number with CFRD was likely higher. More concerning, out of the 7 deaths in the study, 4 (57%) were known to have CFRD, 2 were non-CFRD and 1 was unknown [12].

As of the writing of this manuscript, SARS-CoV-2 has resulted in 1636 confirmed infections and 14 deaths in the CF population. The incidence and mortality rates continue to remain lower than the general population, which may be attributable to established pre-pandemic protective behaviors of the CF population, as well as the generally younger population of CF patients.

Pathophysiology of SARS-CoV-2 and cystic fibrosis

Severe SARS-CoV-2 infection triggers a cytokine response that progresses to acute respiratory distress syndrome, which is a major cause of morbidity and mortality. This process is characterized by the excessive production of pro-inflammatory cytokines resulting in recruitment of monocytes, macrophages, and T cells to the lungs [16].

Cytokine dysfunction has been well studied in CF patients. A characteristic feature of inflammation in CF is neutrophil infiltration in the lung, leading to tissue damage due to excessive production of oxidants and proteases. This underlying cytokine dysfunction parallels the

pathophysiology of COVID-19 [17].

Previously, studies have shown that viral infections lead to approximately 60% of acute pulmonary exacerbations in CF. One factor that contributes to morbidity in CF is reduced antiviral immunity by airway epithelial cells, resulting in increased viral replication. Interestingly, in preliminary reports, SARS-CoV-2 did not lead to poor outcomes in CF patients. As noted above, this is likely attributed to the extraordinary precautions taken by the CF community in terms of social distancing and infection control. Another potential explanation could be that SARS-CoV-2 infects cells by different mechanisms when compared to other viruses such as influenza and respiratory syncytial virus.

Role of angiotensin converting enzyme 2 (ACE2) and Furin in SARS-CoV-2 infection

SARS-CoV-2 enters the host cells by using a spike protein (S protein) to bind to the ACE2 cell membrane protein (Fig. 1). Cellular entry is facilitated by Furin and Transmembrane protease serine 2 (TMPRSS2), as they cleave the S protein. ACE2 has a site that is potentially activated by Furin, which regulates epithelial sodium channel (ENaC) to facilitate sodium reabsorption. Therefore, both of these mechanisms play a critical role in infection. As we know, activation of Furin is increased in CF, which upregulates NLRP3 inflammasome complex, causing inflammation. Secondly, ENaC is significantly increased in CF, promoting inflammation and affecting airway surface liquid homeostasis.

Once intracellular, viral processing induced by hyperinflammation and/or CF-affected cellular processes (ionic imbalance, CFTR dysfunction, increased NLRP3 inflammasome activation) takes place exponentially. This leads to increased production of pro-inflammatory cytokines (IL-1 β , IL-6, IL-18 and TNF α) [17].

SARS-CoV-2, CF and IL-6

In most studies, IL-6 levels are reported to be increased in cases of severe SARS-CoV-2 infection, and these elevated IL-6 levels have been associated with higher mortality. Therefore, IL-6 is considered the key cytokine in the pathogenesis of cytokine storm. Marcinkiewicz et al. investigated cytokines levels in patients with advanced CF lung disease and found that patients' sputum contained extremely low levels of IL-6. Interestingly, IL-6 suppression was limited to the sputum, while systemic IL-6 production was normal [18]. The exact mechanism of IL-6 suppression in CF patients remains unclear. However, these data led the authors to hypothesize that constitutively low levels of IL-6 in the inflamed airway of CF patients may reduce the typical cytokine storm associated with severe SARS-CoV-2 infection, thereby limiting disease severity.

ACE2 Function, expression and variants

ACE cleaves angiotensin I (ANG I) to angiotensin II (ANG II), which is proinflammatory and results in lung damage. ACE2 processes ANG II to angiotensin 1-7, which is anti-inflammatory. Thus, a decrease in ACE and/or an increase in ACE2 would reduce inflammation and lung damage due to SARS-CoV-2. SARS-CoV-2 has also been reported to reduce ACE2 expression (interferon driven) in lungs, which is associated with acute lung injury [19].

Stanton et al. found that ACE2 mRNA was elevated and TMPRSS2 mRNA was decreased in CF airway epithelial cells compared with non-CF cells. Increased ACE2 is predicted to enhance SARS-CoV-2 binding to epithelial cells, but is also predicted to increase conversion of ANG II (pro-inflammatory) to the anti-inflammatory angiotensin 1-7. Thus, increased levels of ACE2 would reduce inflammation and lung damage due to SARS-CoV-2. Furthermore, decreased TMPRSS2 would reduce SARS-CoV-2 entry into airway epithelial cells. These findings could explain the limited severity of SARS-CoV-2 infection in CF patients.

ACE2 variants are rare, but they may account for some of the

Role of ACE and ACE2 in SARS-CoV-2 lung infection

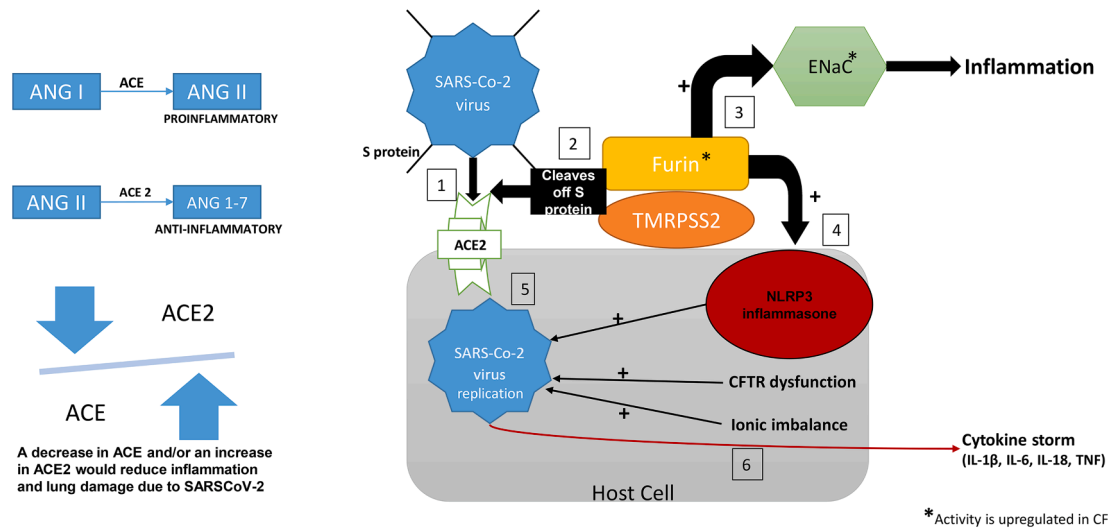


Fig. 1. Role of ACE and ACE2 in SARS-CoV-2 Lung Infection [15].

variability in the respiratory symptoms associated with SARS-CoV-2. Studies have identified several variants of the ACE2 gene, leading to the hypothesis that ACE2 polymorphisms may alter host susceptibility to SARS-CoV-2. Stawiski et al. examined ACE2 variants that predict SARS-CoV-2 susceptibility. They found that S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P, and H378R are predicted to increase binding to the S protein, and thereby increase susceptibility to infection. On the other hand, K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y are predicted to decrease binding to the S protein [20].

Other factors that might reduce susceptibility to SARS-CoV-2 infection in cystic fibrosis

Therapies commonly used in CF such as CFTR modulators and azithromycin may impact susceptibility to SARS-CoV-2. For example, CFTR modulators down-regulate activation of the NLRP3 inflammasome, which is the key regulator of inflammation in CF. In addition, CFTR modulator therapy reduces levels of pro-inflammatory cytokines (IL-1 β and IL-18). Many patients with CF are routinely prescribed azithromycin, which inhibits Furin, thereby reducing SARS-CoV-2 entry into airway epithelial cells. In addition, it reduces ENaC-mediated sodium reabsorption by airway epithelial cells, increasing mucociliary clearance of lung pathogens.

Epidemiology of COVID-19 in diabetes mellitus

Early in the pandemic, there was concern that individuals with diabetes may be more susceptible to infection with SARS-CoV-2 given defects in both innate and cell-mediated immunity [21,22]. Interestingly, several studies have reported a diabetes prevalence in those with SARS-CoV-2 that approximates the local prevalence, challenging the notion that diabetes increases the risk of infection [23].

As cases continue to rise, whether diabetes increases susceptibility to SARS-CoV-2 requires ongoing evaluation. It is clear, however, that diabetes is associated with increased risk of severe disease, as seen in previous outbreaks with H1N1 influenza [24], MERS-CoV [25], and SARS-CoV-1 [26].

Compared to individuals without diabetes, those with diabetes present with higher leukocyte and neutrophil counts [9,10], lower lymphocyte counts [10] and elevated markers of inflammation [10].

They also have evidence of renal dysfunction and abnormal coagulation [9,10]. Those with diabetes also require more intervention throughout their hospitalization including use of antibiotics [9,10], antifungals, systemic corticosteroids, immunoglobulin, vasoactive medications [10], oxygen supplementation [9,10], invasive and non-invasive ventilation [9,10], and extracorporeal membrane oxygenation [9,10].

The prevalence of COVID-related complications such as acute respiratory distress syndrome [9,10], acute heart injury [9,10], acute kidney injury [10] and septic shock [10] are higher in people with diabetes. Diabetes has also been shown to increase the risk of ICU admission and mortality [9–10,27–28]. In fact, compared to those without diabetes, individuals with type 1 and type 2 diabetes have a 3.5 and 2 times higher odds of an in-hospital COVID-related death, respectively [27].

Pathophysiology of COVID-19 and diabetes: Mechanisms of severe outcomes

Despite the overwhelming evidence linking diabetes to COVID-19 severity, the exact cause has yet to be identified. There are several hypotheses including direct impact from hyperglycemia, diabetes-related immune dysregulation or diabetes-associated pro-thrombotic disposition. Factors such as age, obesity and other comorbidities likely play a role as well. In addition, a direct viral effect on the pancreas may occur in some individuals with severe COVID-19 [29]. In the following sections, we review potential mechanisms to explain the more severe disease observed in individuals with diabetes.

Impact of hyperglycemia on illness severity

Hyperglycemia is associated with altered immune function, risk for secondary bacterial infections, and dehydration, all of which may impact COVID-19 severity [30]. It is also likely that hyperglycemia itself influences severity, although the relative contributions from long-term glycemic control, hyperglycemia at admission, and hyperglycemia during hospitalization remain undetermined.

The association between disease severity and glycemic control prior to infection is important, as it is a modifiable risk. While some studies have demonstrated an association between A1c and severity [22,31], others have not [32], and the impact of long-term glycemic control on outcomes remains unknown.

In contrast, the presence of hyperglycemia at the time of presentation

is clearly associated with disease severity [9,33,34]. Zhang and colleagues found that fasting glucose on admission was an independent predictor of death (HR 1.14) among 258 patients admitted with COVID-19 in China [9], many of whom had known diabetes mellitus. Other studies have demonstrated that admission hyperglycemia predicts severe findings on pulmonary radiographs [35] and death [33]. In fact, outcomes may be the worst in patients without a pre-existing diabetes diagnosis who are found to have hyperglycemia [33,36]. Despite evidence that admission hyperglycemia is associated with worse outcomes, the exact mechanism is unclear. Hyperglycemia may directly impair immune function, preventing viral clearance and leading to worse outcomes [37]. Given the physiologic stress of acute illness, it is possible that cortisol release and resulting hyperglycemia is a marker rather than a cause of severe COVID-19.

In-hospital glycemic control also seems to impact COVID-19 severity. Zhu and colleagues compared 282 patients with well controlled diabetes (glucose 70–180 mg/dL) to 528 patients with poorly controlled diabetes (one or more glucose >180 mg/dL). Relative to those whose diabetes was well controlled throughout hospitalization, those with poorly controlled diabetes required more intervention, including the use of oxygen supplementation and ventilation [10]. After adjusting for age, gender, COVID-19 severity, and comorbidities, mortality remained higher in those whose diabetes was poorly controlled during their hospital course [10]. Poor glycemic control during hospitalization is also associated with higher mortality in those without a previous diagnosis of diabetes [33], strengthening the notion that hyperglycemia during hospitalization impacts disease progression.

Direct pancreatic damage

Multiple cases of new onset diabetes in the setting of COVID-19 have been reported across the globe, raising suspicion that SARS-CoV-2 directly impacts the endocrine pancreas. It is unclear what proportion of cases are type 1 diabetes, type 2 diabetes or a novel form of diabetes [38]. The association between new-onset diabetes and severe COVID-19 could be explained by direct pancreatic effects in individuals with high viral load [39]. Interestingly, transient diabetes was also observed during the SARS-CoV-1 epidemic in 2003 [40].

As previously noted, SARS-CoV-2 cell entry is mediated by binding to ACE2, which is expressed in the islets of Langerhans [40]. Potential mechanisms for islet damage in COVID-19 include inflammation from ACE2 inactivation, cytokine-mediated destruction, direct viral infection, pancreatitis, and off-target drug effects [41]. The COVI-Diab registry is prospectively collecting cases of new onset diabetes in the setting of SARS-CoV-2 infection to better characterize this phenomenon [39].

Immune dysregulation in diabetes

Severe COVID-19 disease is characterized by a dysregulated immune response leading to lung inflammation and respiratory failure. Over-activation of innate immunity, apoptosis of T cells, and release of inflammatory cytokines are implicated in disease pathogenesis. Consistent with this view, elevation of the inflammatory markers ferritin and D-dimer, and cytokines IL-6 and IL-10 are associated with worse outcomes [41]. Diabetes itself is associated with immune dysregulation at multiple levels as well as chronic, low grade inflammation [42]. Therefore, patients with diabetes-associated immune dysregulation may be predisposed to the inflammatory cascades that result in severe COVID-19 disease. In fact, three studies have demonstrated higher elevations of inflammatory mediators in individuals with diabetes [10,43,44], supporting this hypothesis.

Thrombotic predisposition in diabetes

Thrombotic dysregulation is also a feature of severe COVID-19 and may contribute to worse outcomes in patients with diabetes. A US study

of 400 adults with COVID-19 found deep vein thrombosis in 4.5% and bleeding events in 4.8%, while disseminated intravascular coagulation (DIC) was rare, affecting <1% [45]. In addition, autopsy studies demonstrate diffuse pulmonary microthrombi in many patients who succumb to COVID-19. Both type 1 and type 2 diabetes are associated with increased thrombotic risk due to alterations in both clotting and fibrinolysis [46]. Altered hemostatic balance may add to the risk of severe COVID-19 lung disease among people with diabetes. In fact, biochemical data has demonstrated elevated D-dimer levels in patients with COVID-19 and diabetes, suggesting that thrombotic dysregulation may contribute to worse outcomes in this population [43,44]. Large vessel thromboses and bleeding events, on the other hand, do not appear to be higher in those with diabetes.

Age and diabetes

It is clear that advanced age is associated with more severe disease. Given the increased prevalence of diabetes in older individuals, age likely contributes to disease severity in this population as well. Indeed COVID-19 mortality increases with increasing age in type 1 and type 2 diabetes [22]. However, it should be noted that, in many studies, the increase in mortality remains significant after adjusting for age [10,27], suggesting that additional factors play a role. Diabetes duration has also been examined as a potential risk factor for severe COVID-19 infection. A prospective study of 26 adults with type 1 diabetes found no association between diabetes duration and COVID-19 severity [47].

Obesity and related comorbidities

Other factors contributing to COVID-19 severity in diabetes include obesity and associated comorbidities. Interestingly, COVID-related mortality in both type 1 and type 2 diabetes tends to be higher in those whose body mass index (BMI) is at either end of the spectrum [22]. It is unclear if this is due to a direct effect or if other factors associated with BMI, such as glycemic control and comorbidities, play a role. However, the CORONADO study found that BMI was the only predictor of intubation and death on multi-variate analysis. This suggests that much of the increased risk for severe COVID-19 in diabetes is mediated by obesity [32].

As with obesity, diabetes is associated with a variety of comorbidities, including cardiovascular disease [9,10], chronic kidney disease [9,10], hypertension and cerebrovascular disease [9] that may influence disease severity. After adjusting for cardiovascular disease, the odds of COVID-related death in those with diabetes is attenuated, but remains significantly higher relative to those without diabetes [27]. Further study is needed to evaluate the influence of other comorbidities on COVID-19 severity in diabetes.

Discussion

In general, SARS-CoV-2 infection is associated with increased morbidity and mortality in those with underlying diabetes, likely related to hyperglycemia, obesity and related co-morbidities with potential effects from immune dysregulation, thrombotic predisposition, increased age, and direct viral effect on the pancreas. As a result, in March 2020, when the WHO declared a pandemic, the medical community hypothesized that individuals with CFRD would be at increased risk for severe disease.

However, data suggest that the SARS-CoV-2 infection rate is lower in those with CF compared to the general population [11–16]. This is likely the result of rigorous infection control measures practiced by the CF community. Other factors, such as reduced TMPRSS2 mRNA expression and increased ACE2 mRNA expression in airway epithelial cells may also play a role. Furthermore, ACE2 variants [20] could alter host susceptibility to SARS-CoV-2 infection by decreased binding to the S protein, though this has not yet been studied in the CF population.

Although COVID-19 outcomes may be worse in those with underlying respiratory disease, there are several studies indicating that those with CF may possess physiologic protective mechanisms that reduce severity of disease. For example, individuals with CF have lower levels of sputum IL-6 compared to the general population, a factor that may attenuate disease severity [18]. Another protective mechanism may include higher levels of ACE2 mRNA [19], which may reduce inflammation and lung damage by increasing conversion of proinflammatory angiotensin II to anti-inflammatory angiotensin 1–7. Finally, CFTR modulators also play a role by down regulating the NLRP3 inflammatory, thus reducing pro-inflammatory cytokine levels. It should be noted, however, that the effect of CFTR modulators on COVID-19 severity has not been thoroughly investigated. Other factors, including the lower prevalence of obesity and airway clearance techniques, may also contribute to reduced disease severity in the CF population.

Evidence to date does not support a higher infectivity rate or increased disease severity in the general CF population [11–16]. However, preliminary data suggest that COVID-19 outcomes may be worse in those with *diabetes* related to CF [12], as seen in individuals with other forms of diabetes. Potential factors contributing to disease severity in diabetes include a direct viral effect on the pancreas [29] or indirect effects related to the hyperglycemia, immune dysregulation or prothrombotic disposition associated with diabetes. Additional factors, such as older age and increased body weight with the introduction of CFTR modulator therapy likely play a role as well. However, CFRD is a unique type of diabetes without the same underlying immune dysfunction or presence of macrovascular complications, which appear to worsen the severity of COVID-19. Therefore, despite limited data suggesting increased COVID-19 severity in patients with CFRD, it remains unclear whether CFRD truly increases morbidity and mortality.

Although significant progress has been made to understand the pathophysiology and outcomes of SARS-CoV-2, the virus remains under intense investigation. This, combined with the rapidly changing landscape of CF treatment, makes it difficult to draw conclusions on the impact of SARS-CoV-2 in CFRD. The widespread use of triple combination therapy, with its beneficial effects of improved pulmonary function, decreased inflammation, increased nutritional status, and decreased progression to CFRD may mitigate the potential COVID-19 risk factors of excess weight and older age also afforded by these therapies. Further studies are needed to determine the impact of SARS-CoV-2 in individuals with CFRD.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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