REVIEW ARTICLE
https://doi.org/10.1590/1806-9282.67.Suppl1.20200814

# Diabetes in the COVID-19 pandemic era

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## SUMMARY

**OBJECTIVE:** To analyze the association between patients with diabetes mellitus and the increased severity and its complications that arise with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

**METHODS:** This is a complementary review of literature in which 14 articles published in 2020 were selected. These reviewed articles were written in both Portuguese and English available in the SciELO and PubMed databases. This review also involved searching on websites of international and national organizations in order to gather information published by these bodies about diabetic population and coronavirus disease (COVID-19)-infected individuals.

**DISCUSSION:** The presence of comorbidities in SARS-CoV-2-infected individuals causes an increase in the expression level of angiotensin-converting enzyme 2, facilitating the entry of the virus into the cell. Diabetes causes metabolic and vascular changes, thus weakening the immune system through the inhibition of the innate immune system and the secretion of various inflammatory cytokines. This hyperinflammation can lead to multiple organ failure. The interaction between this comorbidity and COVID-19 can worsen pre-existing diabetes or predispose the onset of diabetes in non-diabetic individuals.

**CONCLUSIONS:** Diabetes mellitus is related to the increased severity and complications of COVID-19. The association between diabetes and COVID-19 creates a devastating double pandemic, as it worsens the prognosis of COVID-19.

KEYWORDS: Diabetes mellitus. Coronavirus infections. Chronic disease. Pandemics. Betacoronavirus.

## INTRODUCTION

At the end of 2019, a viral disease called coronavirus disease (COVID-19), caused by a coronavirus defined as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged. Since March 2020, COVID-19 has been a major threat to public health worldwide, affecting more than 188 countries and resulting in a global pandemic. The first case of this virus was identified and isolated in Wuhan, Hubei Province, China[1]. According to a report published by the World Health Organization (WHO)[2] as of August 17, 2020, there were 21,732,472 confirmed cases worldwide, with 770,866 deaths.

In Brazil, more than three million cases and a hundred thousand deaths have been confirmed and these numbers have been progressively increasing since early March 2020[3]. The high power of dissemination of this new virus and its ability to cause death, associated with insufficient knowledge of the virus, have created major obstacles in controlling the disease[4].

Since the first reports, many severe and fatal COVID-19 cases have occurred in older patients or people with comorbidities, especially those with diabetes *mellitus* (DM), hypertension, cerebrovascular diseases, and chronic kidney and lung diseases.

Currently, there is no explanation for patients with chronic diseases, particularly hypertension and diabetes, who are more severely affected by COVID-19. However, one of the theories is based on the involvement of the angiotensin-converting enzyme 2 (ACE2) that is present in several tissues, such as

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Conflicts of interest: the authors declare there are no conflicts of interest. Funding: none.
Received on September 22, 2020. Accepted on October 21, 2020.

cardiac, pulmonary, renal, intestinal, and blood vessels. The new coronavirus binds to the ACE2, which is present on cell surfaces and enter cells[5].

## METHODS

This is a complementary literature review of articles published in 2020. The reviewed articles were written in Portuguese and English and they were based on the SciELO and PubMed scientific databases. The descriptors used were 'diabetes mellitus', 'coronavirus infection', 'chronic disease', 'betacoronavirus', and 'pandemics'. The review also involved searching on websites of international and national organizations in order to gather information regarding recommendations published by these bodies for the diabetic population and people affected by COVID-19. These organizations included the World Health Organization (WHO), the International Diabetes Federation (IDF), state health departments, and Brazilian Diabetes Society.

## DISCUSSION

The COVID-19 pandemic reached Latin America around the end of February 2020. The countries, such as Brazil and Mexico, presented a high number of cases and high death rates not only because of their large populations but also because of their conflicting policies regarding travel restrictions and social contact. Other countries, such as Chile, Ecuador, and Peru, were also highly affected by the virus, since they presented great difficulty adjusting to social distancing, due to the high percentage of poor population in these countries. About 50–70% of jobs in Latin American are informal, which leads people to seek their income on the streets[6].

Individuals with chronic diseases present a more severe form of COVID-19. Recently, researchers from Universidade de São Paulo have published a study explaining the possible reasons for increased mortality in patients with chronic diseases. The comorbidities, such as hypertension, DM and asthma, change the metabolism by increasing the expression of ACE-2 gene in the cells of patients affected by the virus[7]. ACE-2 encodes the protein to which the virus binds to enter the cell, i.e. it facilitates the entry of the virus as seen in Figure 1. The increased expression of ACE-2 in patients with chronic diseases facilitates lung cell infection by the coronavirus, thereby increasing the risk of COVID-19 symptom aggravation. This is due to the binding of SARS-CoV-2 with ACE-2 that deregulates its cellular expression, leading to the onset of acute lung injury[7,8].

The relationship between being diabetic and having an increased susceptibility to COVID-19 is not fully proven, but there is evidence that patients with diabetes show an increased risk for both infection and severe disease. The first three coronavirus-related deaths in Hong Kong occurred in patients with diabetes. A Chinese study has showed that the prevalence of diabetes in infected people was 16% in patients with more severe forms of the disease and 5.7% in patients with lighter forms of the disease. In addition, 24% of individuals with severe COVID-19 had hypertension, compared to 13% of people with mild COVID-19, highlighting the increased risk of adverse outcomes in infected ones with other chronic diseases[5].

As diabetes is a chronic inflammatory disorder associated with high rates of glucose, patients with diabetes present metabolic and vascular changes that weaken the body defenses and prevent the immune system from responding properly to viral and bacterial infections in general. It increases the risk of infections, particularly pneumonia and influenza, due to multiple innate immune disorders. Diabetes, especially when poorly controlled, presents impaired phagocytosis, as neutrophils, macrophages, and monocytes as well as neutrophil chemotaxis and complement activation that impact the body negatively[5,9]. Micro and macrovascular complications are also associated with DM, affecting the patient's overall survival[10].

The human pathogenic coronavirus SARS-CoV and SARS-CoV-2 connect to the target cells through ACE-2, which is expressed by the lung, intestine, kidney, and blood vessel epithelial cells. Patients with both type 1 and type 2 diabetes have an ACE-2 production increased due to frequent treatment with ACE-2 inhibitors and angiotensin II type 1 receptor blockers (ARB), which have antihypertensive and nephroprotective effects. Treatment with ACE-2 and angiotensin-receptor blockers inhibitors increases ACE-2 production, which facilitates COVID-19 infection consequently. Therefore, treating diabetes and hypertension with ACE-2 stimulant drugs may increase the risk of developing severe COVID-19, which can be fatal; thus, patients with chronic diseases who use these drugs for treatment should be closely monitored[8,11].

The virus invades the cells and induces apoptosis or necrosis, triggering inflammatory responses characterized by pro-inflammatory cytokine or chemokine activation, resulting in the recruitment of other defense cells. SARS-CoV-2 infects the circulating immune cells and increases lymphocyte apoptosis, thereby affecting clusters of differentiation (CD) 3, 4, and 8 T-cells, among other lymphocyte cells, and, consequently, causing lymphocytopenia. Therefore, the severity of SARS-CoV-2 infection is directly associated with the degree of lymphocytopenia. Innate immune system inhibition occurs when T-cell action decreases, triggering the secretion of many inflammatory cytokines and generating a phenomenon called "cytokine storm," characterized by a significantly increased level

of circulating cytokines, such as interleukins (IL-6), (IL-17), (IL-21), (IL-22); tumor necrosis factor (TNF); and chemokines. This hyperinflammation in the body can lead to multiple organ failure as seen in Figure 2[8].

Besides decreasing immune system response (delayed T-helper 1 and T-helper 17 responses), diabetes also contributes to several specific factors that predispose patients to infections in general, resulting in a worse prognosis of COVID-19 in these patients. Some of these factors are: increased expression of ACE-2; increased furin, which is a membrane-bound protease involved in allowing coronavirus entry into the cell, facilitating viral replication; T-cell impairment that generates lymphocytopenia; and increased IL-6 levels that result in an increased susceptibility to hyperinflammation[9,12].

As diabetes is a chronic inflammatory disease, patients with diabetes have a significantly higher level of IL-6 and increased pro-inflammatory cytokines in their bodies. A treatment that has been widely used, especially in autoimmune diseases, for blocking IL-6 receptors. For example, the monoclonal antibody Tocilizumab, which improves insulin resistance and decreases glycated hemoglobin (HbA1c), has been used in rheumatoid arthritis. This medicine has been suggested for use in the treatment of COVID-19 pneumonia. Some Italian centers are conducting a randomized study on the use of Tocilizumab for treating patients with diabetes infected with COVID-19[13].

In 2019, a study analyzed the data collected from 5,266 patients with diabetes over a period of 6.2 years in the United States to assess the mortality of patients with chronic lower respiratory diseases and the use of metformin. It was reported that the use of metformin, an anti-diabetic with anti-inflammatory and antioxidant properties, significantly decreased the mortality of patients with respiratory diseases[12].

Diabetes is one of the leading chronic non-transmissible pandemic diseases worldwide, affecting over 463 million people[13]. The interaction between diabetes and SARS-CoV-2 infection can follow a two-way model as SARS-CoV-2 worsening pre-existing diabetes or predisposing non-diabetic people to diabetes. The mechanism that allows the entry of the virus into the cell involves ACE-2, which is highly expressed in the liver and pancreas as seen in Figure 3. SARS-CoV-2 infection in pancreatic beta cells can generate insulin resistance and decreased insulin secretion, worsening hyperglycemia in the acute phase of infection, whereas in the chronic phase, it may trigger autoimmunity of these pancreatic cells in predisposed patients. COVID-19 in patients with DM worsens the glycemic profile, thereby intensifying the impairment of innate

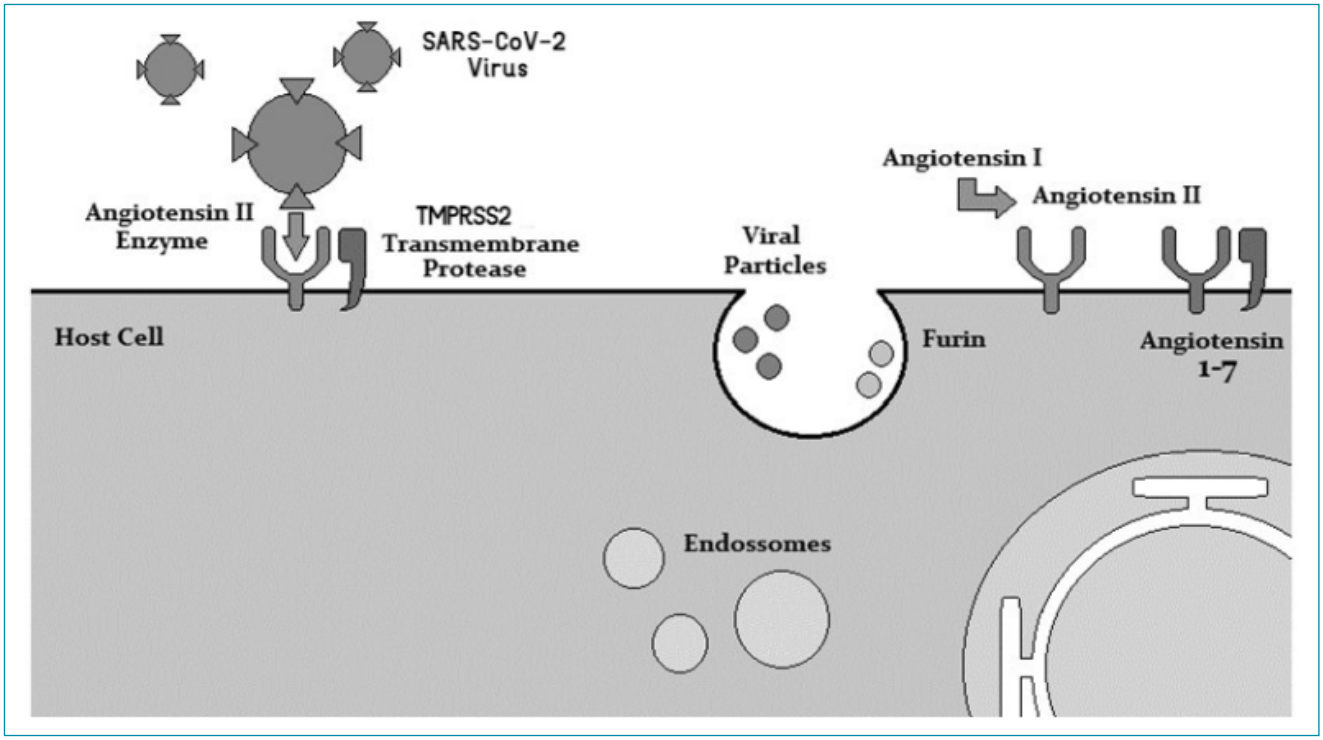


Figure 1. SARS-CoV-2 entry into the cell[8]. The virus needs to bind to the angiotensin-converting enzyme 2, which is present on the cell surface, to get into the cell. Proteases, such as transmembrane serine protease 2 and furin, also help the virus merges with the cell. After being absorbed by the endosomes, the viral particles use the endogenous cellular machinery to multiply. Angiotensin-converting enzyme 2 degrades angiotensin II and I (to a lesser extent) into minor peptides, namely angiotensin 1–7 and angiotensin 1–9, respectively.

immune response and generating pro-inflammatory cytokines that provoke a vicious cycle. Therefore, the complex interaction between these two pandemics produces an extremely high risk of developing severe diseases, such as acute respiratory distress syndrome (ARDS) or even death[14-16].

Hyperglycemia and insulin resistance, as a result from diabetes, induce increased synthesis of advanced glycation end products (AGEs) and pro-inflammatory cytokines that generate oxidative stress. An *in vitro* study, conducted in 2013, showed that the exposure of pulmonary epithelial cells to high glucose concentrations provokes increased influenza virus infection and replication, suggesting that the hyperglycemia state could increase *in vivo* viral replication[9]. In addition, patients with hyperglycemia in type 1 diabetes have a high chance of developing diabetic ketoacidosis (DKA) as well as metabolic complications during an infection[9].

Hyperglycemia can cause endothelial dysfunction, either by diabetes or by increased inflammatory cytokines, resulting in the formation of thrombi, which may damage other organs and result in a fatal disease outcome. This hypothesis was considered after reviewing evidence that high D-dimer levels were found in patients with diabetes, especially those with poor blood glucose control[6].

A study called "CORONADO" was conducted in France in the period between March and April 2020 to evaluate patients with diabetes who were diagnosed with COVID-19. A nationwide multicentric observational study was conducted to evaluate the phenotypic characteristics and prognosis associated with the early severity of patients with diabetes who had been hospitalized with SARS-CoV-2, as well as to estimate the primary outcome that associates death and orotracheal intubation for mechanical ventilation in the first seven days of hospitalization. The study showed that about 20.3% of the population analyzed underwent orotracheal intubation for mechanical ventilation, with 10.6% mortality in the first seven days after admission[17].

Type 2 DM, commonly present in obese people, also aggravates the expressed inflammatory cytokine response, increasing insulin resistance. In addition, vitamin D is another factor that interferes with the amount of blood glucose. The need of social isolation by confining people to their homes, as well as restricted physical activity, result in limited sunlight exposure and vitamin D deficiency. Hypovitaminosis D is characterized as a risk factor for insulin resistance since it worsens the glycemic profile in patients infected with COVID-19 as vitamin D supplementation, on the other hand, improves insulin sensitivity[15].

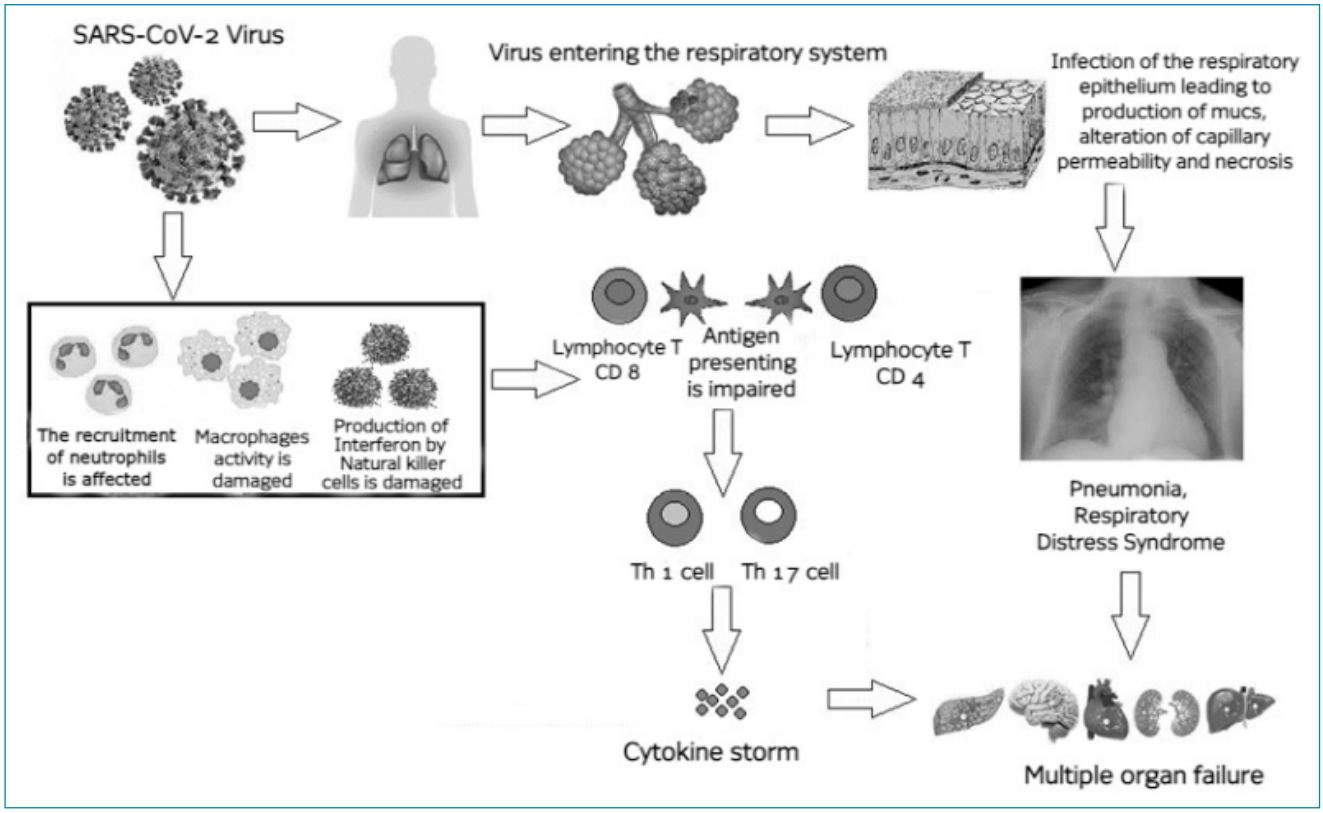


Figure 2. Mechanism that contributes to the increased susceptibility to COVID-19 in patients with diabetes mellitus[8]. Patients with diabetes have increased angiotensin-converting enzyme 2 levels, which may facilitate the existence of a more efficient cell connection and consequently the virus entry into the cells. Multiple innate immune disorders hinder early neutrophil recruitment and macrophage function. The delayed onset of adaptive immunity and cytokine response deregulation in diabetes mellitus can initiate the cytokine storm. Hyperinflammation can lead to multiple organ failure.

Treating diabetes in this current pandemic scenario is a challenge, since most people are confined to their homes with limited physical activity. In addition to this physical barrier, there is psychological stress due to unpredictability of disease and mobility restrictions. New routines imposed by the pandemic can change food intake. In most cases, access to fruits and vegetables has become limited, leading people to choose processed food that presents high calories and saturated and trans fats[12].

Besides the SARS-CoV-2 infection in patients with diabetes, another problem, resulting from the COVID-19 pandemic, has been the lack of access to medication. The outbreak and infection caused by COVID-19 have inhibited people from going to clinics, making it impossible to treat diabetes-related problems. As the supply of health services has been increasingly interrupted and fragmented, there has been enormous difficulty in getting access to basic medical supplies such as insulin. The concern about not having access to medication has generated anxiety and sleep disturbances, which, in turn, affect glucose control. Glucose deregulation may predispose people to complications, such as infections, hyperosmolar coma, ketoacidosis, or even acute cardiac events[5,12].

The treatment during this pandemic period should include medication and non-medication factors. It is necessary to maintain a regular daily diet, focused on not increasing caloric intake. An adequate and balanced diet, with high protein and fiber content and low in saturated fat, helps to maintain glycemic control. Regular physical exercises and the use of antidiabetics and insulin should be maintained. Additionally, if patients have questions about the treatment, they can use telemedicine, a practice widely used in this pandemic period. However, it is necessary to clarify to patients that they should seek medical service urgently in emergency situations as soon as they feel symptoms, such as vomiting, drowsiness, shortness of breath, chest pain, limb weakness, or sensory change[12].

## CONCLUSIONS

Diabetes plays a role in increasing the severity and complications of COVID-19. The association between diabetes and COVID-19 creates a devastating double pandemic by increasing the chances of having a severe form of COVID-19. In addition, concerns about SARS-CoV-2 virus contamination hinder glycemic control in patients with diabetes, as they avoid

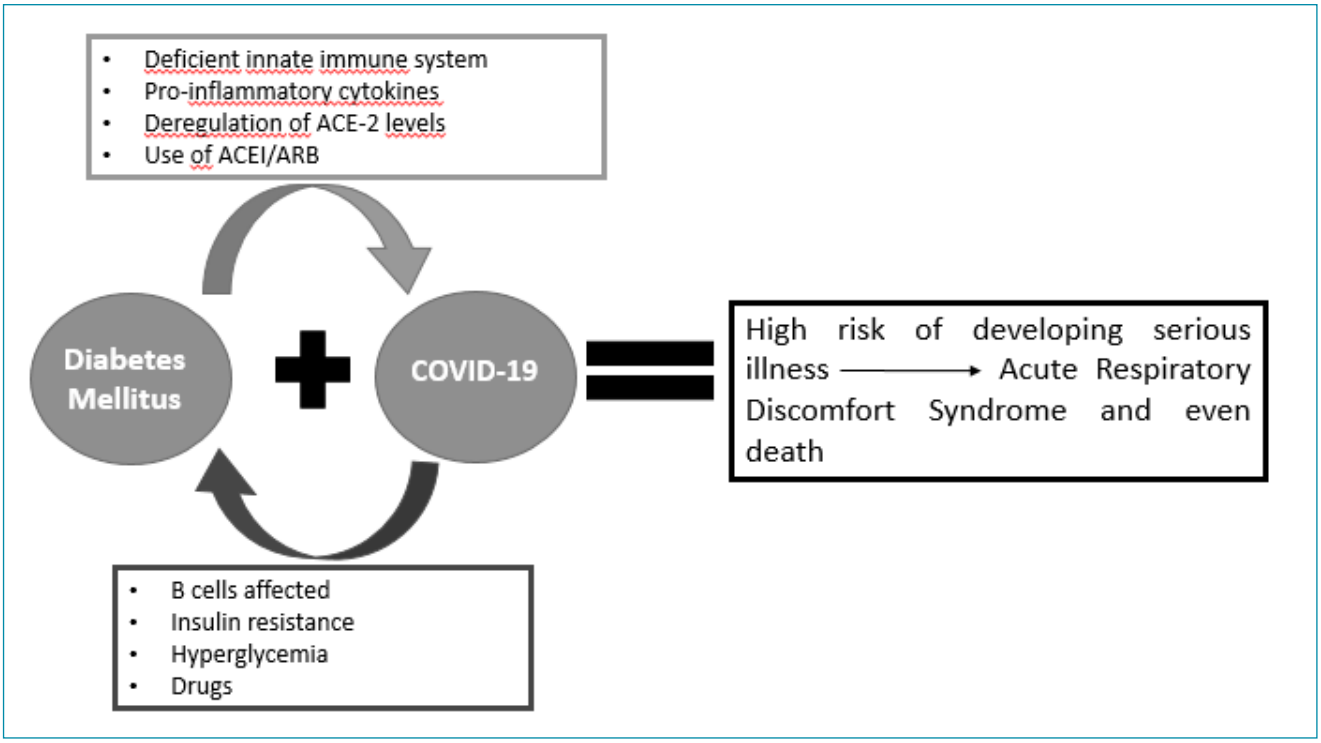


Figure 3. Schematic diagram of the bidirectional interaction between the new coronavirus disease (COVID-19) and diabetes mellitus[15]. Diabetes mellitus worsens COVID-19 prognosis by affecting innate immunity, pro-inflammatory cytokine overreaction, and angiotensin-converting enzyme 2 deregulation. In addition, the use of angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers in individuals with diabetes mellitus can increase COVID-19 severity. On the other hand, COVID-19 leads to a worsened glucose control in individuals with diabetes mellitus, due to pancreatic beta cell damage and increased insulin resistance through cytokines and fetuin-A, causing hyperglycemia. In addition, medicines used to treat COVID-19, such as corticosteroids and lopinavir/ritonavir, can also change blood glucose levels.

seeking healthcare assistance, generating, consequently, additional metabolic and vascular complications. Finally, patients with DM need to maintain regular physical exercise, proper nutrition, and hygiene and exert rigorous blood glucose control during the pandemic.

## AUTHORS' CONTRIBUTIONS

**ACSS:** Conceptualization, Writing – Review & Editing.
**KZ:** Conceptualization, Writing – Review & Editing.
**LPS:** Conceptualization, Writing – Review & Editing.
**TCPB:** Conceptualization, Supervision, Data Curation.

## REFERENCES


1. Shi Y, Wang G, Cai XP, Deng JW, Zheng L, Zhu HH, et al. An overview of COVID-19. J Zhejiang Univ Sci B. 2020;21(5):343-60. https://doi.org/10.1631/jzus.B2000083
2. World Health Organization. Coronavirus disease (COVID-19) pandemic. Geneva: World Health Organization; 2020. [cited on Sep. 03, 2020]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=Cj0KCQjwoaz3BRDnARIsAF1RfLcyr_97XusrC_wn53CKzgugFlCmXLATpa3Qj2utUZKp02AdblrLBYgaAsEHEALw_wcB
3. Brazil. Ministério da Saúde. Secretarias Estaduais de Saúde. Brasília: Ministério da Saúde; 2020. Coronavírus Brasil. [cited on Sep. 03, 2020]. Available from: https://covid.saude.gov.br/
4. Werneck GL, Carvalho MS. A pandemia de COVID-19 no Brasil: Crônica de uma crise sanitária anunciada. Cad. Saúde Pública. 2020;36(5):00068820. [cited on Sep. 03, 2020]. Available from: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-311X2020000500101&tlng=pt
5. Ma RCW, Holt RIG. COVID-19 and diabetes. Diabet Med. 2020;37(5):723-5. https://doi.org/10.1111/dme.14300
6. Caballero AE, Ceriello A, Misra A, Aschner P, McDonnell ME, Hassanein M, et al. COVID-19 in people living with diabetes: an international consensus. J Diabetes Complications. 2020;34(9):107671. https://doi.org/10.1016/j.jdiacomp.2020.107671
7. Pinto BGG, Oliveira AER, Singh Y, Jimenez L, Gonçalves ANA, Ogava RLT, et al. ACE2 expression is increased in the lungs of patients with comorbidities associated with severe COVID-19. J Infect Dis. 2020;222(4):556-63. https://doi.org/10.1093/infdis/jiaa332
8. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736-41. https://doi.org/10.1152/ajpendo.00124.2020
9. Cuschieri S, Grech S. COVID-19 and diabetes: the why, the what and the how. J Diabetes Complications. 2020;34(9):107637. https://doi.org/10.1016/j.jdiacomp.2020.107637
10. Hussain A, Bhowmik B, Moreira NC. COVID-19 and diabetes: knowledge in progress. Diabetes Res Clin Pract. 2020;162:108142. https://doi.org/10.1016/j.diabres.2020.108142
11. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21. https://doi.org/10.1016/S2213-2600(20)30116-8
12. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: prevalence, pathophysiology, prognosis, and practical considerations. Diabetes Metab Syndr. 2020;14(4):303-10. https://doi.org/10.1016/j.dsx.2020.04.004
13. International Diabetes Federation (IDF). IDF Diabetes Atlas 9th ed. Brussels: International Diabetes Federation; 2019. [cited on Sep. 03, 2020]. Available from: https://www.diabetesatlas.org/en/
14. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020;e33213321. https://doi.org/10.1002/dmrr.3321
15. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: an unholy interaction of two pandemics. Diabetes Metab Syndr. 2020;14(4):513-7. https://doi.org/10.1016/j.dsx.2020.04.049
16. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020;e3319. https://doi.org/10.1002/dmrr.3319
17. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia. 2020;63(8):1500-15. https://doi.org/10.1007/s00125-020-05180-x