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REVIEW ARTICLE

Mechanisms influencing the high prevalence of COVID-19 in diabetics: A systematic review

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ABSTRACT

Diabetics have an increased risk of contracting COVID-19 infection and tend to have more severe symptoms. This systematic review explores the potential mechanisms influencing the high prevalence of COVID-19 infections in individuals with diabetes. It reviews the emerging evidence about the interactions between viral and diabetic pathways, particularly how diabetes physiology could contribute to higher viral reception, viral entry and pathogenicity, and the severity of disease symptoms. Finally, it examines the challenges we face in studying these mechanisms and offers new strategies that might assist our fight against current and future pandemics.

Keywords: SARS-CoV-2, COVID-19, ACE2, diabetes, insulin

Introduction

The COVID-19 pandemic has profoundly impacted global health, affecting individuals with various underlying conditions differently. Among these conditions, a significant predictor of morbidity and mortality in COVID-19 patients is diabetes[1-3]. One study found that COVID-19 patients with type-2 diabetes had higher hospital readmission rates and disease severity[4]. Another study estimated that COVID-19 patients with diabetes have a 2 – 3.5 times greater risk of hospital death than non-diabetic patients[1]. However, it remains unclear why diabetics exposed to the SARS-CoV-2 virus have poorer prognoses.

There are several theories as to how diabetes and viral symptoms synergistically influence disease severity and mortality after SARS-CoV-2 infections. Prima facie, diabetes symptoms such as high inflammation, blood coagulation, immune response impairment, etc., could aggravate viral infection and associated symptoms[5-7]. Conversely, SARS-CoV-2 infection could further worsen pre-existing diabetes symptoms, leading to a cytokine storm and excessive inflammation[8,9]; dysregulated inflammation could impact the immune response, leading to a higher likelihood of developing acute respiratory distress, multi-organ failure, and death[10]. Despite these ostensible associations between diabetes and viral symptoms, new details are emerging about how diabetes physiology could specifically influence viral reception, viral entry and pathogenicity, and disease symptoms. In this systematic review, we focus on these recent findings.

Diabetes symptoms influence SARS-CoV-2 reception on cell membranes

One reason why diabetics have a greater risk of contracting COVID-19 could be because they tend to have elevated expression levels of the SARS-CoV-2 receptor, ACE2[11]. Higher ACE2 expression in specific tissues favors increased viral binding and susceptibility to infection. This section elaborates on recent findings about a potential relationship between diabetes and upregulation of ACE2 expression.

A significant portion of confirmed COVID-positive subjects have a history of comorbid conditions[12,13]. To identify the risk factors affecting susceptibility to SARS-CoV-2 infection, Rao et al. conducted a phenome-wide Mendelian randomization study on ACE2 expression[11]; the analysis revealed a positive association between diabetes-related traits and increased ACE2 expression. While the specific mechanisms by which diabetes symptoms alter ACE2 expression are unclear, other studies have suggested that the dysregulated glucose levels in diabetics might contribute toward altered ACE2 levels. For instance, in diabetic mice, hyperglycemia increased renal ACE2 shedding into urine[14,15]. In contrast, insulin treatment of diabetic mice normalized their hyperglycemia and decreased urinary ACE2 secretion[15]. Similarly, in humans, diabetics with poor glucose tolerance have higher urinary ACE2 levels than control subjects with standard glucose tolerance[16].

Although it was previously shown that glucose can induce ACE2 expression in cell lines[17], it was controversial whether diabetes patients had higher or lower expression of ACE2[18,19]. A recent study seems to have put this

controversy to rest: By testing the effect of glucose on ACE2 expression in human kidney organoids, this study showed that an oscillatory glucose treatment led to a significant upregulation of ACE2 expression at the protein and mRNA levels[20]. Other studies comparing kidney biopsies from patients with diabetic kidney disease and healthy patients showed that the ACE2 mRNA expression was increased in diabetes subjects[21,22]. This upregulation of ACE2 expression is likely because hyperglycemia increases the stability of ACE2 mRNA in diabetic organoids[20].

However, an increase in ACE2 expression during diabetes was not restricted to the kidneys. When ACE2 expression was profiled in a non-obese diabetic (NOD) mouse model, the NOD mice, after diabetes onset, had marked upregulation of ACE2 in the serum, liver, and pancreas[23]. When ACE2 protein and mRNA expression levels were evaluated in human lung tissues, it was noted that patients with diabetes had higher ACE2 protein levels than control patients in their lung tissues[24]. Similarly, an evaluation of ACE2 gene expression in heart tissue revealed that diabetics had significantly higher ACE2 gene expression than non-diabetics in their heart tissues[25].

Does an increase in ACE2 expression lead to higher SARS-CoV-2 infectivity? While more studies need to be conducted to answer this question, some studies indicate a positive correlation between increased ACE2 expression within some tissues, such as lungs and kidneys, and a higher risk of SARS-CoV-2 infections[26]. Two other studies using cell lines showed a positive correlation between ACE2 expression levels and susceptibility to SARS-CoV-2[27,28]. Additionally, the efficiency of SARS-CoV-2 replication in 293T cells was found to be dependent on the ACE2 receptor levels in a dose-dependent manner[29].

Together, these findings make it reasonable to speculate that diabetics have a greater risk of contracting COVID-19 due to increased ACE2 expression.

Diabetes symptoms aid SARS-CoV-2 viral entry into cells

In addition to a higher expression of the viral receptor, another reason why diabetics have a greater risk of contracting COVID-19 is because the symptoms associated with diabetes may facilitate viral entry into cells. This is supported by recent findings related to at least three different symptoms of diabetic physiology: (i) altered glycosylation, (ii) increased levels of furin, and (iii) higher expression of fibrinolytic enzymes. Together, these symptoms potentially modify the ACE2 receptor to either increase its affinity for the virus or facilitate viral entry. This section elaborates further on these findings.

(i) Altered glycosylation. A common symptom of diabetics is chronic hyperglycemia. Chronic hyperglycemia can alter the glycosylation patterns of proteins[27,30-36]. Glycosylation—attaching glycans (polysaccharides) to specific amino acid residues—is a post-translational modification of proteins necessary for its proper function[37]. In contrast, an abnormal increase in protein glycosylation could lead to an irreversible accumulation of altered proteins. One protein susceptible to abnormal glycosylation in diabetics is the SARS-CoV-2 receptor, ACE2.

The ACE2 protein is susceptible to chronic and abnormal glycosylation in diabetics due

to its numerous lysine residues available for glycosylation[38-41]. Examination of ACE2's molecular structure revealed that its extracellular domain contains 34 lysines, seven of which are glycosylated[41,42]. At least five of these seven lysines were shown to be relevant for viral interaction: Lys 353, located in the ACE2 binding domain, is a crucial residue for SARS-CoV-2 binding; Lys 619, Lys 631, Lys 659, and Lys 689, all located in the ACE2 neck domain, are involved in ACE2 dimerization[42]. Glycosylation of any of these residues can affect the ACE2 receptor's affinity for SARS-CoV-2.

Long-term effects of diabetes on the glycosylation of the ACE2 receptor can affect its affinity for the SARS-CoV-2 virus by altering viral binding or by enhancing the stability of the virus-receptor complex. First, although glycosylation of Lys 353 was relatively low compared to other lysines, it did influence ACE2's binding affinity to the viral spike protein[42]. Second, glycosylation of lysine residues in the ACE2 neck domain increases ACE2 dimerization; dimeric ACE2 exhibits higher binding affinity for the SARS-CoV-2 spike protein. For instance, the binding kinetics between the SARS-CoV-2 spike protein and ACE2 are more pronounced for engineered dimeric and trimeric ACE2 than the monomeric subunit[42]. Finally, elevated levels of ACE2 dimers on the cell surface could lead to interactions with multiple SARS-CoV-2 receptor binding domains, thereby enhancing the stability of the virus-receptor complex and facilitating the transition from a pre-fusion state to a post-fusion state[42,43].

(ii) Increased levels of furin. Diabetics tend to have elevated plasma levels of furin[44]. Furin, which is expressed in many tissues, including the oral and airway epithelial cells, cardiac tissues, and enteric canals, is a type I membrane-bound serine endoprotease[44]. A host cell's membrane-bound endoproteases are typically exploited by viruses such as the SARS-CoV-2 to cleave their surface glycoproteins and facilitate cell entry. Interestingly, the SARS-CoV-2 S glycoprotein has cleavage sites specific to the furin-endoprotease activity, bestowing furin a vital role during the viral infection[45,46]. In support of this, the co-expression of furin and the viral receptor ACE2 has been detected in the cell membranes of several cell types[47].

In addition to its activity on the host's cell membranes, within cells, furin shuttles between the membranes of the Golgi and endosomal compartments[45,46]. Thus, furin may aid viral infection in two different ways: First, at the level of the cell membranes, furin may form a ternary complex with the ACE2 receptor to help with S glycoprotein cleavage and viral entry[45,47]; second, at the level of organelle membranes, furin may aid in the diffusion of virions during their transport along the secretory pathway[27,48-50].

(iii) Higher expression of fibrinolytic enzymes. Both type I and type II diabetics have elevated levels of plasmin(ogen)[38,51,52]. Plasmin, the proteolytically active form of plasmin(ogen), is a non-specific protease capable of cleaving the SARS-CoV-2 spike protein. Since the cleavage of the virus envelope glycoproteins by host cellular proteases is an important step for the pathogenicity of respiratory viruses, higher levels of plasmin in diabetics, like furin, could further enhance SARS-CoV-2 pathogenicity by facilitating its entry into the host cell.

In vitro studies support plasmin's role in cleaving the SARS-CoV-2 S protein[53]. While *in vivo* studies of plasmin-specific cleavage of

the SARS-CoV-2 S protein are lacking, this idea is further supported by studies of plasmin-specific cleavage of another respiratory virus, the influenza virus: Plasmin cleaves the HA proteins of the influenza virus enabling its spread and pathogenicity[54-58]. Does the SARS-CoV-2 S protein have a plasmin-specific cleavage site? Since plasmin can cleave the furin sites in the γ-subunit of a human epithelial sodium channel, it has been suggested that plasmin also likely targets the SARS-CoV-2 S protein at its furin sites[52,59].

In addition to its alleged role in cleaving the viral S protein, plasmin, typically present in human serum, is responsible for degrading a variety of plasma proteins, especially fibrin clots, via the fibrinolysis cascade[60]. However, when plasmin levels are elevated, as seen in diabetics, it could lead to hyperfibrinolysis. Hyperfibrinolysis results in decreased platelet counts and elevated levels of D-dimer, a protein byproduct of blood clot breakdown. Decreased platelet counts and elevated D-dimer levels are associated with increased hemorrhaging, one of the leading causes of death among COVID-19 patients[61]. Elevated serum D-dimer levels were noted in 97% of COVID-19 patients and increased further in all patients before death[61].

Overall, the increased glycosylation of the ACE2 receptor and the increased expression of proteases such as furin and plasmin in diabetics may directly or indirectly aid in SARS-CoV-2 pathogenicity.

Diabetes increases the severity of COVID-19 symptoms

Once infected with the virus, diabetics tend to have more severe COVID-19 symptoms[11,18-20,22,62,63]. While many factors could influence symptom severity, three observations from recent studies might explain why diabetics tend to have more severe COVID-19 symptoms: (i) increased viral replication, (ii) delayed viral clearance, and (iii) hyperinflammation. Together, these factors can allow SARS-CoV-2 to multiply, persist, and, along with the increased inflammatory response, cause severe disease symptoms in diabetics.

(i) Increased viral replication. Viral replication inside a host cell requires energy and a carbon source to synthesize nucleotides, amino acids, and lipids[64,65]. To fulfill these needs, many viruses, including SARS-CoV-2, hijack the host cell metabolism to increase glycolysis. SARS-CoV-2, in particular, promotes glycolysis by evoking mitochondrial reactive oxygen species (ROS) production[66]. In support of this, increasing glycolytic flux promoted SARS-CoV-2 replication[66]. In contrast, inhibiting glycolysis prevented SARS-CoV-2 replication[67]. Thus, dysregulated glycolysis, as is often observed during diabetes and in diabetics on insulin therapy, can influence SARS-CoV-2 replication[68-70].

Insulin, which is the cornerstone of therapy for diabetic patients, can augment glycolysis by increasing intracellular pH[71,72]. Insulin was shown to stimulate Na^+/H^+ exchange, leading to a decrease in extracellular pH and an increase in intracellular pH[73,74]. Therefore, it is reasonable to hypothesize that an insulin-stimulated acidic external environment promotes SARS-CoV-2 entry[75], while the corresponding alkaline intracellular environment promotes glycolysis and, thereby, SARS-CoV-2 replication[66,70].

(ii) Delayed viral clearance. Diabetes is one of many factors that can delay viral clearance. Chen et al. tested 106 COVID-19 patients using SARS-CoV-2 qRT-PCR and found that diabetes negatively affected viral clearance.[76] Another study on the Omicron variant investigated the risk factors for 7- and 14-day viral clearance post-infection: The Omicron variant clearance was delayed in diabetes patients with elevated fasting glucose levels[77]. While it remains unclear why diabetes might hinder viral clearance, one idea implicates the high plasma lactate levels commonly observed in diabetes patients. Lactate was shown to impair type I interferon (IFN-1) production in response to viral infection[78,79]. Impaired interferon production reduces the innate ability of cells to recruit immune cells for the purposes of viral clearing following an infection[5].

(iii) Hyperinflammation. A pathogen infection of the human body triggers a cascade of events, including an inflammatory response marked by the secretion of proinflammatory cytokines[80,81]. Inflammation is a fundamental immune response designed to protect the body against harmful stimuli like viruses. However, when inflammation becomes dysregulated and persists at high levels, it can contribute to the development and progression of various human diseases. Infection by the SARS-CoV-2 virus dysregulates the host's immune system, causing high levels of inflammation. This situation can be further exacerbated in patients with diabetes who already have blunted anti-viral and dysregulated inflammatory responses.

On the one hand, diabetics have impaired adaptive immunity characterized by reduced T lymphocyte function and a delayed hyperinflammatory response[82-86]; additionally, they exhibit reduced natural killer cell activity[87] and a blunted interferon response[88-91]. On the other hand, SARS-CoV-2 can also dysregulate the host's inflammatory response due to their ability to increase apoptosis of T lymphocytes (CD3, CD4, and CD8 cells)[92]; reduced T lymphocyte function relieves the inhibition of the innate immune system, leading to the secretion of high amounts of proinflammatory cytokines, a phenomenon known as "cytokine storm"[93]. Covid-19 patients have low peripheral counts of CD4+ and CD8+ T lymphocytes and elevated levels of proinflammatory cytokines such as IL-6, TNF-α, CXCL-10, CCL2[94-98]. Overall, the synergic combination of a blunted anti-viral and exaggerated inflammatory response in diabetics and the dysregulated inflammatory response to SARS-CoV-2 infection can lead to hyperinflammation and increased COVID-19 disease severity and duration in diabetics. In support of this, diabetic mice infected with the MERS-CoV virus had more pronounced disease severity and duration than non-diabetic mice[99].

While the primary site of infection and inflammation in COVID-19 is the respiratory system[100], high inflammation has also been observed in the cardiovascular system[101-106], kidneys[102,107-109], liver[102,110-112], gastrointestinal tract[113-115], and the nervous systems[116-119]. Chronic inflammation can damage tissue, impair organ function, and contribute to the development of chronic diseases, including cardiovascular and metabolic disorders[120,121]. Thus, the hyperinflammation observed due to a combination of viral infection and diabetes symptoms may lead to poor disease prognoses.

Discussion

The established view is that diabetes and viral symptoms synergistically influence COVID-19 disease severity and mortality. While these associations may play a significant role, recent studies reveal more details about how diabetes physiology can influence viral reception, viral entry and pathogenicity, and disease symptoms. In this review, we focused on some of these interactions: Hyperglycemia in diabetics can lead to elevated expression of the SARS-CoV-2 receptor, ACE2, making cells more receptive to the virus; symptoms of diabetic physiology such as higher glycosylation, higher levels of furin and fibrinolytic enzymes can alter the function of the ACE2 receptor further increasing its affinity for the virus and facilitating viral entry into cells; other diabetes symptoms influence viral replication, viral clearance, and hyperinflammation, thus contributing to disease severity and mortality.

We note that many of these potential interactions between the diabetic and viral mechanisms remain incompletely understood or clinically tested. A more complete understanding of these interactions is critical before we can devise new strategies to mitigate the risk of COVID-19 infection and disease progression in people with diabetes. In this context, insightful knowledge may be gained by a renewed focus on investigating insulin- and ACE2-specific mechanisms and their potential interactions in different tissues using cell culture and model system research. These study systems offer controllable platforms to more precisely test specific hypotheses to investigate interactions between viral and diabetic mechanisms. Such approaches may lead to new insights and help identify potential drug targets primarily relevant to disease progression in diabetics.

Given that diabetes affects a large percentage of the world's population, we hope this review conveys the urgency for more attention to the interactions between diabetic and SARS-CoV-2 pathways.

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