Minireview *Highlight article*

COVID-19 and diabetes: What do we know so far?

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Impact Statement

Patients with diabetes and COVID-19 are prone to severe infections due to the hyperglycemia-driven increase in virulence of microorganisms and immune dysfunction. As a result, increased hospital admissions, thrombotic complications, and mortality have been observed in patients. Pro-inflammatory states linked with COVID-19 also play a key role in hyperglycemia, thereby worsening COVID-19 prognosis. In this review, we have outlined key factors connected with COVID-19 progression in an effort to understand its complex, bidirectional relationship with diabetes.

Abstract

Coronavirus disease 2019 (COVID-19) management has been challenging for patients with comorbidities. Patients with diabetes and COVID-19, in particular, have shown severe symptoms and rapid progression of the disease. They also have a high mortality rate compared to the non-diabetic population. The high mortality rate is caused in people with diabetes who are in a pro-inflammatory condition; this could worsen COVID-19. In addition, people with diabetes have circulatory issues and COVID-19 infection can lead to further clotting problems. It is critical to understand the mechanisms underlying the adverse clinical outcomes in patients with diabetes and COVID-19. This review discusses various disease conditions contributing to poor prognosis in diabetic COVID-19 patients such as hyperglycemia, insulin resistance, impaired pancreatic function, and production of advanced glycation end products.

Keywords: COVID-19, SARS-CoV-2, diabetics, hyperglycemia, insulin resistance

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Background

COVID-19 is caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). The respiratory syndrome has traumatized the world by infecting and taking the lives of larger population. It emerged in December 2019 in Wuhan, China.[1–3] COVID-19 has been linked to the utmost severe and fatal occurrences in people with pre-existing illness like cancer, hypertension, and diabetes.[4] One of the most prevalent comorbidity conditions in critical COVID-19 patients is diabetes mellitus.[5] Diabetes mellitus is an interlinked metabolic disorder affecting 422 million people worldwide[6] and is recognized by significantly elevated blood glucose levels that destructs the blood vessels and nerves. It also causes long-term injury to various parts of the body such as, eyes, brain, immune system, kidney, and heart.[7] COVID-19 and diabetes are linked to chronic and acute inflammation, respectively. COVID-19 can influence clinical progression and outcome of diabetes and vice versa.[8] Patients with diabetes and COVID-19 have a higher mortality rate (7.3%) compared to non-diabetic subjects with a mortality rate of 2.3%.[9]

Hyperglycemia, pancreatic function, insulin resistance, advanced glycation end products in relationship with COVID-19

Hyperglycemia, or constantly elevated blood sugar levels, is considered to be the most general metabolic modification connected with type 2 diabetes (T2D).[10] Hyperglycemia and immune responses are intricately intertwined and have a direct impact on the severity of SARS-CoV-2 infection.[11] Raised sugar levels proportionally elevate SARS-CoV-2 replication in human monocytes, and glycolysis withstands SARS-CoV-2 replication through the generation of mitochondrial reactive oxygen species (ROS) and the stimulation of hypoxia-inducible factor. In addition, when SARS-CoV-2 enters the pulmonary system, hypoxia occurs, which stabilizes HIF-α (hypoxia-inducible factor 1-alpha), resulting in overexpression of VEGF (vascular endothelial growth factor) and integrins, which causes vascular permeability and release of cytokines. Another hypothesis states that an increase in dead cells generates ROS, which in turn elevates HIF-α, leading glycolysis to be upregulated.[12] This also causes metabolic derangement, which leads to glycol toxicity. In case of glucotoxicity, the illness is exacerbated indirectly as it assaults in a variety of ways, starting with disrupting glucose homeostasis pathways such as polyol, hexosamine, and sorbitol. Upregulation of proteins involved in cell damage, such as pro-apoptotic, Toll-like receptors (TLR), and others, encouraging apoptosis and fibrosis. During the initial period of SARS-CoV-2 infection, diabetic patients acquired persistent hyperglycemia that worsens on a regular basis. Hyperglycemia may promote viral entry and proliferation.[12] In diabetes mellitus patients, infection causes incretin-like glucagon-like peptide and other insulin-secreting protein dysfunction, resulting in an increase in insulin demand. Infection also boosts the release of glucocorticoids and catecholamines, which worsens the glycemic condition and results in the end products of glycation.[13] High glucose levels have been shown to stimulate several immune cell types, resulting in increased generation of pro-inflammatory cytokines (tumor necrosis factor α (TNF-α), interleukin 1 beta (IL-1β), and IL-6).[14]

In patients with diabetes, the hyperglycemia may impair pulmonary function, which can be aggravated by influenza virus. In animal models of diseases, diabetes is connected to multiple structural alterations to the pulmonary system, including increased vasculature permeability and a collapsed alveolar epithelium.[15,16] Uncontrolled hyperglycemia produces aberrant glycated angiotensin-converting enzyme 2 (ACE2) formation not merely in pulmonary system as well as in the nasal pathways, tongue, and oropharynx, potentially increasing viral access sites and disease severity.[17]

Elevated amounts of ACE2 in pancreatic islet β-cells can trigger increased injury in islet cells and impaired insulin secretion.[18] With subsequent viral access into β-cells, there is a downregulation of ACE2, resulting in elevated angiotensin levels, which weakens insulin secretion.[14,19] Probable mechanisms of pancreatic damage comprise (1) direct cytopathic effect of SARS-CoV-2 replication, (2) systemic response to respiratory malfunction, and (3) damaging immune reaction prompted by SARS-CoV-2 infection.[20] Furthermore, COVID-19 is caused due to continuous acute hypoxia which can impact several body parts, including pancreatic islets, and may directly induce β-cell apoptosis directly.[19] SARS-CoV-2, on the other hand, affects macrophages and neutrophils and suppresses the formation of natural killer cells (NKC). The virus assaults the circulating blood and targets the immune system, destroying lymphocytes CD3, CD4, and CD8 cells, resulting in lymphocytopenia[13]. This is specifically related to SARS-CoV-2 infection as the patients with T2D and COVID-19 have higher serum contents of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, and IFN-γ).[14,21] The "cytokine release syndrome, generally called as cytokine storm" is accompanied by other inflammatory indicators like D-dimer, C-reactive protein (CRP), and ferritin in patients with SARS-CoV-2 infection and is connected to intensity of virus.[22] Elevated lactate levels in T2D patients may delay SARS-CoV-2 clearance by blocking the retinoic-acid-inducible RIG-1-like receptor through mitochondrial antiviral signaling protein, resulting in restriction in interferon generation and decreased antiviral response.[23]

Insulin resistance is generally associated with obesity, which is a direct pathophysiologic factor of T2D.[24] Over the past few years, there has been a surge of interest in the study of systemic inflammation. Obese people have a chronic systemic pro-inflammatory state that is defined by unusually excessive circulating levels of immune system in blood.[23] ACE2 is a key catalyst connection among insulin resistance and severe COVID-19, as it serves as a pro-hormone and a receptor at primary cellular entry route for SARS-CoV-2. ACE2 produces angiotensin 1 and octapeptide Ang II which cause vasoconstriction and cell proliferation, whereas Ang 1-7 causes vasodilation and inhibits cell growth.[14,25] Overexpression of ACE in the pulmonary organ favors ACE2 generation and binding to SARS-CoV-2, and even prompts to downregulate cellular expression of ACE2 contributing to chronic lung damage. ACE2 is increased in mice on an elevated sucrose diet to eliminate surplus angiotensin II and reduce their deleterious effects on insulin sensitivity and glucose carriage through the family of glucose transporter proteins. Patients with T2D cases have higher ACE2 receptor levels, which might aid SARS-CoV-2 in prolong cellular binding, increasing viral load and severity of infection.[26] Insulin-deficient monocytes and macrophages respond poorly to a variety of pathogens.[27] Insulin resistance is also related to surplus blood neutrophil count in patients with T2D, especially important in COVID-19, which is described by neutrophilia and monocytopenia.[28]

The pathogenesis of T2D is defined by the non-enzymatic covalent connection of glucose to biomolecules resulting in the development of advanced glycation end products (AGEs) in chronic hyperglycemia of patients with diabetics.[29] AGEs have been recently reported as a contributor to the risk of severe illness from COVID-19 in patients with diabetes.[30,31] AGEs have been demonstrated to bind to a variety of surface receptors, including CD36, scavenger receptors type I and II, and galectin-3.[32] AGEs induce the discharge of pro-inflammatory cytokines in monocytes, lymphocytes, and macrophages upon receptor engagement, promoting vascular inflammation and endothelial dysfunction.[10] AGEs generated in diabetic individuals are shown to stimulate the classical complement pathway by detecting C1q, inactivating

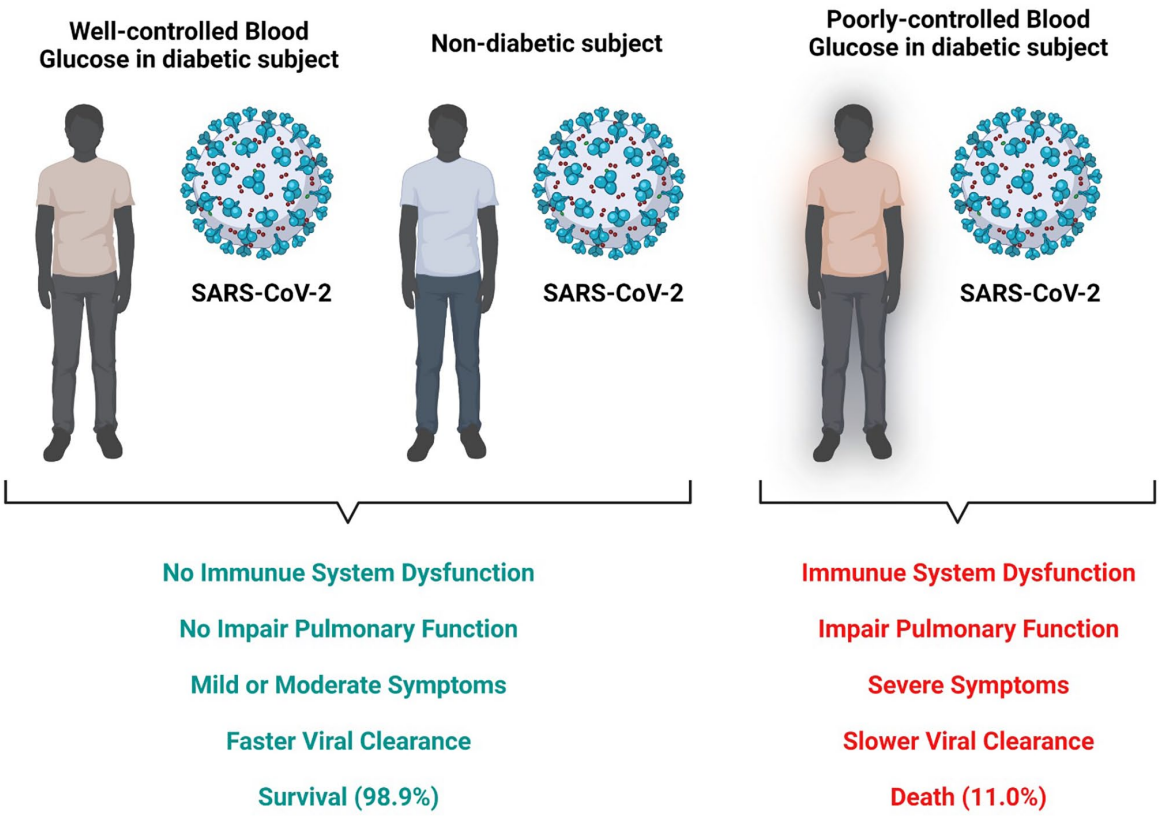

Figure 1. COVID-19 and diabetics.
Source: Created with BioRender.com. (A color version of this figure is available in the online journal.)

CD59 and increasing vascular damage in patients with T2D blood vessels.[33] In line with the theory, membrane attack complex deposits found in pulmonary tissue from severe COVID-19-infected patients have demonstrated complement-mediated injury, which subsequently causes vascular inflammation and leads to long-term lung damage.[34]

COVID-19 is a worldwide pandemic that has ravaged our human race recently. SARS-COV-2 is an extremely contagious virus with a rapid transmission and mutation.[35] Patients with COVID-19 with previous diseases like cardiovascular disease (7%), diabetes (11%), and hypertension (21%), according to current data, have a greater complication risk and require intensive care.[6,36] COVID-19 is more common among diabetics, and the majority of cases are more severe than the non-diabetic population.[37–39]

People with diabetes are susceptible to respiratory diseases as they are prone to multidrug-resistant gram-negative bacteria due to compromised cellular and humoral innate immune response.[25,36] As a result, chances of bacterial infection are high, leading to increased mortality due to uncontrolled pneumonia.[25,40] Moreover, people with diabetes more easily progress to severe symptom, leading to a hospital admission or ICU (intensive care unit) admission more frequently. If the patients show chronic infection, the incidence of nosocomial infection increases and leads to mortality of T2DM which might be increased by decreased immunity of T2DM.[41]

COVID-19 has the highest impact on the first-line immune defense in people with diabetes compared to the non-diabetic population.[25,42] People with diabetes are in pro-inflammatory state which triggers the cytokine response, leading to an increase in IL-6 and CRP levels in the blood.[43] Evidence indicates that increased IL-6 and CRP levels are physiological indicators of subclinical systemic inflammation, hyperglycemia, insulin resistance, and overt T2D.[43,44] These molecules are also linked to cardiovascular diseases, thereby enhancing the risk of cardiovascular complications in patients with diabetes suffering from SARS-CoV-2.[28] CRP has a major role in the acute phase as a downstream mediator.[43] Clinic evidence revealed that 24 patients with COVID-19 and diabetes had high levels of IL-6 and CRP when compared to 26 non-diabetic COVID-19 patients.[40] Increased D-dimer levels have been observed in patients with COVID-19 and diabetes. d-dimers are the smallest fibrinolysis degradation products, players of the hemostatic system of the body, generated as a result of the breakdown of blood clots. It increases the risk of thromboembolism.[39,45]

ACE2 present in the lungs is known to exhibit anti-inflammatory and antioxidant properties in various disease conditions. Unfortunately, ACE2 is also a receptor for SARS-CoV-2, allowing the entry of virus in the host.[14,25] In addition, serum ferritin levels in patients with diabetes and COVID-19 are nearly twofold greater than in non-diabetic patients.[40] Ferritin is important in the generation of monocytes and macrophages; both play key roles in hypertension. As a result, individuals with diabetes and COVID-19 are more likely to develop hypertension. As macrophages are more abundant when hypertension occurs, diabetic patients can acquire hypertension during corona.[46,47] Similarly, in diabetic COVID-19 patients, erythrocyte sedimentation rate (ESR), an inflammation-related biomarker, is higher than in non-diabetic patients[40] (Figure 1).

Challenges

Hyperglycemia is believed to affect the function of the immune response to injections, which leads to the uncontrolled spread of pathogens (including viruses, e.g., SARS-CoV-2) in diabetic subjects. The condition of hyperglycemia does not increase the vulnerability of patients to be infected with SARS-CoV-2. Still, the disease severity of COVID-19 can be increased by the comorbidity of diabetics.[13,48,49] COVID-19 may influence the blood levels of glucose;[50,51] in such conditions, clinical guidelines should be strictly managed in subjects with diabetes. Recent several studies have discovered that many mechanisms are believed to be responsible for a highlighted clinical severity of COVID-19 in people with diabetes,[13] so scientists and clinicians required more time and studies to understand further in detail about mechanisms involved in COVID-19 and diabetes. This will enable clinicians to prescribe medicine for subjects with diabetes during infections and recovery from COVID-19. Other challenges include the lockdown of standard outpatient clinics, decreased inpatient capacity, medicine shortage, staff shortage, and very importantly undiagnosed cases/events.

Conclusions

Better scientific knowledge about the molecular mechanism by which immune dysfunctions occur in subjects with diabetes can lead to novel treatments and even preventions for infections, thus improving the outcome of COVID-19 patients with diabetics. Evidence suggests that vaccines are effective against COVID-19, so subjects with diabetes should be vaccinated as soon as available. A better and improved strict guideline for management of subjects with diabetes should be in place. Finally, it is necessary to adhere to strict social distancing protocols to block the chain of infection.

AUTHORS' CONTRIBUTIONS

PG, HP, SHSR, MPJ, CMH, BA, UMR, SG, AK, PR, and KS contributed to the preparation of the initial draft and subsequent revisions. All authors approved the final version of the article.

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