COVID-19 and the hidden threat of diabetic microvascular complications

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic affected at least 200 million individuals worldwide and resulted in nearly 5 million deaths as of October 2021. According to the latest data from the International Diabetes Federation (IDF) in 2021, the diabetes pandemic has affected 537 million people and is associated with 6.7 million deaths. Given the high prevalence of both diabetes and COVID-19 and common pathological outcomes, a bidirectional relationship could have a catastrophic outcome. The increased risk of COVID-19 in those with obesity and diabetes and higher morbidity and mortality has received considerable attention. However, little attention has been given to the relationship between COVID-19 and microvascular complications. Indeed, microvascular complications are associated with an increased risk of cardiovascular disease (CVD) and mortality in diabetes. This review assesses the evidence for an association between diabetic microvascular complications (neuropathy, nephropathy, and retinopathy) and COVID-19. It draws parallels between the pathological changes occurring in the microvasculature in both diseases and assesses whether microvascular disease is a prognostic factor for COVID-19 outcomes in diabetes.

Keywords: COVID-19, diabetes, microvascular complications, nephropathy, neuropathy, retinopathy

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Collision of two pandemics

The first coronavirus disease 2019 (COVID-19) case was detected in China in December 2019, the disease rapidly spread worldwide, and COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. As of October 2021, COVID-19 had affected >200 million individuals worldwide and caused nearly 5 million deaths. COVID-19 patients with pre-existing conditions such as obesity, cardiovascular disease (CVD) and diabetes have increased morbidity and mortality. Prior to the coronavirus 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), we had the severe acute respiratory syndrome coronavirus-1 (SARS-CoV1) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, although neither reached pandemic levels. Diabetes is a serious global health threat that has reached pandemic levels. The International Diabetes Federation (IDF) estimated that in 2021, 537 million adults were living with diabetes and this number was estimated to reach 643 million by 2030 and 784 million by 2045. The estimated diabetes-related health expenditure in 2021 was around 966 billion US dollars. Based on data from previous acute respiratory infection outbreaks, diabetes was quickly identified as a major risk factor for COVID-19-related adverse outcomes and the potential synergistic relationship was confirmed. A high proportion of patients with COVID-19 have comorbid diabetes. The underlying mechanisms resulting in poor outcomes in diabetic patients with COVID-19 are binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor which results in acute inflammation and release of cytokines. In patients with diabetes, this worsens the already impaired immune system and increases the risk of cytokine storm, creating a
pro-inflammatory and pro-coagulative state. Moreover, age, sex, presence of other co-morbidities such as hypertension and CVD and obesity all contribute to the increased risk. Data from China (n = 72,314) estimated that mortality in diabetic patients with COVID-19 was near 10%. Another study (n = 7336) showed that the mortality rate from COVID-19 was 50% higher in people with diabetes than in those without, and good glycaemic control was associated with better outcomes than in those with poor glycaemic control. Furthermore, there is evidence that the relationship between COVID-19 and diabetes is bidirectional, as COVID-19 may affect the development and progression of diabetes. One study suggested that SARS-CoV1 may have precipitated acute-onset type 1 diabetes mellitus (T1DM) by entering pancreatic islet cells through ACE2 receptors and inducing islet cell apoptosis. It is also possible that in people predisposed to autoimmunity, COVID-19 may trigger immune-mediated onset of T1DM. In fact, a surge of new-onset T1DM was reported from multi-centre regional data in the United Kingdom (UK) during the COVID-19 pandemic and similar findings have been reported in other patient populations. More severe metabolic complications such as diabetic ketoacidosis (DKA) and hyperosmolar coma have been reported in patients with diabetes and COVID-19. In a study of inpatients with diabetes (n = 6014), those with COVID-19 infection were 3.6 times more likely to die than those without COVID-19. There have also been reports indicating that COVID-19 increases the risk of new-onset type 2 diabetes mellitus (T2DM), and corticosteroid therapy used in the treatment of severe COVID-19 infection was associated with the development of DKA in patients with T2DM, especially in poorly controlled individuals.

**COVID-19 structure in context**

COVID-19 is caused by severe acute respiratory syndrome-2 (SARS-CoV2) and belongs to the coronavirus (CoV) family which is made up of single-stranded enveloped RNA viruses which are divided into four genera: Alpha, Beta, Delta and Gamma CoVs. The Alpha and Beta genera are primarily associated with infections in mammals. In general, the structure of CoVs consists of four proteins: the nucleocapsid (N) protein, the spike (S) protein, the membrane (M) protein and the envelope € protein. SARS-CoV1, SARS-CoV2 and MERS-CoV belong to the Beta-genus of CoVs, SARS-CoV1 and SARS-CoV2 share ~79% similarity of the genome sequence, and present with similar symptoms. The overlap in symptoms is consistent with the structural homology seen between the virus’s S-protein, which mediates the entry of the virus into the host cell. Extensive studies have identified ACE2 as a functional receptor for SARS-CoV1, which mediates the processes of infection and transmission of the virus. Comparison of S-protein sequences for the COVID-19 virus and SARS-CoV1 has revealed overall sequence similarities of about 76–78% for the whole protein, 73–76% for the receptor-binding domain (RBD) and 50–53% for the receptor-binding motif (RBM). These high similarities strongly suggest that the two viruses share the same access door to their host cells, ACE2. Similar to the association observed between diabetes and COVID-19, diabetes was found to be an independent risk factor for complications and death during the SARS-CoV1 outbreak in 2002–2003 and was prevalent in nearly 50% of patients with MERS-CoV in 2012.

**Overlapping pathology and epidemiology in COVID-19 and diabetes**

It is generally accepted that SARS-CoV2 enters the cells through the ACE2 receptor, an important regulator of the renin–angiotensin system (RAS) which regulates systemic vascular resistance. ACE2 is expressed in most organs and is highly expressed in lung cells, providing a portal of entry for the virus in humans. SARS-CoV2 gains access to epithelial cells of the lungs by binding its S-protein to ACE2 receptors expressed on the cell surface. Host cell proteases cleave the virus S-protein and ACE2 receptor, leading to viral internalization. Figure 1 shows the mechanism of SARS-CoV2 entry into cells as well as ACE2 expression in human tissues. Infection leads to cell death, triggering inflammatory cytokine production and immune cell recruitment. Circulating immune cells infected by the virus also undergo apoptosis and cytokine secretion which causes a “cytokine storm” contributing to SARS-CoV2-driven multiorgan damage and disrupted endocrine signalling. ACE2 expression in extrapulmonary tissues results in tropism which likely also contributes to multiorgan injury. ACE2 expression is also amplified in key metabolic organs such
as the liver, pancreas, adipose tissue and small intestine, which may play a role in the development and progression of insulin resistance, impairment of insulin secretion and ultimately worsening hyperglycaemia (Figure 1). High ACE2 expression is also present in a variety of other tissues including the heart, kidney and nerves. There is increasing evidence that pulmonary microvascular thrombosis is an important determinant of the clinical severity of COVID-19 and that the adult respiratory distress syndrome (ARDS) caused by COVID-19 is distinctively different from that in typical ARDS. The highly expressed ACE2 receptors in vascular endothelial tissue are likely to be the entry point of the virus leading to vasoconstriction and proinflammatory cytokine release contributing to microvascular disease. Interestingly, it has been suggested that there are microvascular complications of diabetes affecting the lungs ‘diabetic lung’ and that the reduction in pulmonary diffusing capacity for carbon monoxide (DLCO) may be a result of diabetic microvascular disease. Moreover, the degree of functional impairment correlates with glycaemic control and severity of diabetic microvascular complications (retinopathy, neuropathy and microalbuminuria). Diabetes is characterized by chronic, low-grade inflammation, impaired glycaemic control, endothelial dysfunction, hypercoagulability and slow progressive multi-tissue injury in the form of microvascular and macrovascular complications. The pathological changes occurring in diabetes are thus very similar to the acute changes occurring in COVID-19 infection, but with a more prolonged or chronic course. Figure 2 illustrates the similarities in pathology that occur in diabetes and COVID-19. Many pro-inflammatory molecules released in the COVID-19 cytokine storm, for example, C-reactive protein (CRP) and interleukin 6 (IL-6), are the same as those produced by the diabetes-related inflammatory process, which may fuel a vicious cycle of cytokine release and widespread multiorgan damage, particularly in tissues already affected by diabetes. Acute COVID-19 could amplify pre-existing inflammation, dysglycaemia and multiorgan damage in patients with diabetes.

The mechanistic association between COVID-19 and diabetes confirms and explains the epidemiological overlap witnessed from all around the world to a great extent. Studies have shown that COVID-19 is extremely common in patients with diabetes ranging from 5.3% up to 36%. Thus, during acute COVID-19, tight control of glucose levels for the prevention of development and progression of diabetes complications is crucial. However, many of the pharmacological agents under investigation for treatment of COVID-19 such as corticosteroids can affect glucose metabolism warranting a need for close glucose monitoring.
COVID-19 therapies such as corticosteroids and immunotherapies affect the relationship between COVID-19 and diabetes and its microvascular complications are required.

Associations between microvascular complications and COVID-19

Early data from China showed that diabetes in COVID-19 patients was associated with worse outcomes and this has now been confirmed from data across the world. McGurnaghan et al. compared the whole Scottish population (n=5,463,300) to people with diabetes (n=319,349) in the first wave of the pandemic in Scotland and showed that individuals with diabetes, hypertension and severe obesity had a higher risk of infection with COVID-19 with an odds ratio (OR) of 1.40 [95% confidence interval (CI): 1.30–1.50, p < 0.0001] in people with diabetes compared with people without diabetes. Moreover, those with diabetes and microvascular complications (nephropathy and retinopathy) infected with COVID-19 were more likely to die or require critical care treatment. The Coronavirus SARS-CoV2 and Diabetes Outcomes (CORONADO) study (n=1317) from France showed that the risk of death on day 7 was associated with age (OR=2.48, 95% CI: 1.74–3.53, p < 0.0001), microvascular complications (OR=2.14, 95% CI: 1.16–3.94, p=0.0153), macrovascular complications (OR=2.54, 95% CI: 1.44–4.50, p=0.0013) and treated obstructive sleep apnoea (OR=2.80, 95% CI: 1.46–5.38, p=0.0020). Furthermore, a composite index of microvascular disease, defined as advanced retinopathy and diabetic kidney disease and history of diabetic foot ulcer, in patients with COVID-19 was associated with early mortality (Table 1).

Why is microvascular disease important?

Macrovascular and microvascular complications are responsible for much of the burden of diabetes. The most common microvascular complications are neuropathy, nephropathy and retinopathy as a consequence of metabolic perturbations in endothelial cells in the retinal vessels, mesangial cells in the renal glomeruli, and axons and Schwann cells in peripheral nerves. As demonstrated by the Diabetes Control and Complications Trial (DCCT) in T1DM and the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM, intensive blood glucose control delays the onset and progression of diabetic microvascular complications. It is generally accepted that glucose-mediated endothelial damage, oxidative stress due to superoxide overproduction, and the production of sorbitol and advanced glycation end-products (AGEs) occur due to hyperglycaemia. Recently, it has been shown that microvascular disease affects the risk of developing CVD in individuals with both T1DM and T2DM. In 2016, data from a population-based cohort of people with T2DM from the UK Clinical Practice Research Datalink (n=49,027) were used to estimate the hazard ratio (HR) for development of a first time major cardiovascular event (CVE) (defined as cardiovascular death, non-fatal myocardial infarction or non-fatal ischemic stroke). The primary outcome was significantly associated with retinopathy (HR=1.39, 95% CI: 1.09–1.76), peripheral neuropathy (HR=1.40, 95% CI: 1.19–1.66) and nephropathy (HR=1.35, 95% CI: 1.15–1.58) and when individuals with one, two or three microvascular complications were compared with those with no microvascular disease, the HR for the primary outcome increased in a dose-dependent manner: HR for one, two and three microvascular complications (HR=1.32, 95% CI: 1.16–1.50),
Table 1. Clinical studies investigating the relationship between COVID-19 and diabetic microvascular complications.

| Author               | Study design                                                                 | Findings                                                                                                                                 |
|----------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Cariou et al.⁵⁰      | Nationwide multicentre observational study \(n=1317\) in people with diabetes hospitalized for COVID-19 in 53 French centres. | Risk of death on day 7 was associated with microvascular complications \(\text{OR}=2.14, 95\% \text{CI: } 1.16–3.94, \text{p}=0.0153\); a composite index of microvascular disease defined as advanced retinopathy and diabetic kidney disease and history of diabetic foot ulcer in patients with COVID-19 was associated with early mortality. |
| Corcillo et al.⁷⁸     | Single centre study \(n=187\) of patients with diabetes hospitalized with COVID-19. Data on diabetic retinopathy status and grade were obtained via NHS Diabetic Eye Screening data within 12 months of COVID-19 hospitalization. | Retinopathy \(\text{OR}=5.81, 95\% \text{CI: } 1.37–24.66, \text{p}<0.001\) was independently associated with increased risk of intubation. |
| Landecho et al.⁷⁶     | Asymptomatic subjects with COVID-19 \(n=27\) were evaluated 14 days after hospital discharge with retinal fundus photos, optical coherence tomography (OCT) and OCT angiography. | Twenty-two percent had cotton wool spots, without signs of vitreoretinal inflammation usually seen with viral retinitis. |
| Leon-Abarca et al.⁸³ | Data from the Mexican Open Registry of COVID-19 \(n=2834\).                  | Patients with diabetic nephropathy had an 87% higher chance of developing COVID-19 pneumonia, 5% higher chance of being admitted, 101.7% increased chance of intubation and 20.8% increased chance of a fatal outcome \(\text{p}<0.01\). |
| Marinho et al.⁷⁷      | Subjects \(n=12\) were examined 11–33 days after COVID-19 symptom onset with OCT angiography. | Four subjects presented with subtle cotton wool spots and microhaemorrhages.                                                      |
| McGurnaghan et al.⁴⁹  | Cohort study of data from the first wave of the pandemic in Scotland \(n=5,463,300\). Participants were the total population of Scotland, including all people with diabetes who were alive 3 weeks before the start of the pandemic. | People with diabetes and microvascular complications (nephropathy and retinopathy) infected with COVID-19 were more likely to die or require critical care treatment; the presence of retinopathy had an \text{OR} of 1.67, 95\% \text{CI: } 1.38–2.03, \text{p}<0.0001 \text{for admission to the critical care unit, compared with individuals without diabetes.} |
| Odriozola et al.⁷⁴    | Observational study \(n=4\) of patients with diabetes and severe COVID-19 requiring non-invasive ventilation underwent neurologic evaluation. | Widespread sensory neuropathy with loss of taste and smell and abnormal thermal thresholds was seen in all four patients without a prior diagnosis of diabetic neuropathy. |
| Rivero et al.⁸⁴      | Multicenter, observational study of deceased patients with COVID-19 \(n=85\) in Mexico City evaluating postmortem kidney biopsy. | Severe AKI in 54\% and diabetic nephropathy were found in 27\% of biopsies.                                                        |
| Schiller et al.⁸⁵     | Observational study examining a cohort of COVID-19 patients \(n=75\) treated at a German community hospital. | Diabetic nephropathy was associated with the worst outcome.                                                                       |

AKI, acute kidney injury; CI, confidence interval; OCT, optical coherence tomography; OR, odds ratio.
Collectively, these data indicate that in addition to the local disease burden of microvascular complications, they also increase the risk of CVD.

Diabetic neuropathy and COVID-19
Diabetic neuropathy is caused by damage to the peripheral and autonomic nervous systems and is the leading cause of non-traumatic foot amputation and autonomic failure. Its prevalence ranges from 10% within the first year of diagnosis to 50% in people with diabetes duration greater than 25 years. Due to painful diabetic neuropathy, it has a substantial negative effect on the quality of life of affected individuals. There are various forms of diabetic neuropathy, but distal symmetric polyneuropathy and autonomic neuropathy are the most common. Diabetic neuropathy initially targets mainly sensory and autonomic axons, and later affects motor axons. The prevailing view is that hyperglycaemia and dyslipidaemia with impaired insulin signalling results in DNA damage, endoplasmic reticulum stress, mitochondrial dysfunction, and cellular injury and death affecting the endothelial cells and neurons.

Neurological manifestations of COVID-19 include alterations in taste, smell and hearing, as well as neuropathic pain in patients with COVID-19 pneumonia. Other CoVs (SARS-CoV1 and MERS-CoV) may initially invade peripheral nerve terminals and gain access to the central nervous system (CNS). A recent systematic review by the Infectious Disease Panel of the European Academy of Neurology concluded that detailed studies are warranted for the investigation of neurological disease caused by SARS-CoV2. It has been hypothesized that diabetic neuropathy could be a significant risk factor for severe COVID-19 due to an impairment of the自主神经系统 and the inflammatory reflex resulting in a pro-inflammatory state in diabetic patients with COVID-19. It has also been suggested that because of the cytokine alterations in patients with diabetic foot disease, a bidirectional relationship between COVID-19 and diabetic foot disease may exist.

We have recently shown a widespread sensory neuropathy with loss of taste and smell and abnormal thermal thresholds in four diabetic patients hospitalized with severe COVID-19, without a prior diagnosis of diabetic neuropathy. Longitudinal studies using objective measures of neuropathy could help us better understand the development and progression of COVID-19-related neuropathy in patients with and without diabetes.

Diabetic retinopathy and COVID-19
Diabetic retinopathy is the leading cause of adult blindness, with 90% of patients with diabetes having evidence of retinopathy within 15 years of diagnosis and about 25,000 cases of blindness due to diabetic retinopathy occurring per year. The recent position statement of the American Diabetes Association (ADA) describes retinopathy as ‘a highly specific neurovascular complication’ of diabetes. In a study of 27 subjects with COVID-19 evaluated 14 days after hospital discharge with retinal fundus photos, optical coherence tomography (OCT) and OCT angiography, 22% had cotton wool spots, without signs of vitreoretinal inflammation usually seen with viral retinitis. These findings confirmed an earlier report describing similar retinal changes in four COVID-19 patients. McGurnaghan et al. showed that after adjusting for age, sex, diabetes duration and type of diabetes, the presence of retinopathy had an OR of 1.67, 95% CI: 1.38–2.03, \( p < 0.0001 \) for admission to the critical care unit, compared with individuals without diabetes. Furthermore, in a single centre study (n = 187) of patients with diabetes hospitalized with COVID-19, multivariable logistic regression found that younger age (OR = 0.89, 95% CI: 0.84–0.95, \( p < 0.001 \)) and retinopathy (OR = 5.81, 95% CI: 1.37–24.66, \( p < 0.001 \)) were independently associated with increased risk of intubation.

Diabetic nephropathy and COVID-19
Chronic kidney disease (CKD) is an established risk factor for poor outcomes in COVID-19. A recent systematic review found that approximately one-third of patients hospitalized with COVID-19 had developed acute kidney injury (AKI). Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the world, affecting approximately 40% of people...
Moreover, diabetic nephropathy is an independent risk factor for CVD, CVD mortality and all-cause mortality.79 The development and progression of diabetic nephropathy is multifactorial, with hyperglycaemia induced metabolic and haemodynamic changes in genetically predisposed individuals.79 Indeed, hyperglycaemia and hypertension are the main modifiable risk factors for diabetic nephropathy.80–82 A study using data from the Mexican Open Registry of COVID-19 (n = 2834) found that those with diabetic nephropathy had an 87% higher chance of developing COVID-19 pneumonia, 5% higher chance of being admitted, 101.7% increased chance of intubation and 20.8% increased chance of a fatal outcome (p < 0.01).83 The renal histopathologic characteristics of deceased patients have been determined from post-mortem tissue of patients with COVID-19 (n = 85) and demonstrated severe AKI in 54% and diabetic nephropathy in 27%.84 In a cohort of COVID-19 patients (n = 75) treated at a German community hospital, diabetic nephropathy and obesity were associated with the worst outcome, occurring in 70% of non-survivors.85 None of the studies available have compared between patient groups based on the severity of diabetic nephropathy, and future work needs to examine this relationship.

**Long COVID and microvascular disease in diabetes**

Although the main focus of COVID-19 has been on the acute illness, it is becoming evident that there may be long-term consequences of the disease that require attention (Figure 3). Symptoms beyond 4 weeks after the acute infection have been classified into short and long term.86 Post COVID-19 syndrome (PCS), also referred to as ‘Long COVID’, has been defined as ‘having signs...’
and symptoms that develop during or after infection with COVID-19, are present for more than 12 weeks, and are not attributable to alternative diagnoses. PCS presents as a plethora of debilitating symptoms and conditions, affecting multiple organ systems (Figure 3) and can be comprised of persisting symptoms from the acute infection or new symptoms affecting various organs with a significant decline in the quality of life. Moreover, these symptoms can aggravate pre-existing symptoms associated with chronic diseases. PCS was found to be more prevalent in people with more severe disease, higher antibody titers, women, older age, obesity and diabetes. It has been estimated that 10–35% of people who do not require hospitalization with COVID-19 develop PCS, but this increases to 80% in those with severe disease or who require hospitalization. Alarminglly, it has been found that persistent symptoms are present in 19% of fully vaccinated people. There is recent evidence that people with long COVID could develop new-onset diabetes. In a study aiming to characterize the risk and burden of diabetes in the post-acute phase, it was found that there is an increased risk (HR = 1.4, 95% CI: 1.36–1.44) and excess burden (13.46, CI: 12.11–14.84, per 1000 people at 12 months) of incident diabetes, and therefore, it was concluded that post-acute COVID-19 care should include identification and management of diabetes. DKA has been observed in patients without a known history of diabetes, weeks to months after resolution of COVID-19 symptoms. The underlying pathophysiology of PCS is unclear, but it is generally accepted that there is underlying multiorgan damage and dysregulated immune and inflammatory responses. Indeed, we have recently used corneal confocal microscopy to show that patients with long COVID have increased neuropathic and musculoskeletal symptoms with corneal nerve damage suggestive of a small fibre neuropathy and increased dendritic cells, suggestive of ongoing immune activation.

People with diabetes may be predisposed to develop PCS as it increases the risk of severe COVID-19 infection and hospitalization. In theory, it is possible that the same pathophysiological overlap seen in patients with diabetes and COVID-19 could also underlie an increased risk for PCS, and the development and progression of microvascular damage.

### Conclusion

COVID-19 has superimposed on the pre-existing diabetes pandemic with a potential for a significant impact on the individual, society and economy. Diabetes worsens outcomes in patients with COVID-19, particularly those with microvascular and macrovascular complications, because of common pathologies between diabetes and COVID-19. A growing body of data suggests that there is a relationship between the presence of diabetic microvascular complications and adverse outcomes in those with acute COVID-19. Patients with diabetes, especially those with microvascular complications, may also be at increased risk of PCS. More research is warranted on the bidirectional relationship between diabetes and its complications, and both acute and post-acute disease in COVID-19.

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Author contributions

**Hadeel Zaghloul:** Conceptualization; Data curation; Methodology; Visualization; Writing – original draft.

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