

THE CONNECTION BETWEEN COVID-19 INFECTION AND MICROVASCULAR COMPLICATIONS IN DIABETIC PATIENTS

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ABSTRACT: This paper investigates the connection between COVID-19 and microvascular complications in diabetic patients. Through a systematic review of the literature, databases such as PubMed, Medline, Embase, Scopus, and Web of Science were utilized to identify relevant studies. Research questions and keywords were first defined, including "COVID-19," "diabetes," "microvascular complications," "cytokine storm," and "blood clots." Inclusion criteria encompassed clinical studies, health organization guidelines, and peer-reviewed articles in English published since 2020. After the initial review and removal of duplicates, relevant articles were analyzed to identify key risk factors and mechanisms contributing to the development of severe symptoms in diabetics infected with COVID-19. The results indicate a significantly increased risk of severe outcomes, including cytokine storm and a tendency toward blood clot formation, further exacerbating the compromised immune system in diabetics. A bidirectional relationship between COVID-19 and diabetes was also established, where COVID-19 may accelerate the onset of type 1 and type 2 diabetes and cause serious metabolic complications such as diabetic ketoacidosis and hyperosmolar coma. Based on the findings, diabetic patients who recover from COVID-19 require special medical attention and tailored therapy to reduce the risk of further complications. Stricter glycemic control and caution in the use of corticosteroids in COVID-19 treatment are recommended due to the potential increased risk of diabetic complications. These findings highlight the need for targeted healthcare and further research to better understand the long-term effects of COVID-19 on diabetic patients.

Keywords: COVID-19, microvascular complications, post-COVID, risk.

INTRODUCTION

COVID-19, caused by the SARS-CoV-2 virus, can significantly impact the vascular system. This virus has the ability to attack and damage endothelial cells, which form the inner layer of blood vessels. This leads to various vascular manifestations and complications in infected patients (Simić-Ogrizović & Kuzmanović-Pfćurica, 2015). One of the main vascular manifestations of COVID-19 is endothelial dysfunction. Endothelial cells play a key role in regulating blood flow, maintaining normal vascular function, and preventing blood clotting. Damage to the endothelium can disrupt normal function and lead to vasoconstriction (narrowing of blood vessels) or vasodilation (widening of blood vessels), resulting in disturbances in blood flow (Jovičić, Milutinović, 2018). Another important vascular manifestation is hypercoagulability, or the tendency of COVID-19 patients to develop blood clots. Endothelial dysfunction can stimulate clot formation in blood vessels, which can lead to serious complications such as pulmonary embolism or stroke. Vascular inflammation (vasculitis) can also occur in some COVID-19 patients. This immune response to infection can cause damage and inflammation in blood vessels, further worsening vascular complications. Thrombosis, or the formation of blood clots in blood vessels, is a common complication in severe cases of COVID-19. Endothelial damage, hypercoagulability, and vascular inflammation can contribute to the development of thrombosis, especially in the lungs, brain, heart, and other organs (Simić-Ogrizović, Kuzmanović-Pfćurica, 2015). Dysregulation of vasoconstrictor and vasodilator molecules has also been observed in COVID-19 patients. An imbalance of these molecules can disrupt blood flow regulation and lead to abnormal vascular responses (Stanković et al., 2018). All these vascular manifestations of

COVID-19 contribute to the severity of the disease and can have serious consequences for infected patients. Understanding the mechanisms by which the virus affects the vascular system is crucial for developing targeted therapies and preventing complications in COVID-19 patients (Simić-Ogrizović, Kuzmanović-Pfličurica, 2015).

RESEARCH SUBJECT, PROBLEM, AIM, AND METHODOLOGY

The subject of this study is the connection between COVID-19 and microvascular complications in diabetic patients, with a focus on specific microvascular complications such as retinopathy, nephropathy, and neuropathy, and their role in the development of severe symptoms in COVID-19-infected individuals with diabetes. The aim of this research is to analyze clinical studies investigating this relationship through a systematic literature review, focusing on the risk and mechanisms of complication development.

Data Collection Methodology: This paper is a systematic review of the literature, and the approach to data collection was structured in accordance with PRISMA guidelines. Relevant databases, including PubMed, Medline, Embase, Scopus, and Web of Science, were searched using predefined keywords: “COVID-19,” “diabetes,” “microvascular complications,” “retinopathy,” “nephropathy,” “neuropathy,” “cytokine storm,” and “blood clots.” The search included clinical studies and peer-reviewed articles in English published since 2020 to cover the latest information. Inclusion criteria involved studies examining the correlation between COVID-19 and microvascular complications in diabetic individuals. After the initial review, duplicates were removed, and relevant articles were assessed according to set criteria. Only articles that met quality and validity criteria were included in the final analysis to provide a reliable picture of the current state of research.

This systematic approach identified key risk factors and mechanisms contributing to the development of severe symptoms and complications, enabling a deeper understanding of the impact of COVID-19 on microvascular complications in diabetic patients. Special attention was given to specific microvascular complications, such as retinopathy, nephropathy, and neuropathy, and their role in the development of severe symptoms and complications in diabetic patients infected with COVID-19.

Through a detailed analysis of clinical study results, the research aims to better understand the connection between COVID-19 and microvascular complications and to identify potential risk factors and mechanisms that may explain this relationship. Based on the findings, the study also aims to highlight the importance of special attention and tailored care for patients after recovering from COVID-19 and to provide guidelines for improving healthcare for this population.

The problem addressed by this research lies in the growing body of evidence suggesting that COVID-19 affects not only the respiratory system but also numerous other organs, including the microvascular system. It is particularly concerning that individuals with diabetes are at an increased risk of developing more severe complications following COVID-19 infection. Existing research has not fully explained the mechanisms behind the connection between COVID-19 and microvascular complications such as retinopathy, nephropathy, and neuropathy, which creates a lack of clear guidelines for clinical management of this condition. This issue is further complicated by regional variations in the prevalence of microvascular complications, which may indicate the existence of factors that have not yet been sufficiently explored. This lack of detailed data makes it difficult to optimize medical care and long-term support for individuals who have recovered from COVID-19 and are burdened with microvascular complications.

To gather relevant information for this research, a method of systematic review of literature and research articles was used. The analysis of available data included identifying the prevalence of microvascular complications, risk factors associated with their occurrence, and examining the connection between

these complications and the recovery process in patients. Additionally, data on microvascular complications across different regions were compared to obtain a more comprehensive picture of the situation and any potential regional trends. It is important to note that all data were used in accordance with ethical guidelines and that proper credit was given to sources in line with citation practices.

STRUCTURE OF COVID-19 AND ITS RELATIONSHIP WITH OTHER CORONAVIRUSES

COVID-19 is a disease caused by the SARS-CoV-2 virus, which belongs to the coronavirus (CoV) family and can lead to the development of severe acute respiratory syndrome. This virus family consists of single-stranded RNA viruses with an envelope, divided into four genera: Alpha, Beta, Delta, and Gamma CoV. The Alpha and Beta genera are primarily associated with infections in mammals (Perlman, Netland, 2021). Generally, the structure of coronaviruses consists of four proteins: nucleocapsid protein (N), spike protein (S), membrane protein (M), and envelope protein (E). SARS-CoV1, SARS-CoV2, and MERS-CoV belong to the Beta genus of coronaviruses (Zhao, Li, 2020). SARS-CoV1 and SARS-CoV2 share approximately 79% genome sequence similarity and cause similar symptoms. These overlapping symptoms are due to structural similarity in the viral S protein, which mediates the virus's entry into host cells (Li et al., 2003).

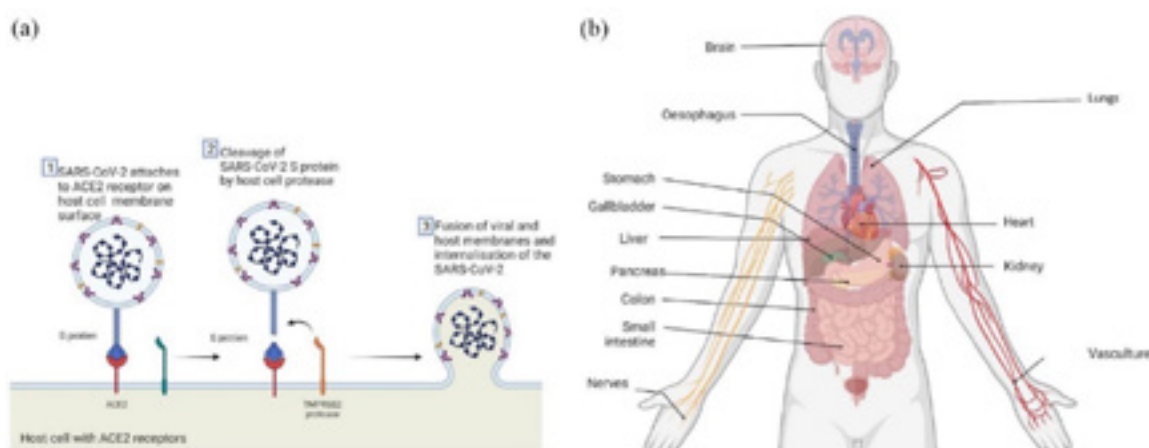


Figure 1. Mechanism of SARS-CoV-2 Entry into Host Cells and ACE2 Expression in Human Tissues (Hamming I, Timens W, Bulthuis ML, 2004)

Numerous studies have identified ACE2 as the functional receptor for SARS-CoV-1, which mediates viral infection and transmission processes (Liu et al., 2020). A comparison of the COVID-19 virus's S-protein sequence with that of SARS-CoV1 shows overall similarities of approximately 76-78% for the entire protein, 73-76% for the receptor-binding domain (RBD), and 50-53% for the receptor-binding motif (RBM). These high similarities indicate that both viruses use the same entry pathway through ACE2 receptors in host cells. Similar to the observed link between diabetes and COVID-19, diabetes was also an independent risk factor for complications and mortality during the SARS-CoV-1 outbreak in 2002-2003 and was present in nearly 50% of MERS-CoV patients in 2012 (Singh, Gupta, Ghosh, 2020).

RESEARCH RESULTS

The first case of coronavirus disease 2019 (COVID-19) was identified in China in December 2019. It quickly spread worldwide, and the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 (Guan et al., 2020). As of October 2024, COVID-19 has affected over 200 million people globally, causing nearly 5 million deaths (Worldometer, 2021). Individuals with pre-existing health

conditions such as obesity, cardiovascular disease (CVD), and diabetes are at greater risk of complications and mortality (Wu L, Peng, 2020). Before the COVID-19 pandemic, we had already experienced the Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) in 2002 and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, though neither reached pandemic proportions.

Diabetes poses a serious global health threat that has reached pandemic proportions. The International Diabetes Federation (IDF) estimates that in 2021, 537 million adults were living with diabetes, and by 2030, this number is expected to rise to 643 million and to 784 million by 2045 (Wit, Doremalen, Falzarano, 2016). The estimated healthcare costs associated with diabetes for 2021 were approximately \$966 billion (IDF, 2021).

Based on data from previous acute respiratory infection outbreaks, diabetes was quickly recognized as a major risk factor for negative outcomes associated with COVID-19, a link that has since been confirmed (Yang, Feng, Yuan, 2006). A high percentage of COVID-19 patients have concurrent diabetes. The primary mechanisms leading to poor outcomes in patients with diabetes and COVID-19 include the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) receptor, which triggers acute inflammation and cytokine release (Alqahtani, Aleanizy, Mohamed, 2019). In individuals with diabetes, this further weakens an already compromised immune system and increases the risk of a cytokine storm, creating an inflammatory, prothrombotic state. Additionally, age, gender, and the presence of other health issues such as hypertension, CVD, and obesity also contribute to increased risk (Apicella, Campopiano, Mantuano, 2020). Data from China show that mortality among patients with both diabetes and COVID-19 was close to 10% (Zhu, She, Cheng, 2020). Another study showed that the mortality rate from COVID-19 was 50% higher in individuals with diabetes than in those without, and good glycemic control was associated with better outcomes (Rubino, Amiel, Zimmet, 2020). Evidence also suggests a bidirectional relationship between COVID-19 and diabetes, where COVID-19 may influence the development and progression of diabetes. Some studies suggest that SARS-CoV-1 may have triggered the acute onset of type 1 diabetes (T1DM) by entering pancreatic islet cells via ACE2 receptors, while COVID-19 may similarly initiate an immune-mediated onset of T1DM in genetically predisposed individuals (Yang, Lin, Ji, 2010). During the COVID-19 pandemic, an increase in newly diagnosed T1DM cases was observed, and similar findings emerged in other patient populations (Rubino et al., 2020). Severe metabolic complications in patients with diabetes and COVID-19, such as diabetic ketoacidosis (DKA) and hyperosmolar coma, have also been reported (Caruso, Longo, Esposito, 2020). In one study, patients with diabetes infected with COVID-19 had a 3.6 times higher risk of death than those without COVID-19 infection (Spanakis, Yoo, Ajayi, 2021). Additionally, reports indicate that COVID-19 may increase the risk of developing type 2 diabetes (T2DM) (Narayan, Staimez, 2022), and corticosteroid therapy used to treat severe COVID-19 infection can lead to the development of DKA in patients with T2DM, particularly in those with poor glycemic control (Mondal, DasGupta, Lodh, 2021).

PATHOLOGY AND EPIDEMIOLOGY OVERLAP IN COVID-19 AND DIABETES

Generally, SARS-CoV-2 is known to enter cells through ACE2 receptors, a key regulator of the renin-angiotensin system (RAS), which controls systemic vascular resistance (Dimitrov DS, 2003). ACE2 is present in most organs, particularly highly expressed in lung cells, providing an entry point for the virus in humans (Hamming I, Timens W, Bulthuis ML, 2004). SARS-CoV-2 binds its S-protein to ACE2 receptors on lung cell surfaces. Host cells then break down the viral S-protein and ACE2 receptor, leading to virus internalization. The infection causes cell death, triggering the release of inflammatory cytokines and attracting immune cells (Hoffmann M, Kleine-Weber H, Schroeder S., 2021). Infected circulating immune cells also undergo apoptosis, releasing cytokines and resulting in a “cytokine storm” that contributes to SARS-

CoV-2-induced multi-organ damage and disrupted endocrine signaling (Felsenstein S, Herbert JA, McNamara PS, 2020). ACE2 expression in extrapulmonary tissues may also contribute to multi-organ damage (Bindom SM and Lazartigues E, 2009). ACE2 is also found in metabolically important organs such as the liver, pancreas, adipose tissue, and small intestine, potentially playing a role in the development of insulin resistance, reduced insulin secretion, and worsening hyperglycemia (Felsenstein S, Herbert JA, McNamara PS, 2020). Pulmonary microvascular thrombosis also plays an important role in the clinical severity of COVID-19, and the acute respiratory distress syndrome (ARDS) caused by COVID-19 differs from typical ARDS (Puelles VG, Lütgehetmann M, Lindenmeyer MT, 2020). Diabetic patients have a higher predisposition for microvascular complications that can affect the lungs. Diabetes is characterized by chronic inflammation, poor glycemic control, endothelial dysfunction, hypercoagulability, and the progression of microvascular and macrovascular complications. Pathological changes seen in diabetes resemble the acute changes occurring during COVID-19 infection but with a longer duration. Consequently, pre-existing inflammation, dysglycemia, and multi-organ damage may be exacerbated in COVID-19-infected diabetic patients (Bindom SM and Lazartigues E., 2009). Epidemiological data confirm and explain the mechanistic link between COVID-19 and diabetes. Numerous studies have shown that COVID-19 is more common in diabetic patients, with prevalence rates ranging from 5.3% to 36% (Feldman EL, Savelieff MG, Hayek SS, 2020). During the acute phase of COVID-19, strict glucose control is essential to prevent the development and progression of diabetic complications. However, care must be taken with pharmacological agents used in COVID-19 treatment, such as corticosteroids, as they can affect glucose metabolism, requiring careful monitoring of glucose levels (Gattinoni L, Coppola S, Cressoni M., 2020).

RELATIONSHIP BETWEEN MICROVASCULAR COMPLICATIONS AND COVID-19

Early data from China indicated an association between diabetes in COVID-19 patients and poorer outcomes, and this link has been confirmed by data worldwide (Goyal P, Choi JJ, Pinheiro LC, 2020). A study conducted in Scotland by McGurnaghan et al. (McGurnaghan SJ, Weir A, Bishop J, 2021) compared the entire Scottish population ($n = 5,463,300$) with individuals with diabetes ($n = 319,349$) during the first wave of the pandemic, showing that people with diabetes, hypertension, and severe obesity had a higher risk of COVID-19 infection, with an odds ratio (OR) of 1.40 [95% confidence interval (CI): 1.30-1.50, $p < 0.0001$] for individuals with diabetes compared to those without diabetes. Additionally, people with diabetes and microvascular complications (nephropathy and retinopathy) who contracted COVID-19 were more likely to experience mortality or require critical care (Liang W, Liang H, Ou L, 2020). The CORONADO study conducted in France ($n = 1317$) showed that the risk of death on day seven 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 apnea (OR = 2.80, 95% CI: 1.46-5.38, $p = 0.0020$) (Cariou B, Hadjadj S, Wargny M., 2020). Moreover, a composite index of microvascular disease, defined as advanced retinopathy, diabetic kidney disease, and a history of diabetic foot, was associated with early mortality.

Macrovascular and microvascular complications place a significant burden on diabetes management. The most common microvascular complications include neuropathy, nephropathy, and retinopathy, resulting from metabolic disorders in endothelial cells of retinal vessels, mesangial cells in the kidneys, and axons and Schwann cells of peripheral nerves (Li et al., 2015). Studies such as the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) for type 2 diabetes demonstrate that intensive blood glucose control delays the onset and progression of diabetic microvascular complications (Nathan, Genuth, Lachin, 1993). It is acknowledged that endothelial damage

caused by elevated glucose levels, oxidative stress due to excessive superoxide production, as well as the formation of sorbitol and advanced glycation end products (AGE) resulting from hyperglycemia, contribute to these microvascular complications (Inzucchi, Bergenstal, Buse, 2012). Recent research indicates that microvascular diseases also affect the risk of cardiovascular disease development in people with type 1 and type 2 diabetes (Brownrigg, Hughes, Burleigh, 2016). Data from a 2016 study conducted on a population of individuals with type 2 diabetes, including 49,027 participants from the UK Clinical Practice Research Datalink, showed that the presence of 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) (Gardner, Antonetti, Barber, 2002) was associated with an increased risk of the first major cardiovascular event (defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) (Garofolo, Gualdani, Giannarelli, 2020). This risk was dose-dependent, with the presence of one, two, or three microvascular complications leading to a progressively higher risk of cardiovascular events. Similarly, a study conducted on individuals with type 1 diabetes (n = 774) showed that the presence of microvascular diseases increases the risk of major cardiovascular events and all-cause mortality (Garofolo, Gualdani, Giannarelli, 2019).

Overall, these data highlight the importance of microvascular diseases in the context of diabetes. They not only contribute significantly to the disease burden but also increase the risk of cardiovascular events. Additionally, recent data show that patients with microvascular complications of diabetes have poorer outcomes when infected with COVID-19. Studies have shown that such patients are more likely to develop severe symptoms, experience mortality, or require critical care (Porte, Sherwin, Baron, 2003). This association between microvascular complications, COVID-19, and poor outcomes underscores the need for special attention and treatment for diabetic patients with such complications.

The following table presents clinical studies investigating the relationship between COVID-19 and diabetic microvascular complications:

Table 1. Clinical studies on the association between COVID-19 and diabetic microvascular complications

Auhtor	Study	Findings
Cariou et al.	National multicenter observational study	The 7-day mortality risk was associated with microvascular complications; a composite index of microvascular disease was associated with early mortality.
Corcillo et al.	Single-center study	Retinopathy was independently associated with an increased risk of intubation.
Landecho et al.	Asymptomatic COVID-19 subjects	Twenty percent had cotton wool spots, without signs of vitreoretinal inflammation.
Leon-Abarca et al.	Data from the Mexican Open COVID-19 Registry	Patients with diabetic nephropathy had higher odds of developing COVID-19 pneumonia, requiring intubation, and dying.
Marinho et al.	Case studies of tested subjects	Four subjects had subtle cotton wool spots and microhemorrhages.
McGurnaghan et al.	Cohort study	People with diabetes and microvascular complications infected with COVID-19 had significantly worse outcomes.
Odrizola et al.	Observational study	Widespread sensory neuropathy was observed in all four patients.
Rivero et al.	Multicenter observational study	Postmortem kidney biopsies revealed diabetic nephropathy.
Schiller et al.	Observational study	Severe acute kidney failure and diabetic nephropathy were found in biopsies.

The listed studies provide significant insights into the relationship between COVID-19 and diabetic microvascular complications, as well as their impact on disease outcomes.

CONCLUSION

Research has shown that patients who have recovered from COVID-19 may develop various microvascular complications that impact their post-COVID recovery. Some of the most common microvascular complications in the post-COVID period include:

1. **Endothelial Dysfunction:** COVID-19 can cause damage to endothelial cells lining the blood vessels, leading to vascular dysfunction. This can result in reduced blood flow, an increased risk of thrombosis, and other vascular disorders.
2. **Microthrombosis:** COVID-19 patients may be prone to the formation of microthrombi, small blood clots, within their microvascular systems. This can cause reduced blood flow and organ damage.
3. **Capillary Dysfunction:** COVID-19 can affect capillaries, the smallest blood vessels in the body, which can disrupt the adequate exchange of nutrients and oxygen between blood and tissues.

These microvascular complications can have long-term health consequences for patients following a COVID-19 infection. They may experience symptoms such as fatigue, shortness of breath, reduced cognitive function, concentration issues, and mental health problems. These symptoms are sometimes referred to as post-COVID syndrome or long COVID. It is important to note that research on microvascular complications in the post-COVID period is still ongoing, and more detailed information can be found in professional literature and research papers on this topic.

Based on the analysis of clinical studies investigating the link between COVID-19 and microvascular complications, we can conclude that there is a clear association between diabetes and more severe COVID-19 symptoms, as well as worse outcomes in infected individuals with diabetes. Diabetic patients, especially those with microvascular complications such as retinopathy, nephropathy, and neuropathy, are at a higher risk of severe complications and mortality associated with COVID-19. These findings highlight the need for special attention and tailored protection for diabetic patients during the COVID-19 pandemic. Glycemic control, monitoring of microvascular complications, and timely management of other risk factors such as hypertension and obesity may be key to reducing the severity of the disease and improving outcomes in infected individuals with diabetes.

Further research is needed to better understand the mechanistic link between COVID-19 and diabetic microvascular complications. Identifying specific pathological mechanisms that explain this connection could lead to the development of targeted therapies and preventive measures for this vulnerable population.

Overall, these conclusions emphasize the importance of an integrated approach to caring for diabetic patients during the COVID-19 pandemic and the need for further research to better understand the complex interaction between diabetes and COVID-19.

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