COVID-19 and diabetes mellitus: how one pandemic worsens the other

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Abstract

In light of the most challenging public health crisis of modern history, COVID-19 mortality continues to rise at an alarming rate. Patients with co-morbidities such as hypertension, cardiovascular disease, and diabetes mellitus (DM) seem to be more prone to severe symptoms and appear to have a higher mortality rate. In this review, we elucidate suggested mechanisms underlying the increased susceptibility of patients with diabetes to infection with SARS-CoV-2 with a more severe COVID-19 disease. The worsened prognosis of COVID-19 patients with DM can be attributed to a facilitated viral uptake assisted by the host’s receptor angiotensin-converting enzyme 2 (ACE2). It can also be associated with a higher basal level of pro-inflammatory cytokines present in patients with diabetes, which enables a hyperinflammatory “cytokine storm” in response to the virus. This review also suggests a link between elevated levels of IL-6 and AMPK/mTOR signaling pathway and their role in exacerbating diabetes-induced complications and insulin resistance. If further studied, these findings could help identify novel therapeutic intervention strategies for patients with diabetes comorbid with COVID-19.

Keywords COVID-19 · Diabetes mellitus · Angiotensin-converting enzyme 2 · Cytokine storm · Mechanistic target of Rapamycin (mTOR) · Adenosine monophosphate kinase (AMPK)

1 Introduction

Over the last two decades, severe acute respiratory infection outbreaks have accompanied a generalized global health concern. Two prominent coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV), have been associated with a high pathogenicity and mortality in humans [1]. SARS-CoV-1, which emerged from 2002 to 2003, caused over 8000 confirmed cases of infection and about 800 deaths, while MERS-CoV, which was first reported in 2012, is still present to date and has infected over 2300 individuals worldwide [1, 2]. Yet, these two coronaviruses never reached a level of pandemic.

In December of 2019, a series of pneumonia cases with unknown etiology were reported in Wuhan, a city in the Hubei province of China. High-throughput sequencing from lower respiratory tract samples revealed a novel coronavirus named 2019 novel coronavirus (2019-nCoV). However, as suggested by a recent study based on validated satellite imagery data of hospital parking lots and Baidu search queries of disease related terms, the virus may have already been circulating when the outbreak was declared. This recent evidence shows an upward trend in hospital traffic and search volume beginning in late Summer and early Fall 2019 as well as an increase in searching for the terms ‘cough’ and ‘diarrhea’, the latter being a more specific symptom for COVID-19 [3]. The increasing number of cases urged the World Health Organization (WHO) to declare a Public Health Emergency
of International Concern on January 30, 2020. The novel virus was then formally referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease as coronavirus disease 2019 (COVID-19). As testing became more available, the number of new cases increased exponentially, and on March 11, 2020, the WHO declared the outbreak a global pandemic [4].

Ever since its discovery in late 2019, SARS-CoV-2 has quickly spread to more than 200 countries around the world. As of June 28, 2020, more than 10 million cases of COVID-19 have been reported with a death toll of 501,469 individuals. Despite the low mortality rate of COVID-19, patients with co-morbidities such as hypertension, cardiovascular disease, and diabetes mellitus seem to be prone to more severe symptoms and to a higher mortality rate than others [5, 6]. Obesity also appears to worsen the prognosis of patients with COVID-19, specifically in younger obese individuals who seem to also be susceptible to a more severe disease [7]. Increasing evidence highlight diabetes mellitus as a distinct comorbidity associated with acute respiratory distress syndrome (ARDS) and increased subsequent mortality [6, 8, 9].

In the realm of social distancing imposed by the pandemic, the health care management system was found to be overwhelmed by the rapidly increasing demand on health facilities. The lack of previous preparedness was further challenged by fears of an imminent worldwide economic crisis that accelerated the race to understand the pathogenesis of SARS-CoV-2 in order to develop novel therapeutic strategies.

COVID-19 clinical signs are diverse, ranging from an asymptomatic state to ARDS and multi-organ dysfunction [10], with respiratory failure from ARDS being the leading cause of mortality [11]. COVID-19 symptoms generally manifest after an estimated incubation period of approximately one week (mean = 7 days, range = 0–24 days) [6]. The most common clinical features include fever, cough, and fatigue, while other symptoms include headache, hemoptysis, diarrhea, dyspnea, and lymphopenia [4, 12–15]. In a subset of patients, the disease rapidly progressed to severe chest pain, pneumonia and ARDS by the end of the first week [4]. In severe cases, SARS-CoV-2 virus targets both the upper and lower respiratory tract, causing irreversible injuries, notably pulmonary fibrosis [8, 16, 17]. COVID-19-associated pulmonary complications are exacerbated in patients with co-morbidities such as hypertension, cardiovascular disease, obesity and diabetes mellitus [5–7].

In this review, we detail our present understanding of the pathogenesis of SARS-CoV-2 and elucidate possible mechanisms behind the increased susceptibility of patients with diabetes to infection with more serious complications.

2 COVID-19 pathogenesis

2.1 The immune response to SARS-CoV-2

COVID-19 belongs to the coronavirus family, a large family of single-stranded enveloped RNA viruses that is divided into four genera: Alpha-, Beta-, Delta- and Gammacoronavirus [18]. Coronaviruses from the genera Alpha- and Betacoronavirus are primarily associated with infections in mammals, while viruses in the genera Gamma- and Deltacoronavirus mainly infect birds [18]. Both SARS-CoV-1, the virus responsible for the 2002 outbreak, and SARS-CoV-2, belong to the β-genus [19]. Many of the symptoms caused by SARS-CoV-2, such as ARDS, are quite similar to those resulting from SARS-CoV-1 [15]. These similarities can be traced back to the structural analogy between the two virus’ envelope-anchored spike (S) protein, which mediates their entry into the host cells [20]. Extensive studies on SARS-CoV-1 have identified key interactions between its S protein receptor-binding domain (RBD) and its host receptor angiotensin-converting enzyme 2 (ACE2), which control its cross-species and human-to-human transmissions [20, 21]. SARS-CoV-1 and SARS-CoV-2’s respective S proteins share a 76% to 78% sequence analogy for the whole protein and a 73% to 76% sequence similarity for the RBD, strongly suggesting that both viruses share the same access door to host cells: the angiotensin-converting enzyme 2 (ACE2) [19] (Fig. 1).

Besides, SARS-CoV-2 infection leads to an increased release of pro-inflammatory cytokines and chemokines including interleukins IL-1β, IL-4, and IL-10, monocyte chemoattractant protein 1 (MCP-1), interferon-γ (IFN-γ), and interferon-gamma-induced protein 10 (IP-10) [15]. Notably, ICU patients with severe disease had significantly elevated plasma levels of IL-2, IL-6, IL-7, IL-10, granulocytes colony stimulating factor (GCSF), IP-10, MCP-1, macrophage inflammatory protein-1A (MIP-1A), and tumor necrosis factor-α (TNF-α), suggesting a potential “cytokine storm” correlated with COVID-19 disease severity [15, 22]. The release of pro-inflammatory cytokines and chemokines may potentially be attributed to massive epithelial and endothelial cell apoptosis and to vascular leakage resulting from rapid viral replication [23]. Of the released pro-inflammatory cytokines, IL-1β and IL-6 are of particular interest and appear to be closely related to the occurrence of severe COVID-19 in adult patients [24]. This hypercytokinemia seems to play a crucial role in the development of pulmonary fibrosis [25] and is associated with increased viral load, loss of lung function, lung injury, and increased mortality [26].

IL-1β was shown to be increased in the bronchoalveolar lavage fluid and in the plasma of patients with ARDS [27]. Similarly, IL-6 functions as a proinflammatory factor and...
was shown to play an important role in the progression of lung fibrosis [28]. IL-6 is an important pleiotropic cytokine that significantly contributes to acute inflammation. Elevated IL-6 levels were correlated with increased severity of COVID-19-associated pneumonia. In mild cases, systemic levels of IL-6 were less than 100 pg/mL. However, in critical cases, IL-6 levels were greater than 100 pg/mL, a concentration above which we usually witness the emergence of an “inflammatory storm” [29]. Consequently, it was reported that the inhibition of both IL-1β and IL-6 is beneficial in many viral infections [24]. A retrospective study observing the efficacy of tocilizumab (IL-6R antagonist) in treating COVID-19 suggested that tocilizumab might be an effective treatment in patients with the severe form of the disease [30]. Currently, several clinical trials on the safety and efficacy of tocilizumab in the treatment of severe COVID-19-associated pneumonia in adult inpatients have been registered [31, 32]. Interestingly, IL-6 activation is directly correlated with the Mechanistic Target of Rapamycin (mTOR) pathway activation, a pathway involved in cell survival, proliferation, and growth [33]. In that spirit, cytokine IL-37, which has the ability to suppress both the innate and the acquired immune responses and to inhibit inflammation by acting on IL-18Rα receptor, was also shown to suppress the production of IL-1β and IL-6 by modulating mTOR pathway and increasing the adenosine monophosphate kinase (AMPK) [24]. IL-38 is another inhibitory cytokine of IL-1β and other pro-inflammatory IL-family members [24]. Both IL-38 and IL-37 were suggested to serve as potential therapeutic cytokines by inhibiting inflammation caused by COVID-19, providing a novel pertinent approach to treating the disease.

2.2 The protective role of angiotensin-converting enzyme 2 against lung injury

The pathophysiology of SARS-CoV-2 infection has not yet been extensively investigated, but it is speculated that it can resemble that of SARS-CoV-1 overall. Infection with SARS-CoV-1 results in an aggressive inflammatory response that begins with binding to the membrane-bound ACE2 receptor [19] followed by entry into the cell and subsequent viral replication [34]. Similarly, a possible mechanism of SARS-CoV-2-mediated inflammatory responses consists of downregulation and shedding of ACE2, a terminal carboxypeptidase that degrades angiotensin II to angiotensin (1–7), thus acting as a negative regulator of the renin-angiotensin system [35]. While ACE, which converts angiotensin I to angiotensin II, induces lung edema and promotes lung injury, ACE2 appears to protect the lungs from acute injury [36] (Fig. 1). In several studies, loss of pulmonary ACE2 expression resulted in increased inflammation, enhanced vascular permeability, increased lung edema, and accumulation of neutrophils, eventually leading to decreased lung function [35–38]. Previous studies on SARS-CoV-1 have shown that once bound to ACE2 the virus’ S protein downregulates ACE2 [39, 40] and leads to the shedding of its ectodomain, an enzymatically active domain termed soluble ACE2 (sACE2) [41–43]. The biological function of sACE2 remains poorly investigated. Inflammatory cytokines such as IL-1β and TNF-α were also shown to increase ACE2 shedding [41–43]. Thus, for SARS-CoV-2 pathogenesis, ACE2 not only serves as a portal entry for the virus but also plays a protective role against lung injury. These observations hypothesize that increased ACE2 shedding, which is correlated with the uncontrolled inflammation in SARS-CoV-
1 infection, might also be involved in the hyperinflammation seen with SARS-CoV-2 infection.

After reviewing the epidemiology and pathogenesis of SARS-CoV-2, it is well recognized that DM increases morbidity and mortality in patients with COVID-19 by aggravating the pathogenesis of the disease [6, 8, 9, 44, 45]. Herein, we aim to elucidate the pathological mechanisms in relation to diabetes and COVID-19 and suggest potential therapeutic strategies for managing the complications emanating from the viral infection.

3 Diabetes mellitus: A risk factor for the progression of COVID-19

Diabetes mellitus is one of the leading causes of morbidity worldwide, and it is projected to remain on the rise over the next few decades. A large body of evidence has highlighted an increased susceptibility of patients with diabetes to infectious diseases [46–48], which is possibly attributed to a defective immune system in diabetes [49]. Given the decreased immunity in patients with diabetes, pneumonia has now become a considerable mortality factor in diabetes [50]. In patients with SARS, diabetes and plasma glucose levels were both shown to be independently associated with higher morbidity and mortality [51]. In Hong Kong, the first three deaths from SARS-CoV-2 infection were patients with diabetes. In a study conducted on a group of 52 ICU patients infected with SARS-CoV-2, the most common comorbidities between the 32 non-survivors of the group were diabetes (22%) and cerebrovascular disease (22%) [8]. Recently, The Chinese Center for Disease Control and Prevention published the largest study relevant to patients with diabetes in Mainland China which involved 72,314 cases of COVID-19. While patients who reported no co-morbidities had a case fatality rate of 0.9%, patients with diabetes had a significantly higher case fatality rate (7.3%) [52]. Furthermore, a meta-analysis of 76,993 patients infected with SARS-CoV-2 revealed that hypertension, cardiovascular disease, history of smoking, and diabetes were the most common underlying diseases with incidences of 16.37%, 12.11%, 7.63%, and 7.87%, respectively [53]. In another study conducted on 1099 COVID-19-infected patients in China, 173 cases (16%) were classified as severe [6]. Out of these severe cases, 16.2% (28 individuals) had diabetes, while only 5.7% (81 individuals) of the non-severe cases had diabetes [6]. Furthermore, a retrospective study in Wuhan, China conducted on 174 patients with COVID-19 revealed a higher risk of severe pneumonia in patients with diabetes (n = 24) who did not suffer from any other complication [54]. These patients also presented with a higher risk of tissue injury-related enzyme release and an overexpressed uncontrolled inflammation. Dysregulated glycemia also appeared to lead to a hypercoagulable state through the activation of plasmin, thrombin and monocytes-macrophages and through the secretion of different tissue factors, a resultant of the inflammatory storm itself [54]. According to the CDC, as of May 30, 2020, in a population of about 1.3 million individuals infected with SARS-CoV-2 in the USA, around 30% of those individuals who have underlying health conditions (86,737 individuals) have diabetes mellitus [55]. The different studies presented suggest that patients with diabetes may not only be prone to a more severe COVID-19 disease, but also to an increased risk of infection with SARS-CoV-2. However, several studies have shown that, despite these latter findings, no increased infectivity was observed in patients with COVID-19 comorbid with diabetes [56]. In fact, the prevalence of diabetes in the patient population with COVID-19 is not so different from the prevalence of diabetes in the general population [56].

4 Elucidating the crosstalk between COVID-19 and diabetes mellitus

Several mechanisms were suggested to explain the increased susceptibility of patients with DM to severe COVID-19 disease, including higher-affinity cellular binding, efficient viral entry, reduced viral clearance, reduced T cell function, enhanced susceptibility to hyperinflammation and cytokine storm, and the presence of cardiovascular diseases [57]. Phagocytosis by neutrophils, monocytes, and macrophages was shown to be defective in patients with diabetes who happen to also suffer from malfunctions in neutrophil chemotaxis, bactericidal activity, and innate cell-mediated immunity [58]. Interestingly, even short-term hyperglycemia was found to dampen their innate immune response [59]. In addition to their defective innate response, patients with diabetes also demonstrate an impaired adaptive immune response [49].

4.1 Angiotensin-converting enzyme 2 expression in diabetes mellitus and its role in COVID-19 infectivity

Although plausible hypotheses for the increased risk of COVID-19 infection in patients with diabetes and other chronic diseases like hypertension are still under investigation, ACE2 seems to play a key role in the association between COVID-19 and DM [60] (Table 1). In fact, both DM and hypertension are correlated with the activation of the renin-angiotensin system in different tissues [71], a system that regulates blood volume and the systemic vascular resistance [72]. Treating type 1 and type 2 diabetes with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) was found to increase the expression of ACE2 in the renal and cardiovascular systems [61, 62]. However, there is no sufficient evidence to support an increase in ACE2 levels in the respiratory system secondary to the use of ACE/ARBs.
There is also no sufficient experimental evidence to support the hypothesis that switching people from ACE inhibitors or ARBs to other drugs might decrease the risk of infection and the severity of COVID-19. A more favorable SARS-CoV-2 binding was demonstrated with increased ACE2 expression in alveolar AT2 cells, as well as in the myocardium, kidneys, and pancreas in humans [63–65]. In rodents with DM, an increased expression of ACE2 was also reported in the lungs, kidneys, heart, and pancreas [66, 67], thus possibly favoring SARS-CoV-2 entry. Hypoglycemic agents such as thiazolidinediones (TZDs; pioglitazone) and glucagon-like peptide-1 (GLP-1) agonists (liraglutide), statins and ibuprofen were all also found to increase ACE2 expression [73–76]. This explains why concerns were initially raised regarding the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen in patients with COVID-19. The WHO later denied this assumption, stating that no severe adverse effects were observed with the use of NSAIDs in patients with COVID-19 [77]. Until recently, the association between DM and ACE2 expression levels in human lungs remained poorly investigated. A phenome-wide Mendelian randomization analysis carried out by Rao et al. suggested that higher ACE2 expression in the lungs increased susceptibility to SARS-CoV-2 infection with more severe complications and was causally correlated with diabetes [68]. The genome-wide association study (GWAS) on patients with type 2 diabetes (N = 898,130) revealed that type 2 diabetes is causally linked to increased ACE2 expression. Another study showed that patients with diabetes have increased levels of furin [78], a cellular protease that cleaves the S1 and S2 domains of SARS-CoV-2’s spike protein [79], possibly facilitating viral entry.

The role of ACE2 in the crosstalk between COVID-19 and DM is still a matter of debate. Some studies recognized decreased levels of ACE2 in diabetes, perhaps secondary to glycyrilation [80]. In kidney biopsies of patients with diabetes presenting with nephropathy, glomerular expression of ACE2 was also found to be reduced [69]. Therefore, by adopting the hypothesis that increased ACE2 expression leads to higher

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**Table 1** Angiotensin Converting Enzyme 2 expression in different experimental models

| Reference                  | Study Type                          | Results                                                                                                                                                                                                 |
|----------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (Ferrario et al., [61])   | Animal Model                        | Selective blockade of either Ang II synthesis or activity upregulates cardiac ACE2 gene expression and cardiac ACE2 activity                                                                                 |
| (Ishiyama et al., [62])   | Animal Model                        | Blockade of Ang II receptors upregulates cardiac ACE2                                                                                                                                                   |
| (Liu et al., [63])        | Public Database, Study Cohort        | Expression of ACE2 is higher in the pancreas than in the lung of control subjects favoring SARS-CoV-2 binding                                                                                               |
|                           |                                     | Single-cell RNA sequencing data shows that ACE2 is expressed in both exocrine glands and islets of the pancreans                                                                                           |
|                           |                                     | Pancreatic injury is noted in some COVID-19 patients, mainly in patients with severe illness.                                                                                                             |
| (Lukassen et al., [64])   | Transcriptome data on single cell level of healthy human lung tissues, including surgical lung specimen and subsegmental bronchial branches | ACE2 is predominantly expressed in a transient secretory cell type in lung tissue                                                                                                                       |
| (Zou et al., [65])        | Genetic Study (Single-cell RNA-sequencing (scRNA-seq) datasets derived from major human physiological systems) | Single-cell RNA-seq data analyses on the receptor ACE2 expression reveals the organs at risk, such as lung, heart, esophagus, kidney, bladder, and ileum, and located specific cell types which are vulnerable to 2019-ncov infection. |
| (Wysocki et al., [66])    | Animal Model                        | ACE2 expression is increased at the posttranscriptional level in renal cortex of the db/db STZ-induced diabetic mice.                                                                                 |
| (Roca-Ho, Riera, Palau, Pascual, & Soler, [67]) | Animal Model | Diabetes up-regulates ACE2 mainly in serum, liver, and pancreas of non-obese diabetic (NOD) mice model                                                                                                      |
| (Rao, Lau, & So, [68])    | A phenome-wide Mendelian Randomization study | Diabetes and related traits may upregulate ACE2 expression, which may influence susceptibility to SARS-CoV-2 infection                                                                                   |
| (Reich, Oudit, Penninger, Scholey, & Herzenberg, [69]) | Renal biopsies from diabetic and control subjects | Kidney disease of patients with type 2 diabetes is associated with a reduction in ACE2 gene and protein expression                                                                                       |
| (Monteil et al., [70])    | Cell lines, Engineered human blood vessel organoids and human kidney organoids | Clinical-grade human recombinant soluble ACE2 (hrsACE2) significantly inhibited viral growth in the monkey kidney cell line                                                                                   |
|                           |                                     | hrsACE2 prevented SARS-CoV-2 infection in engineered human blood vessel organoids and human kidney organoids at the early stage of infection                                                               |
viral infectivity, it would be reasonable to infer that diabetes, with its diminished ACE2 expression, is associated with a lower risk of infection with SARS-CoV-2. However, as previously mentioned, diabetes was shown to be associated with a higher risk of severe COVID-19 disease and a poorer prognosis. This highlights the presence of other factors that explain the positive association between diabetes and COVID-19. Treatment with ACE inhibitors, ARBs, TZD or GLP-1, higher levels of furin, delayed viral clearance, immune dysfunction, comorbidities, and other confounding factors could all explain the higher prevalence of COVID-19 in patients with diabetes.

Remarkably, other studies argue that having higher ACE2 expression does not lead to increased infectivity and severity of COVID-19 disease. On the contrary, some consider that increased ACE2 could play a beneficial role in patients with COVID-19 [81, 82]. Patients with diabetes treated with ACE inhibitors or ARBs might be at an advantage over non-treated patients with diabetes [81, 82]. As previously mentioned, loss of pulmonary ACE2 expression leads to decreased lung function. This justifies why treatment with ACE inhibitor or ARBs has been advanced as a possible therapeutic strategy for COVID-19 [81, 82]. Moreover, it has been lately proposed that treatment with a soluble form of ACE2, which lacks the membrane anchor, may act as a competitive interceptor of SARS-CoV-2 by inhibiting the binding of the virus’ S protein to the surface-bound, full-length ACE2 [83]. A recent study has shown that treatment with clinical-grade human recombinant soluble ACE2 (hrsACE2) significantly inhibited viral growth in the monkey kidney cell line, Vero-E6, by a factor of 1000-5000. It also prevented SARS-CoV-2 infection in engineered human blood vessel organoids and human kidney organoids at the early stage of infection [70]. Collectively, these findings highlight the need for a better understanding of the underlying pathobiology of ACE2 in DM and COVID-19.

Based on these studies, the interplay between diabetes and COVID-19 appears to be bi-directional. Diabetes was shown to be associated with an increased risk of severe COVID-19. New-onset diabetes and severe metabolic complications of preexisting diabetes, such as diabetic ketoacidosis and hyperosmolarity, were also noted in patients with COVID-19, which was proposed to be due to the binding of SARS-CoV-2 to ACE2 receptors in key metabolic organs, possibly resulting in variations in glucose metabolism [84–87]. ACE2 expression is particularly amplified in key metabolic organs such as the liver, the endocrine pancreas, adipose tissue, the kidneys and the small intestine, which might play a role in the emergence of insulin resistance, as well as in the impaired secretion of insulin [88, 89]. Thus, it could be hypothesized that SARS-CoV-2 infects metabolic organs, leading to hyperglycemia exacerbation. More importantly, a subclinical inflammatory reaction, in particular a combined elevation of IL-1β and IL-6, has been shown to precede the onset of type 2 diabetes [90], further suggesting that COVID-19 might increase the risk of developing new-onset diabetes.

4.2 Diabetes mellitus and COVID-19: In the eye of the “cytokine storm”

Another potential reason for the increased risk of severe COVID-19 disease in patients with diabetes might be attributed to the hyperinflammatory response, referred to as “cytokine storm” (Fig. 2). Patients with diabetes suffer from a continuous low-grade inflammation facilitating the emergence of a cytokine storm, which in turn appears to be directly related to the severity of COVID-19 pneumonia cases and to subsequent death [91]. Patients with diabetes appear to have an impaired adaptive immune response characterized by an initial delay of Th1 cell-mediated immunity and a late hyperinflammatory response [49]. In the absence of an immunostimulant, diabetes is associated with an increased pro-inflammatory cytokine response marked by increased secretion of IL-1, IL-6, IL-8 and TNF-α [58]. Elevated basal cytokine levels might also be attributed to advanced glycation end products (AGEs) [92], which consist of residues of glucose and lysine/arginine [58]. It was noted that extended emergence of AGEs occurred in poorly regulated patients with diabetes. Separate studies have established an increase in cytokine levels following AGE binding to non-diabetic cells, without direct stimulation [93–95]. As such, elevated AGE production in patients with diabetes could be implicated in raising resting cytokine production [58]. Other studies evaluated the responsiveness of peripheral blood mononuclear cells (PBMCs) and isolated monocytes in patients with diabetes after being subjected to stimulation. Interestingly, IL-1 and IL-6 secretion resulting from exposure to lipopolysaccharide (LPS) was found to be diminished in patients with diabetes [58, 96, 97]. One might speculate that the high resting value of diabetic cells could favor tolerance to direct stimulation, with
an ensuing decrease in the cytokine secretion response. This type of event has already been reported in non-diabetic cells [98]. In short, the mere availability of high glucose causes an increase in resting cytokine production; yet, subsequent to stimulation, cytokine production lessens in comparison to a condition without glucose. This reduction in interleukin production upon stimulation might also be attributed to intrinsic cellular defects in patients with diabetes [58, 99].

Chronic inflammation reported in DM is further amplified with SARS-CoV-2 infection, resulting in an aggressive inflammatory response. A study done on a humanized mouse model of MERS-CoV infection revealed that the disease was more severe and prolonged in male diabetic mice and was characterized by alterations in CD4+ T cell counts and abnormal cytokine responses [100]. In accordance with this animal study, other studies conducted on patients with diabetes comorbid with COVID-19 have observed decreased peripheral CD4+ and CD8+ T cells counts and increased cytokine levels [6, 8, 9, 45, 101]. A recent study revealed that patients with diabetes comorbid with COVID-19, despite having significantly lower absolute lymphocyte counts in peripheral blood, had notably higher absolute neutrophil counts in comparison to non-diabetic patients [54]. Among the different markers of inflammation found to be elevated in COVID-19 cases with diabetes, IL-6 warrants particular attention since it has been shown to be associated with lung injury and poorer prognosis [28, 102]. Interestingly, serum levels of IL-6 in diabetic patients without COVID-19 were significantly higher compared to those in non-diabetic patients [54]. This might be correlated with the increased cytokine baseline level observed in DM, which is further amplified in COVID-19. These findings indicate that IL-6 might be a good predictor of disease severity and prognosis. They also further suggest that patients with both diabetes and COVID-19 are susceptible to a more aggressive inflammatory storm, ultimately leading to rapid deterioration.

Taken together, these observations suggest that tocilizumab (IL-6R antagonist) may markedly help in the treatment of COVID-19 pneumonia. In fact, tocilizumab is now being used off-label in some Italian centers in patients with COVID-19 and is currently being assessed in an ad hoc randomized controlled trial [31]. Moreover, IL-37, which is a cytokine that exists in 2 complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The two subtypes consist of distinct sets of protein-binding partners [105]. mTORC1 comprises mTOR, mLST8 and rapamycin-sensitive adaptor protein of mTOR (Raptor) and is known to mediate many of its downstream effects including protein synthesis and cell size through p70S6 kinase (p70S6K)/S6 kinase 1 (S6K1) and 4E-binding protein 1 (4E-BP1) [106–108]. mTORC2, with its essential components mTOR, mSIN1, mLST8, and the rapamycin-insensitive subunit Rictor, mediates its actions through the phosphorylation of protein kinase B (PKB/Akt) at Serine 473 [109]. mTORC2 has been implicated in controlling cell survival and cytoskeletal organization [109]. When cellular energy levels are low, AMPK is activated to stimulate glucose uptake in skeletal muscles and fatty acid oxidation in adipose tissues. It also reduces hepatic glucose production. A large body of evidence underlines a dysregulation in AMPK signaling in metabolic syndrome and DM [110–113]. More importantly, it has been previously shown that AMPK activation can improve insulin sensitivity by enhancing glucose transport and uptake and by stimulating fatty acid oxidation [114]. In 2001, metformin was reported to act as an AMPK activator and is now a widely used drug for the treatment of type 2 diabetes [115], and recently for type 1 diabetes [116]. Strong evidence demonstrates that AMPK negatively regulates the mTOR pathway. It inhibits mTORC1 indirectly through the phosphorylation of Tuberous sclerosis 2 (TSC2), thus favoring a TSC1-TSC2 association, an upstream inhibitor complex of mTORC1. Furthermore, AMPK modulates mTORC1, independently from TSC2 by raptor phosphorylation and inactivation of mTORC1 [117].

During the progression of DM, AMPK is inactivated leading to chronic overactivation of mTORC1 [118–120]. Overactivation of mTOR signaling pathway has been associated with insulin resistance and progression of diabetes-induced complications. For instance, our group has previously shown that hyperglycemia was associated with increased activation of mTORC1/p70 S6Kinase and Rictor/mTORC2 pathways through the inactivation of AMPK, eventually leading to podocyte injury. Intriguingly, inhibition of mTORC1 by rapamycin or of

4.3 The interplay between COVID-19 and AMPK/mTOR signaling pathway in diabetes mellitus

AMPK is a key physiological energy sensor whose activity is regulated by glucose. AMPK signaling modulates multiple biological pathways such as cellular metabolism, growth and proliferation to maintain cellular energy homeostasis [104]. A major downstream signaling pathway regulated by AMPK is the mTOR pathway. mTOR is a serine/threonine protein kinase that exists in 2 complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The two subtypes consist of distinct sets of protein-binding partners [105]. mTORC1 comprises mTOR, mLST8 and rapamycin-sensitive adaptor protein of mTOR (Raptor) and is known to mediate many of its downstream effects including protein synthesis and cell size through p70S6 kinase (p70S6K)/S6 kinase 1 (S6K1) and 4E-binding protein 1 (4E-BP1) [106–108]. mTORC2, with its essential components mTOR, mSIN1, mLST8, and the rapamycin-insensitive subunit Rictor, mediates its actions through the phosphorylation of protein kinase B (PKB/Akt) at Serine 473 [109]. mTORC2 has been implicated in controlling cell survival and cytoskeletal organization [109]. When cellular energy levels are low, AMPK is activated to stimulate glucose uptake in skeletal muscles and fatty acid oxidation in adipose tissues. It also reduces hepatic glucose production. A large body of evidence underlines a dysregulation in AMPK signaling in metabolic syndrome and DM [110–113]. More importantly, it has been previously shown that AMPK activation can improve insulin sensitivity by enhancing glucose transport and uptake and by stimulating fatty acid oxidation [114]. In 2001, metformin was reported to act as an AMPK activator and is now a widely used drug for the treatment of type 2 diabetes [115], and recently for type 1 diabetes [116]. Strong evidence demonstrates that AMPK negatively regulates the mTOR pathway. It inhibits mTORC1 indirectly through the phosphorylation of Tuberous sclerosis 2 (TSC2), thus favoring a TSC1-TSC2 association, an upstream inhibitor complex of mTORC1. Furthermore, AMPK modulates mTORC1, independently from TSC2 by raptor phosphorylation and inactivation of mTORC1 [117].

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mTORC2 by using antisense oligonucleotides that target Rictor attenuated glomerular injury and prevented podocyte loss/depletion [110, 112].

Although not well elucidated, the effects of metformin are thought to be mediated by the regulation of AMPK and mTOR. Intriguingly, a recent study has shown that B cell function and influenza vaccine responses attenuated by type 2 diabetes and obesity were improved by metformin [121]. Moreover, metformin decreased B cell intrinsic inflammation and increased antibody responses when used in vitro to stimulate B cells isolated from patients with recently diagnosed type 2 diabetes [121]. These findings suggest that metformin activates AMPK consequently leading to an improvement in B cell responses and a decrease in B cell intrinsic inflammation. Therefore, AMPK is proposed as a potential therapeutic target in viral infections.

Increasing evidence also highlight mTORC1 as a key player in controlling the replication of viruses such as Andes orthohantavirus and coronavirus [122, 123]. In patients with H1N1 pneumonia and acute respiratory failure, treatment with corticosteroids and an mTOR inhibitor effectively blocked viral protein expression and virion release, attenuated hypoxia and multiorgan dysfunction and improved patients’ prognosis significantly [124]. Furthermore, a recent study revealed that treatment with sirolimus, an mTOR inhibitor, decreased MERS-CoV infection by more than 60% [103]. It has also been previously shown that optimal West Nile Virus (WNV) growth and protein expression are dependent on mTORC1-mediated activation of downstream signaling pathways, 4E-BP1 and eukaryotic initiation factor 4F (eIF4F) [125]. More importantly, a recent study aiming to identify drug combinations that may provide a synergistic effect in potentially treating SARS-CoV-2 with precise mechanism of action by network analysis revealed sirolimus plus dactinomycin as a potential drug combination for SARS-CoV-2 [126].

However, other studies have described an anti-viral role for mTOR. Recent findings have demonstrated that PI3K/AKT/mTOR signaling pathway is crucial for cytokine responses in IL-15 primed natural killer (NK) cells. Moreover, mTOR inhibition using rapamycin results in defects in both proliferation of NK cells and production of IFN-γ and granzyme B, leading to increased viral burdens upon murine cytomegalovirus infection [127]. These findings describe a link between the metabolic sensor mTOR and NK cell anti-viral responses.
In addition, a recent study has shown that metformin, by up-regulating the expression of AMPK and inhibiting mTOR-mediated pathway, decreases IFN-α expression following seasonal vaccination (SV) with trivalent influenza vaccine (TIV) and is associated with impaired antibody responses in patients with type 2 diabetes [128]. mTOR has also been described to play a role in suppressing hepatitis C virus (HCV) RNA replication, proposing that the activation of mTOR by HCV is an anti-viral response by the cells [129]. Taken together, these findings suggest that extensive research on the exact role of mTOR in viral infections is still strongly warranted.

On another note, the metabolic sensor mTOR is negatively regulated by Regulated in Development and DNA Damage Responses 1 (REDD1) [33]. IL-6, which was closely related to the occurrence of severe COVID-19 in adult patients, was shown to reduce basal as well as stress-induced REDD1 in a Signal Transducer and Activator of Transcription 3 (STAT3) dependent manner, resulting in the activation of mTOR [33]. Remarkably, rapamycin was shown to ameliorate IL-6-induced insulin resistance in liver cells [130]. Based on these observations, we suggest that COVID-19 associated cytokine storm might worsen the prognosis of DM by dysregulating the AMPK/mTOR signaling pathway (Fig. 3). Collectively, these observations suggest that activating AMPK and/or inhibiting mTOR-mediated signaling pathway could be used as novel drug targets for therapeutic intervention strategies.

5 Conclusion

In this review, we describe three potential mechanisms underlying the increased susceptibility of patients with diabetes to a more severe COVID-19 disease, leading to higher morbidity and mortality. Several studies have tried to explain a possible increased susceptibility to infection with SARS-CoV-2 in patients with diabetes. However, no data has shown, to date, that these patients are at higher risk of contracting COVID-19. SARS-CoV-2 enters the host cell through the ACE2 receptor. While a consensus has still not been reached on the role of ACE2 in the crosstalk between diabetes and COVID-19, some argue that patients with diabetes have an elevated ACE2 expression, thus facilitating viral entry and subsequent replication. Others show that patients with diabetes have low levels of ACE2 and that the observed increase in ACE2 is due to other factors such as treatment with ACE/ARBs, hypoglycemic agents and statins. Patients with diabetes present with elevated basal levels of cytokines, such as IL1-β and IL-6, and with a state of low-grade chronic inflammation that seems to further intensify the hyperinflammation observed in response to SARS-CoV-2. This so-called “cytokine storm”, particularly with the increase in IL-6, is also suggested to alter AMPK/mTOR signaling pathway in patients with diabetes, possibly aggravating insulin resistance and diabetes-induced complications. Therefore, despite the need for further research investigation, one can speculate that treatment with human recombinant soluble ACE2, IL-6 antagonists, AMPK activators or mTOR inhibitors may be considered as potential therapeutic strategies to alleviate and even halt the complications associated with COVID-19 disease.

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Conflict of interest The authors declare that they have no conflict of interest.

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