

Diabetes Mellitus and COVID-19: Possible Interactions and Mechanisms in Comorbid Patients

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Abstract:

Beginning in December 2019 and still ongoing, coronavirus disease 2019 (COVID-19) infections have posed a public health challenge worldwide. There have been reports of diabetes mellitus (DM) as one of the most prevalent comorbidities in patients with COVID-19. Although the interactions and possible mechanisms of this association have not been fully established, the existence of DM is believed to aggravate the adverse effects of COVID-19 infection. Hence, the need for this paper. Findings from other studies have shown different possible mechanisms of how COVID-19 and DM aggravate the severity of each other. Among the hypothetical mechanisms reported between COVID-19 and DM in this paper are: COVID-19 causes complications of DM through the following: (1) Destruction of β -cells in the pancreas by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. (2) Cytokine storm generation which mediates tissue inflammation resulting in organ damage and (3) The use of corticosteroid drugs which have been found to be highly diabetogenic. Similarly, DM facilitates internalizing of SARS-CoV-2 symptoms through increasing expression of angiotensin-converting enzyme 2 (ACE2) and the furin protein, viral load, entrance and replication of SARS-CoV-2, glycosylation, and compromising of the immune response that worsens COVID-19. Having a clear understanding of the biochemical mechanisms of interactions between COVID-19 and DM may be useful for future research of agents targeted as therapeutic remedies for managing patients with diabetes infected with COVID-19 and vice versa.

Keywords: COVID-19, diabetes mellitus, hyperglycaemia, SARS-CoV-2

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Introduction

The coronavirus disease 2019 (COVID-19) is a viral infection caused by a virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The viral infection spread rapidly and thus has affected a large number of people globally since it was identified.¹ This incited the World Health Organisation (WHO) to promulgate it as a pandemic on 11 March 2020.² The disease manifests in symptoms such as fever, dry cough, dyspnoea, chest-pain, myalgia and fatigue with less common symptoms including sputum production, haemolysis, headache and diarrhoea. These symptoms are similar to the 2003 severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and middle-eastern respiratory syndrome (MERS-CoV) infections.^{3,4} However, SARS-CoV-2 differs slightly by showing prominent upper respiratory tract signs and symptoms such as rhinorrhoea, sneezing, or sore throat as observed in some patients confirmed to have been infected with the disease.³

Since the time COVID-19 was declared as a pandemic to date, it has caused serious disruptions to humans and is still a significant health challenge worldwide. Despite several different scientific approaches to curtail the disease, it still manifests in many individuals across the world. From 11th February 2020 to 26th July 2022, 259,485 confirmed cases, 3,302 active cases, 253,037 discharged cases and 3,146 deaths have been reported in Nigeria.⁵ Globally, there have been 566,977,818 confirmed cases, including 6,376,503 deaths, reported by the WHO.⁶ One of the things that makes COVID-19 more problematic is its ability to interact with several diseases including diabetes mellitus (DM) and intensify their complexities on human health. There have been various possible pathophysiologies of COVID reported, including mediation of viral cell entry via angiotensin-converting enzyme 2 (ACE2), tissue damage, and dysregulation of the renin-angiotensin-aldosterone system (RAAS).⁷ COVID-19 has been reported

to interact with multiple pre-existing abnormal conditions, including hypertension, cancer, cardiovascular disease, acute kidney injury, and diabetes mellitus, which have demonstrated high risks all of which can act to increase the severity of the COVID infection, as well as a high risk of increasing the risk of death.⁸⁻¹⁰ Diabetes mellitus is the most common comorbidity that has been reported as significantly associated with COVID-19.¹¹ In a study by the WHO¹² on COVID-19 in Africa, diabetes was reported as the predominant underlying condition or comorbidity in those who tested positive for COVID-19. The same study reported a 10% case fatality rate in COVID-19 patients with diabetes as against 2.5% for those who had only COVID-19. The study concluded that the fatality rate of COVID-19 patients with diabetes was twice as high as those who had COVID-19 plus some other comorbidity.¹²

It is a known fact that diabetes alters several metabolic pathways in the human body resulting in multiple types of complications. The disease can affect anyone regardless of age, gender, or social-economic status.^{13,14} It was found that patients with diabetes have a small amount of chronic inflammation caused mainly by imbalance visceral adipose tissue that affects the homeostatic blood sugar control and peripheral insulin sensitivity.¹⁵ Long-term high blood glucose and inflammation have been reported to cause irregular immune responses that are not effective resulting in diminished mobilisation of chemotaxis, phagocytic activity and polymorphonuclear leukocytes, diminished production of cytokines such as interleukin-1 (IL-1) and IL-6, inhibition of Tumour Necrosis Alpha (TNF α) activity by T-cells and glycation of immunoglobulin.¹⁵

Persons with DM have been reported to be at high risk of infection from viruses and to have worse prognoses once infected.¹⁶⁻¹⁸ Recent findings have indicated that DM may be the comorbidity associated with the highest number of comorbidity associated deaths.^{10,12,19} Similar association had earlier been noted from a literature survey which

found DM was the most common comorbidity in people who died from COVID-19 infections, SARS-CoV1 and MERS-CoV, suffered from diabetes mellitus, implying that diabetes mellitus is a major factor in the severity of as well as mortality from COVID-19.²⁰ Different studies have provided some hypotheses on how COVID-19 and DM interact which could explain the increased severity when they occur together. However, there have to date been no studies on the exact mechanism(s) of association between the two diseases, COVID-19 and diabetes mellitus. Hence, this study was undertaken to investigate certain hypothetical mechanism(s) of the association between COVID-19 and diabetes mellitus from the available literature with the aim of elucidating the mechanisms of interaction with the exact interaction mechanism(s) between COVID-19 and diabetes mellitus severity.

Pathogenesis of COVID-19 and diabetes mellitus

Various studies have reported that comorbid diabetes in patients with COVID-19 is connected with worse disease manifestations and even death. To examine this claim, COVID-19 patients with and without diabetes were investigated by Guo et al.²¹ Their study found that people with both COVID and diabetes were generally more severely than patients with COVID without diabetes, possibly due to high prevalence of organ injury and hypercoagulability as well as elevated levels of inflammatory factors.

A literature survey indicates that overstressed pro-inflammatory cytokine response, tumour-necrosis factor (TNF)-alpha, and interleukins including IL-1 and IL-6 as well as inappropriate responses of the immune system were associated with diabetes mellitus.¹⁵ These have been confirmed by some experimental studies. For instance, a study by Zhu et al.²² compared the levels of some immune system from patients with diabetes and those without diabetes but with COVID-19 infection (Table

1). The authors observed that greater occurrences of elevated neutrophil counts and reduced lymphocyte counts and increased levels of IL-6 were recorded in the serum of patients with diabetes. Increased IL-6 in diabetes has a harmful effect in the progression of diabetic complications such as retinopathy by serving as a mediator of vascular leakages.²³ The authors' findings could be traced to an earlier study on related infections using an experimental model of MERS mice with diabetes, where the immune response was found to have been altered due to the MERS infection.²⁴ Significantly high levels of blood glucose and lactate dehydrogenase activities were reported in COVID-19 patients with diabetes.^{25,26} The summary reports of the influence of coronavirus disease 2019 on the biochemical parameters of patients with diabetes mellitus are presented in Table 1.

Another important finding (Table 1) is the elevation of blood glucose levels in patients with diabetes compared with those without diabetes but infected with COVID-19 as reported by Zhu et al.²² Blood glucose control is essential in COVID-19 infected patients or those with related infections.²⁷ For instance, findings from patients with related infections such as SARS-CoV-1 and influenza H1N1 revealed that poor glycaemic control led to an increased risk of complications and death.^{26,28} The studies reported that SARS-CoV-1 can damage β -cells of pancreatic islets, causing elevation of blood glucose.^{26,28} This was shown by a study conducted on individuals without pre-existing diabetes but with SARS-CoV-1 infection. The study suggested that the hyperglycaemia recorded which persisted for some time after recovery from SARS might be due to β -cells damage.²⁴ One of the pathophysiologies of COVID-19 is tissue damage, including damage to the pancreatic β -cells.⁷ Another study by Singh et al.²⁷, suggested that lack of exercise and mental stress set in due to the unpredictability of the COVID-19 disease, which altered people's daily routines in respect to dietary intake

and access, leaving them eating foods high in calories, which in turn contributed to increased blood glucose levels. Based on the above statement, by implication, it shows that viral infection interferes with blood glucose control in patients with diabetes contributing to its elevation, hence worsening diabetes mellitus. This justified the hypothesis that diabetes worsens viral infections linked to hyperglycaemia, which was also reported earlier by Forbes et al.²⁹

Among other parameters that have been reported to have been altered in patients with DM compared to non-DM individuals but with COVID-19 (Table 1) are serum C-reactive protein (CRP) and lactate dehydrogenase (LDH).²² C-reactive protein is a well-established marker of systemic inflammation, and severe infections like COVID-19 promote its concentration.³⁰ In addition, its concentration was also found to be elevated in patients with severe H1N1 influenza pneumonia.³¹ Presently, LDH is one of several routine parameters used in assessing the severity of COVID-19.^{32,33} A high level of LDH was reported to be due to an increase in the production of lactate, which is an indication of changes in the glycolytic pathway and/or low oxygen conditions that occur in the context of infection and/or activation of cells.^{34,35} Other studies have reported that

when SARS-CoV-2 infected the lungs it caused a decrease in the oxygen supply as a result of increased inflammatory events that interrupted the glycolytic pathway, and in turn promoted glucose uptake. This may have consequences on cell function leading to dysfunction in several organs and/or increased generation of reactive oxygen species (ROS).^{36,37}

Diabetes mellitus is associated with many complications where the pathogenesis has been in part reported to be due to cellular hypoxia, which is induced by hyperglycaemia. This postulation was confirmed in a study conducted by Sada et al.³⁸, where endothelial cells were incubated with high glucose and later cellular hypoxia was observed. From this report, one may hypothesize that reduced cellular oxygen content due to the inability of cells affected with SARS-CoV-2 to carry oxygen plus cellular hypoxia induced due to hyperglycaemia might play a significant role in speedy increase in the progression of diabetes disease complications.

Severe inflammatory infection has been reported to induce the failure of many organs such as the heart, liver, and kidneys.^{9,39} In a study by Zhu et al.²² on patients with and without diabetes, they found that there was a

Table 1 Summary of reports on the influence of coronavirus disease on biochemical parameters of patients with diabetes mellitus

Selected studies	Zhou et al. ¹⁰	Kulcsar et al. ²⁴	Yang et al. ²⁵	Yang et al. ²⁶
Effect on the immune system				
lymphocyte counts	Decreased	ND	ND	ND
neutrophil counts	Increased	ND	ND	ND
monocytes	ND	Decreased	ND	ND
interleukin-6	Increased	Decreased	ND	ND
Effect on biochemical Parameters				
Blood glucose level	Increased	ND	Increased	Increased
C-reactive protein	Increased	ND	ND	ND
Lactate dehydrogenase	Increased	ND	Increased	ND

ND=not determined

greater occurrence of septic shock (3.8% versus 1.0%), acute respiratory distress syndrome (ARDS) (16.9% versus 7.2%), acute heart injury (7.3% versus 3.0%), disseminated intravascular coagulation (0.5% versus 0.2%), and acute kidney injury (3.9% versus 0.8%) in the diabetic patients. Increasing incidences of organ damage related to diabetes, such as neuropathy, nephropathy, and retinopathy, has been reported in COVID-19 patients. Several studies have found that one of the key challenges of a SARS-CoV-2 infection is the formation of a cytokine storm^{15,37,40,41}, a drastic increase in immune cell production of inflammatory cytokines which in turn lead to tissue inflammation resulting in organ damage.⁴⁰ Experimental evidence has shown that inflammatory cytokine storms are associated with adverse outcomes of SARS-CoV or MERS-CoV infections.^{41,42}

Hypothetical mechanisms of interactions between COVID-19 and diabetes mellitus

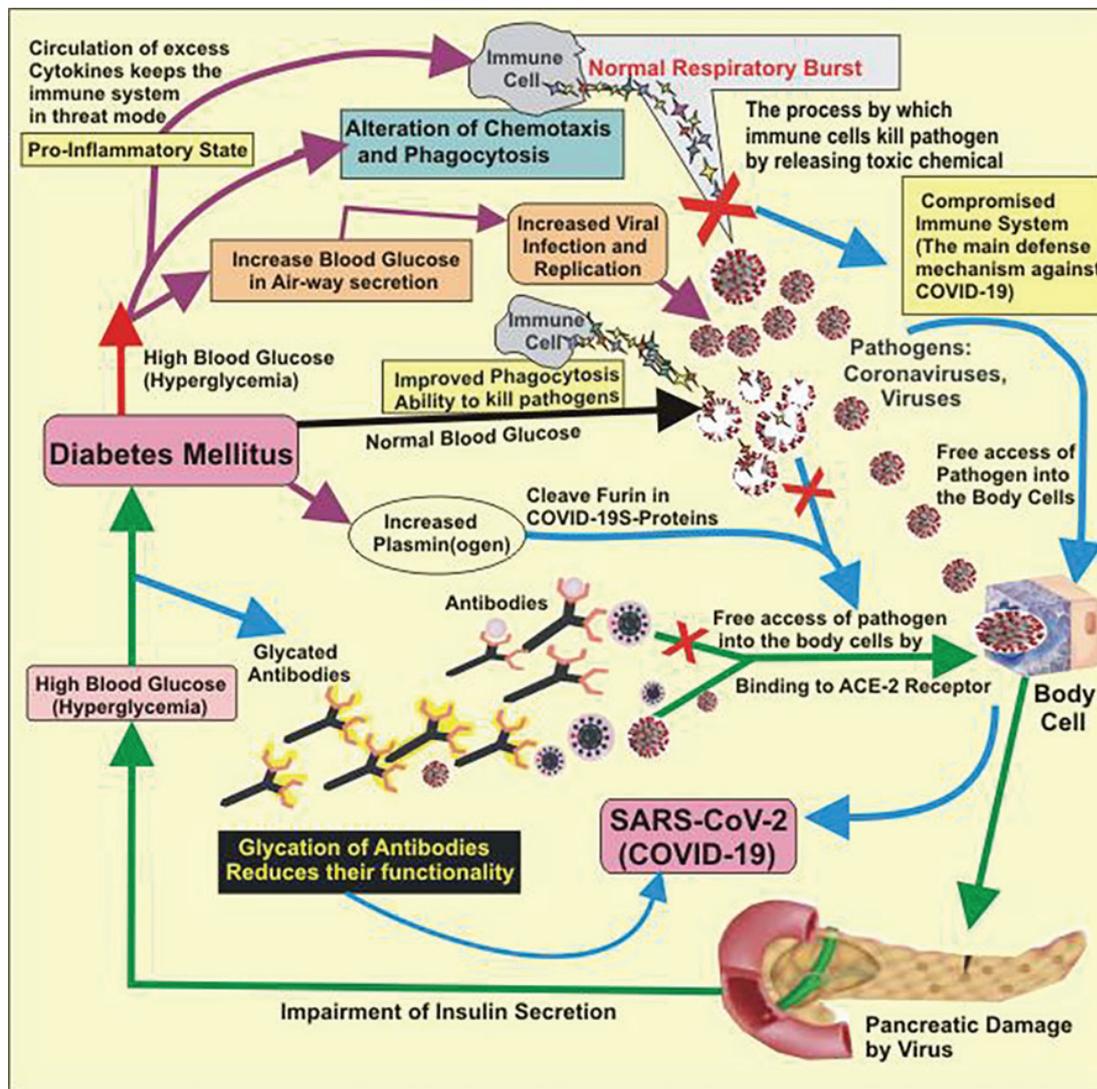
Highlights from some key postulated mechanisms of COVID-19 pathophysiology such as endothelial cell damage, direct viral toxicity, thromboinflammation, dysregulation of the immune response, and dysregulation of the renin-angiotensin-aldosterone system (RAAS), etc. have been reported in several articles.^{7,43,44} In this review, the most likely mechanism(s) that have clearly attempted to explain how COVID-19 aggravates diabetes severity are emphasised. These include the mechanism by which SARS-CoV-2 infection influences β -cells damage, cytokine storm formation, the consequences of the use of corticosteroid drugs for the treatment of SARS-CoV-2 infection, and observing COVID-19 lockdown rules/self-home quarantine measures, etc. These mechanisms were carefully and diligently sorted out from selected articles and are holistically harmonised in subsequent sections of this review. The development and progression of Type-1 diabetes mellitus is reported to be mainly via β -cells destruction. A literature survey found that one of the

pathophysiologies of COVID-19 is tissue damage, including to the pancreatic β -cells.⁷ In this article, the mechanisms by which SARS-CoV-2 infection destroys the pancreatic β -cells amongst other factors that lead to greater severity of Type-1 DM are also discussed.

Hyperglycaemia due to diabetes mellitus alter several metabolic processes in the body that may result in increases complexities of the disease symptoms. This study also highlights some of the hypothetical mechanisms by which hyperglycaemia in association with existing abnormalities such as COVID-19 comorbidity can lead to greater severity of the latter ailment. The mechanisms considered include how hyperglycaemia promotes angiotensin-converting enzyme 2 expression (a vehicle used for the entry of SARS-CoV-2 into cells), increases viral load, compromises innate immunity and promotes the glycosylation of haemoglobin.

Destruction of β -cells during SARS-CoV-2 infection: Part of the pathophysiology of COVID-19 according to Gupta et al.⁷ is tissue damage inclusive of pancreatic β -cells. However, how the β -cells are damaged by SARS-CoV-2 is still a subject of debate and several mechanisms explaining β -cells destruction by SARS-CoV 2 have been proposed. A study by Unnikrishnan and Misra⁴⁵ suggested that when SARS-CoV-2 enters the pancreatic β -cells, it can subsequently destroy the cell, leading to the process in the progression of insulin-requiring diabetes in patients with COVID-19 (Figure 1). A larger number of pancreatic β -cells need to be destroyed for this type of non-autoimmune diabetes to develop following an infection of the virus. But how exactly the viral infection destroys the insulin-producing cells remains a key point to be researched. Studies examining the etiopathogenesis of Type-1 diabetes following infection with viruses like the Coxsackie B virus, mumps virus, cytomegalovirus, rubella virus, or enteroviruses have found that the viruses act by stimulating an autoimmune attack against antigens of the pancreatic β -cells leading to the activation of auto-reactive

T-lymphocytes, resulting in an autoimmune response that finally destroys the remainder of the insulin-producing cells in diabetes patients, leading to the development of diabetes complication.⁴³



COVID-19 infection damages the pancreatic β -cells when SARS-CoV-2 enters the body cells and promotes the elevation of blood glucose by impairing insulin secretion. This aggravates diabetes mellitus complications. On the other hand, diabetes mellitus aggravates COVID-19 by promoting viral entry and replication, and compromising the immune network, which is the main defence network against SARS-CoV-2 infection. The resultant consequences from the interaction of the two diseases lead to excessive inflammation, which can worsen severity and increase fatality.

Figure 1 An illustration of a hypothetical mode of interaction between diabetes mellitus and COVID-19

To date researchers have not been able to apply the results of such studies to COVID studies, as the data are too new. Other studies on the post-acute phase have been able to find clearly increased risks of incident diabetes in people who had had COVID-19 compared with people who had not contracted SARS-CoV-2.⁴³ According to Wang and colleagues⁴⁶, several mechanisms of pancreatic injury following a SARS-CoV-2 infection have been identified including the effect of SARS-CoV-2 replication on cells, respiratory failure from a systemic response, and a harmful response by the immune system.

It is clear that β -cells damage is a major factor in SARS-CoV-2 infection, however, how the cells are being destroyed is still a subject of debate. Based on other scientific perspectives, SARS-CoV-2 might have destroyed β -cells through the generation of free radicals or reactive oxygen species (ROS). ROS generation can result from SARS-CoV as earlier demonstrated with HL-CZ cells.⁴⁷ This hypothesis was also supported by experimental evidence from a study where the SARS-CoV infection was found to induce lung injury because of ROS production.^{48,49}

In agreement with the above statement, Santos et al.⁵⁰ hypothesized that, once SARS-CoV-2 is inside a cell, it activates a mechanism that damages the mitochondrial oxidative pathway, which promotes intracellular production of reactive oxygen species that increase cell damage. The pancreas has few antioxidant defences and SARS-CoV-2 can gain entrance into the pancreas thereby enhancing ROSs that destroy the β -cells resulting in failure of insulin secretion, hence compromising blood glucose regulation resulting in its elevation (Figure 1).¹² One study reported that diabetes mellitus resulted from either an absolute lack of insulin or cellular failure to properly utilize insulin.⁵¹ The hallmark of diabetes is chronic hyperglycaemia that brings about glucose toxicity via the formation of advanced glycation end products in the body.⁵² Chronic complications of diabetes such as cardiovascular disease, neuropathy, nephropathy, and retinopathy result from such mechanisms.

ROS generation in a SARS-CoV-2 infection can also occur via the activation of NADPH oxidase. NADPH oxidase is an enzyme complex found in the cells of several tissues, including macrophages and neutrophils. NADPH oxidase acts in the production of oxygen radicals in various cells and tissues as its primary and sole function using NADPH which is produced following the pentose phosphate pathway.⁵³ NADPH serves as an electron donor during the production of ROS.^{50,54} However, ROS can be produced by several other enzymes such as cytochrome P450 oxidase, lipoxygenase, monoamino oxidase, uncoupled nitric oxide synthase, xanthine oxidase, and the mitochondrial electron transport chain. These enzymes were found in one study to produce ROS only after ROS disrupts them.⁵⁵ Another study reported that a SARS-CoV-2 infection activates NADPH oxidase when the viral protein spike binds with the angiotensin II receptor.⁵⁶

Diabetic ketoacidosis (DKA): Diabetic ketoacidosis is an acute and life threatening complication of diabetes distinguished by hyperglycemia, ketoacidosis, and ketonuria. It occurs when there is total or comparative insulin deficiency that hinders the ability of glucose to enter cells for usage as metabolic fuel, the result being that the liver swiftly breaks down fat into ketones to utilize as a fuel source. DKA has been reported as one of the prevalent outcomes in patients with Type-1 DM.⁵⁷ Several studies have reported a significant increase in incidences of diabetic ketoacidosis associated with SARS-CoV-2 infection. Among the several studies are a study by Vamvini et al.⁵⁸, which reported 14.28% of diabetic acidosis compared to 7.14% in Type-1 diabetic patients without COVID-19. Other studies include that of Ebekozien et al.⁵⁹, which reported that diabetic ketoacidosis was about 3-fold higher in Type-1 diabetic patients with COVID-19 (45.5%) compared to 13.3% in patients without COVID-19.

Early studies on COVID-19 reported that Interleukin-6 (IL-6) may play a part in the mechanistic explanation of how the incidence of DKA is higher in Type-1 diabetics

with COVID-19.⁶⁰ Another study suggested that the higher rates of DKA in Type-1 diabetics with COVID-19 may be due to the interactions between SARS-CoV-2 and the renin angiotensin-aldosterone system (RAAS).⁶¹ Another study hypothesized that entry of SARS-CoV-2 into pancreatic islet cells may directly lead to β -cells injury⁶², while down-regulation of ACE-2 after viral entry can in turn lead to un-opposed angiotensin II which may impede insulin secretion.⁶³ We further hypothesize that the above scenarios might contribute to the mild reductions in pancreatic β -cells function as well as precipitating DKA. The interaction between SARS-CoV-2 and the RAAS can complicate DKA management in Type-1 diabetes, hence worsen the disease.

Cytokine storm generation: A cytokine storm is a phenomenon that refers to excessive inflammation. Inflammation generally plays a vital role in healing, however chronic/excessive inflammation increases the risk of a disease. Excessive inflammation is reported to be one of the key problems associated with COVID-19. Cytokine storms are characterised by a drastic increase in immune cell production of inflammatory cytokines, which mediates tissue inflammation resulting in organ damage.⁴⁰ Several studies have indicated widespread inflammation affecting several organs such as the lungs, kidney, heart, and liver.⁵⁶ For instance, COVID-19 has been shown to induce different degrees of liver dysfunction, however, the exact underlying mechanism is still unknown.

It has been hypothesised that viruses can cause organ damage including hepatic injury due to their cytotoxicity or injury can result from the usage of medications such as lopinavir/ritonavir, macrolides, quinolones, or acetaminophen (paracetamol) in treating viral infections such as COVID-19.⁶⁴ Another factor may be from the use of high levels of positive end-expiratory pressure, which can lead to hepatic congestion when the right atrial pressure is full thereby preventing venous return.⁶⁵ One

study reported that once SARS-CoV-2 gains entry into the host cells, its major acts are the induction of an inflammatory reaction with T helper cells and the production of interferon γ .²⁷ This process culminates into the generation of other inflammatory cells, which in turn have an effect known as a 'cytokine storm' according to Singh et al.²⁷ Cytokine storms in patients with diabetes may exacerbate diabetic complications.

Corticosteroids use in People with COVID-19: One study reported that corticosteroids such as dexamethasone were effective when used for the management of severe COVID-19.⁶⁶ This drug prevents COVID-19 patients from developing pneumonia. However, it was found to be highly diabetogenic. It promotes the elevation of blood glucose levels and also imposes some changes on the metabolism of macromolecules including carbohydrates, resulting in insulin resistance, hyperglycaemia and glycosuria.⁶⁷ One of the ways by which dexamethasone alters carbohydrate metabolism is by increasing hepatic gluconeogenesis through activation of glucose 6-phosphatase, fructose-1,6-bisphosphatase and phosphoenolpyruvate carboxykinase activities.⁶⁸ In addition, another study reported that the drug decreased peripheral glucose utilisation, leading to high blood glucose levels.⁶⁹ When a corticosteroid drug was used on patients with diabetes and COVID-19 infection, several complications such as worsening diabetes, avascular necrosis, and psychosis were recorded.^{70,71} Another study reported that a corticosteroid drug could cause a raise in blood glucose by 80% increasing mortality in patients with coronavirus infection.²⁶

COVID-19 lockdown policies/self-home quarantine measures: Another study reported that a silent but important factor that aggravated diabetes during a SARS-CoV-2 infection was the COVID-19-induced lockdown policies. During the COVID-19 lockdowns, many people were exposed to lifestyle changes associated with dietary habits, physical activity, and so on.⁷² The study

reported that both diabetes and non-diabetes individuals worldwide were faced with some difficulties such as accessing healthy foods, getting adequate amounts of physical activity, regular visits to the hospital for check-ups, etc. during the pandemic due to fear of contracting the virus.⁷³ According to Ghosal et al.⁷⁴, one of the consequences of the COVID-19 pandemic on diabetes patients was a deterioration in glycaemic control with no options other than for it to become elevated. This was also reported in a study where it was suggested that the elevation of blood glucose in patients with diabetes during the COVID-19 pandemic was likely a result of a combination of lack of physical exercise, poorly balanced diet, and financial challenges, as well as difficulty in visiting hospitals during the lockdown.⁷⁵ In Africa, the WHO¹² reported that during the COVID-19 pandemic, access to diabetes care was interrupted. Deliberate lockdowns to minimise the spread of COVID-19 prevented access to several types of health care and some basic health management factors, such as routine glucose checks and eating a balanced diet.

Another study found that during the self-home quarantine periods observed by patients with diabetes suspected to have been infected with SARS-CoV-2 rises in blood glucose levels were also common. This observation may have been related to insufficient glucose control causing numerous acute and chronic complications.⁷⁶

Hyperglycemia promotes the expression of ACE2: a vehicle for cell entry of SARS-CoV-2: SARS-CoV-2 gain entry into a cell using a membrane protein known as ACE2.⁷⁷⁻⁷⁹ The coronavirus (SARS-CoV-2) uses its spike (S) protein to bind to the angiotensin-converting enzyme 2 receptors on target cells, forming protein-receptor complexes which are internalised with the help of respiratory epithelial or innate immune system cells, according to Zhang et al.³³ Type-1 diabetes mellitus is an autoimmune disorder involving immune-mediated recognition of islet β -cells by auto-reactive T-cells.⁸⁰ This subsequently leads to the liberation of pro-inflammatory cytokines and reactive

oxygen species which destroy the pancreatic β -cells in the islets of Langerhans leading to loss of insulin secretion. Pancreatic β -cells are sensitive to cytotoxic damage caused by reactive oxygen species and so activate antioxidant molecules including ACE2 which play a vital role in normal physiology as anti-inflammatory and anti-oxidant agents. One study found that ACE2 expression was high in the pancreas compared to other tissues including the lungs.⁸¹ Continuous degradation of the β -cells by reactive oxygen species may lead to an increased expression of ACE2 to counteract the free radicals in the pancreas, but which will then have the adverse effect of becoming accessible for larger numbers of SARS-CoV-2 viruses to gain entrance into the cells. One study reported that diabetes mellitus interfered with the angiotensin-converting enzyme 2 in different tissues of the body.⁸² ACE2 plays a vital role in normal physiology as anti-inflammatory and anti-oxidant agents against ARDS in various organs like the lungs. By implication, the activity could be successfully achieved when ACE2/angiotensin (1-7) are in the proper proportion. Angiotensin (1-7) is obtained from the degradation of angiotensin II to angiotensin I by the ACE2. ACE2 has been reported to be significantly expressed by epithelial cells in several tissues such as the lungs, renal tissues, intestinal cells and blood vessels.⁸³

Other studies have reported the expression of high amounts of ACE2 in patients with diabetes, particularly those who were treated with drugs such as angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.^{84,85} The overexpression of ACE2 was suggested to be due to the response from the adaptive immune system to counteract elevated levels of angiotensin-2 and angiotensin-1. By this process, SARS-CoV-2 entrance into cells is facilitated to become more severe and fatal in the host cells.⁸⁶ This has been experimentally demonstrated using pioglitazone and liraglutide on animals with diabetes where ACE2 expression was found to be up-regulated.^{87,88}

In addition, it was observed that the rate at which SARS-CoV-2 gains entrance into cells and exerts its effect depend on the shedding of ACE2.³³ A study by Lambert et al.⁵³ indicates that ACE2 could be shed by chemical compounds such as a disintegrin or metalloproteinase 17. The study found that disintegrin or metalloproteinase 17 were able to shed the external part of the membrane-bound cell sticking area and exposing the rudimentary site of the angiotensin converting enzymes 2 for binding by the SARS-CoV-2.⁵³ When this was experimentally demonstrated using compounds such as using phorbol myristate acetate⁵², it was found that the compounds were able to shed the ACE2 enzymatic active site.

Long term uncontrolled hyperglycaemia is associated particularly with Type-2 DM due to the inability of the pancreatic cells to eternalize and utilize glucose as a result of insulin resistance. A continuous presence of high glucose levels at the peripheral cells may result in several abnormalities that favour both bacterial and viral infection.⁸⁹ The exact consequence of hyperglycaemia favouring viral infections such as SARS-CoV-2 infection is discussed in subsequent sections.

Hyperglycaemia increases viral load: Under normal conditions, glucose is not present in airway secretions, but appears only where hyperglycaemia or epithelial inflammation arises (Figure 1). A study by Philips et al.⁹⁰, found that high blood glucose levels directly increase the concentration of glucose in airway secretions. Elevated airway glucose concentrations were found to play a part in worsening respiratory disease by promoting local inflammation in a study by Gill et al.⁹¹ where the authors hypothesised that increased airway glucose caused by hyperglycaemia could lead to increased bacterial loads. In their study they observed that respiratory tract bacterial colonisation in critical care patients was significantly higher in patients with hyperglycaemia. In another study conducted

by Codo et al.⁹² on SARS-CoV-2-infected monocytes cultured in different concentrations of glucose, it was found that higher levels of glucose were associated with higher viral loads. By implication, persons with a high level of circulating glucose may be at higher risk of contracting SARS-CoV-2.

Hyperglycaemia promotes the entrance and replication of SARS-CoV-2: A protein known as furin has been associated with COVID-19 patients who have diabetes.⁸⁸ A study suggested that high levels of furin in plasma could lead to dysmetabolic conditions, particularly DM.⁹³ Singh et al.²⁷ reported that an enzyme form of furin was found to be associated with diabetes. This protein was significantly elevated in the diabetic state in patients with diabetes.⁹³ Furin is a Type-1 membrane-bound protease belonging to the family of proprotein convertase subtilisin/kexin. It was found to be involved in facilitating the entrance of coronaviruses into the cell and their replication.^{93,94} Furin enhances viral entry into the cell by cleaving the S protein of SARS-CoV-2 into two subunits, subunit 1 (S1) and subunit 2 (S2) during processing and maturation in cells infected with the virus. Subunit 1 binds to the ACE2 receptor, while subunit 2 holds the S protein to the virus.⁷⁹ However, furin acts by cleaving the spike glycoprotein creating a C-end peptide, which binds to neuropilin-1 (NRP1) and facilitates the entry of SARS-CoV-2 into the cell. Viral cell entry driven by NRP1- is thought to be facilitated in cells which express low ACE2, such as the olfactory endothelial cells.⁹⁵ A study reported that diabetes is associated with a high level of plasmin(ogen) in the plasma (Figure 1).⁹⁶ Plasmin(ogen) influences COVID-19 severity by cleaving the S protein of SARS-CoV-2, making it available and accessible for binding with the receptors of the angiotensin-converting enzyme 2 of the host cells, which enhances the entrance of the virus into cells.⁹⁶ (Figure 2).

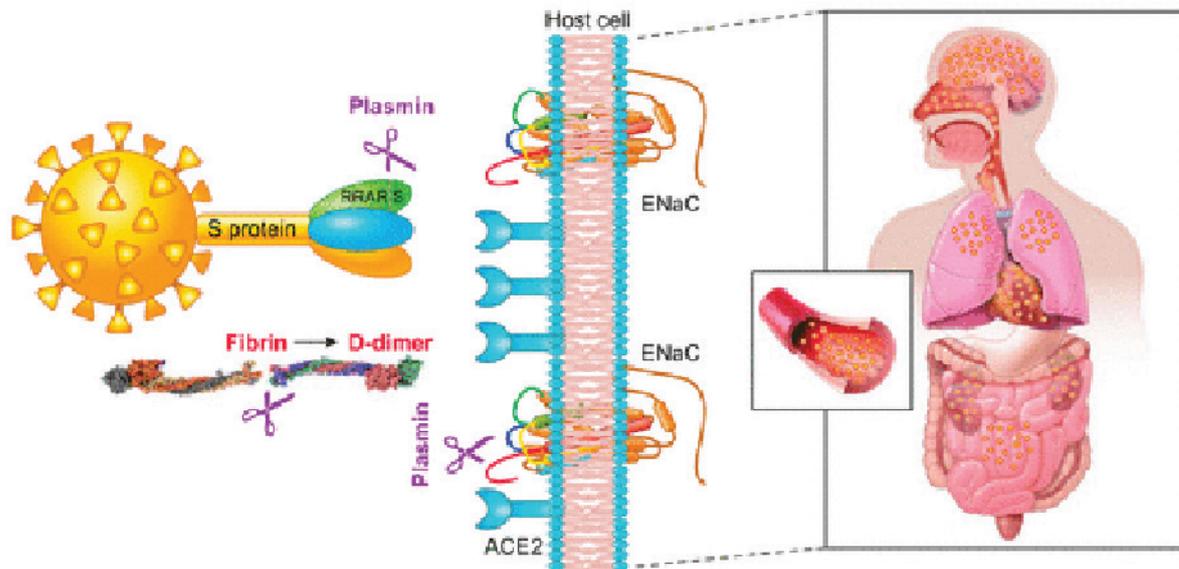


Figure 2 Plasmin (ogen) increases the pathogenicity of COVID-19.⁹⁶

In another dimension, high blood sugar could increase the replication of SARS-CoV-2 by playing a part in making cells highly glycolytic. Codo et al.⁹² found that cells infected with SARS-CoV-2 became highly glycolytic, which facilitated virus replication. In the experiment CoV-2-infected monocytes were cultured in different concentrations of glucose solutions: 2.5 mM equivalent to 40 mg/dL (low), 5.5 mM equivalent to 100 mg/dL (normal), 11.1 mM equivalent to 200 mg/dL (high), and 22.2 mM equivalent to 400 mg/dL (extremely high). The study found that higher doses of glucose results in higher parameters such as viral load, ACE2 concentration, and Interleukin-1b expression in the cultured CoV-2-infected monocytes.⁹² In summary, the data from the study indicates that high glucose levels promote viral cell entrance and replication.

Hyperglycemia compromises the immune response: Hyperglycemia is the hallmark of diabetes mellitus. In a study by Bode et al.⁹⁷, hyperglycaemia was found to be strongly associated with worse COVID-19 disease. Graves and Kayal⁹⁸ found that diabetes mellitus seemed to compromise an immune response known

as innate immunity, which is the defence mechanism against viruses such as SARS-CoV-2. In their study hyperglycaemia was found to disrupt the innate immune network as evidenced by the massive production of TNF-alpha.⁹⁸ High production of TNF-alpha was reported also in their study to be due to a polyol interaction which was activated by diabetes mellitus (hyperglycaemia) as accompanied by the activation of protein kinase C, increased superoxide and production of glycated end products.

On the other hand, hyperglycemia was reported to induce inflammation in innate immune cells e.g. macrophages via a mechanism that interferes with the tolerogenic haemoglobin-haptoglobin scavenging process of the CD163, which could lead to elevated heme toxicity contributing to endothelial damage and susceptibility to vascular complications.⁹⁹ This was demonstrated in the same study reported above that was conducted by Matuschik et al.⁹⁹ to examine whether hyperglycemia was able to amplify inflammation via haemoglobin-haptoglobin complex interactions with the immune system. The study used macrophage M(IFN γ), macrophage M(IL-4),

and control macrophages which were differentiated out of primary human monocytes in normo- (5 mM) and hyperglycaemic (25 mM) conditions, and found that CD163 gene expression was decreased by 5.53 times in M(IFN γ) with a further decrease of 1.99 times in hyperglycaemic patients. They also found that hyperglycemia could induce an inflammatory response of innate immune cells to human haptoglobin variants (Hb-Hp1-1 and Hb-Hp2-2) uptake, converting the silent Hb-Hp complex clearance that prevents vascular damage into an inflammatory process, thereby increasing the susceptibility of diabetic patients to vascular complications.

The literature review found various studies reporting that interactions between the innate immune system and viruses limited the rate of viral spread within host cells but exerted a consequential effect on the adaptive immune response.¹⁰⁰ Dendritic cells (DCs) and macrophages (MPs) are the first line components of the innate immune network; DCs produce many Type-1 interferons (IFN) that induce direct antiviral responses while MPs produce pro-inflammatory cytokines inducing antiviral protection.¹⁰⁰ Compromising the defence system against SARS-CoV-2 increases the severity of its pathological inflammation effect known as a cytokine storm. Viral-introduced cytokine storms are implicated in increased immune cell production of inflammatory cytokines, a major mediator of inflammation.⁴⁰

The mechanism behind a compromised DM immune system is associated with the induction of immune response imbalance resulting in dysregulation of certain immune modulator.²⁴ This dysregulation was found to decrease CD3⁺ T cell counts, which in turn alters adaptive immunity resulting to chronic inflammation. A report found low levels of lymphocyte and T-lymphocyte subtypes, including CD3, CD4, and CD8, which are responsible for lymphocytopenia in diabetic individuals.¹⁰¹ Another study found that antigen expression and immunity against invaded pathogens, including CoV was achieved by the production of a molecule

known as interferon gamma (IFN- γ), where CD4⁺ T helper (Th1) cells were reported to play a significant role in the production of interferon gamma (IFN- γ). In another study, SARS-CoV-2 was found to enhance apoptosis of CD4⁺ T-cells, hence compromising the production of interferon gamma (IFN- γ).⁸⁵

Vascular dysfunction and thrombotic complications: Another clinical study found that COVID-19 patients could develop thrombotic diseases like microvascular thrombosis as well as venous or arterial thrombosis.¹⁰² This finding was investigated from a study of necropsy and post-mortem biopsies of persons who died of SARS-CoV-2 infection which found both macro and micro-vascular thrombosis in all the organs analysed.¹⁰³ It is a clear fact that diabetes is associated with both micro- and macro-vascular complications.¹⁰⁴ Other studies reported that Type-2 diabetes, which is characterized by insulin resistance and hyperglycemia along with other metabolic abnormalities, impaired vascular walls through a number of biochemical events which could lead to vasoconstriction and thrombus development.^{105,106} This scenario has been found to significantly aggravate COVID-19 in developing thrombotic diseases in patients infected with SARS-CoV-2.¹⁰²

Glycosylation in diabetes mellitus patients: Uncontrolled diabetes is associated with glycosylation which may result in the formation of high deoxygenated haemoglobin levels in the blood. Studies have shown that glycosylation alters the structure and function of haemoglobin.^{107,108} An *in vivo* study found that high levels of glycosylated-haemoglobin (HbA_{1c}) increase glucose conversion to fructose through the polyol-pathway thus increasing fructose concentrations¹⁰⁹, which in turn, according to Bose and Chakraborti¹¹⁰, induces structural and functional conformational changes in haemoglobin thereby weakening its affinity for oxygen thus leading to elevated deoxygenated haemoglobin. It has been reported that

both oxygenated and deoxygenated haemoglobin is easily attacked by SARS-CoV-2.^{107,108} However, deoxygenated haemoglobin was found to be more susceptible to the attack.¹¹¹ This may imply that the higher the deoxygenated haemoglobin content the higher the risk of attack by SARS-CoV-2, hence increasing the risk of catching COVID-19. This may result in an increased SARS-CoV-2 viral load and its subsequent spread since it worsens the risk of the disease. On the other hand, glycosylation was found to reduce ACE2 expression.^{7,63} This may promote an increased predisposition to severe damage to the lungs and ARDS by SARS-CoV-2.^{83,112} The summary of findings related to the influence of diabetes that results in compromised factors responsible for mitigating a SARS-CoV-2 infection is presented in Table 2.

Outcome of COVID-19 and diabetes mellitus interactions

From this study, it is concluded that COVID-19 causes elevation of blood glucose via the destruction of β -cells of the pancreas which aggravates DM severity, while DM facilitates the internalising of SARS-CoV-2 via increasing expression of ACE2 and furin, and compromises the immune response leading to worse COVID-19 infection. It is also concluded that interactions between the two diseases have reciprocal effects, in that COVID-19 contributes to

the severity of diabetes mellitus and vice versa. It is also observed that both diseases promote excessive cellular inflammation. Various studies have reported that excessive inflammation was reported to be responsible for both morbidity and mortality in COVID-19 patients.¹¹³⁻¹¹⁶ A post-mortem study of patients who died of COVID-19 found that most of them had high levels of circulating cytokines, profound lymphopenia and substantial mononuclear cell infiltration, which are responsible for inflammation, in organs such as the lungs, heart and kidneys.^{117,118} One study found that hyperglycaemia contributed to chronic inflammation by mediating the formation of advanced glycosylation end-products, which in turn elevated inflammatory indices.¹¹⁹ This was also found in a study by Esposito et al.¹¹⁴ where increasing circulating cytokine concentrations were recorded after the elevation of blood glucose following administration of a glucose solution. Coronavirus causes elevation of blood glucose, possibly due to destruction of the β -cells of pancreatic islets, a postulate confirmed in a study by Yang et al.²⁵, where blood glucose elevation was found to be associated with damage to the β -cells of the pancreatic islets by SARS coronavirus.

Inflammation generally plays a vital role in the healing process. However, chronic/excessive inflammation increases the risk of a disease. One of the key problems associated with COVID-19 is the cytokine storm. The

Table 2 Studies on the influence of diabetes mellitus on the immune system

Study	Morey et al. ⁹⁴	Jafar et al. ¹¹³	Graves and Kayal. ⁹⁸	Esposito et al. ¹¹⁴	Geerlings and Hoepelman ¹¹⁵
Effect on immune System					
TNF-alpha	Increased	ND	Increased	Increased	Increased
Neutrophil counts	ND	Decreased	ND	ND	ND
Interleukin-6	Increased	ND	ND	Increased	Increased
Chemokines	Increased	ND	ND	ND	ND

Where TNF-alpha: tumour-necrosis factor alpha, ND=not determined

cytokine storm is characterised by a drastic increase in immune cell production of inflammatory cytokines, which mediates tissue inflammation resulting to organ damage.¹²⁰ An autopsy study of lungs from patients who died of COVID-19 revealed endothelial cells damaged, damage to the alveoli, suggesting excessive inflammation. Another study reported blood clots in the kidney and liver following post-mortem investigations, which implies damage to endothelial cells showing an underlying process correlated with activation of the coagulation cascade and persistent elevation of blood markers of inflammation.¹²¹

Conclusion

The possible interactions and mechanisms that exist between diabetes mellitus and COVID-19 in comorbid patients are complex and complicated. COVID-19 promotes the elevation of blood glucose by destruction of β -cells of the pancreas, while diabetes mellitus promotes SARS-CoV-2 cell entrance via increasing expression of ACE2/furin and compromises the immune response, particularly the innate immune system, which are in the frontline of defence against SARS-CoV-2. The significant point of this investigation is that it summarises the postulated mechanisms of the association between COVID-19 and diabetes mellitus making it easily accessible to scientists and researchers in future research. Understanding the clear biochemical mechanisms of interactions between COVID-19 and DM may be useful for future research of agents targeted as therapeutic remedies for managing patients with diabetes infected with COVID-19 and vice versa.

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Conflict of interest

There are no conflicts of interest to declare.

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