Review Article

Diabetes and coronavirus disease-2019 (COVID-19)

Ranjit Unnikrishnan, Banshi Saboo[1], Jothydev Kesavadev[2], Neeta Deshpande[3], Sosale Ramachandra Aravind[4], Shashank Joshi[5], Ranjit Mohan Anjana, Akhtar Hussain[6], Viswanathan Mohan

Department of Diabetology, Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India, [1]Department of Diabetology, Dia Care – Diabetes Care and Hormone Clinic, Ahmedabad, Gujarat, India, [2]Department of Diabetology, Jothydev's Diabetes Research Centers, Trivandrum, Kerala, India, [3]Department of Diabetology, Belgaum Diabetes Centre, Belgaum, Karnataka, India, [4]Department of Diabetology, Diacon Hospital, Bengaluru, Karnataka, India, [5]Department of Diabetology, Joshi Clinic, Mumbai, Maharashtra, India, [6]Department of Diabetology, Nord University, Bodø, Norway

Abstract

Ever since the coronavirus disease (COVID) pandemic started hitting the world, the connection between diabetes and coronavirus disease-2019 (COVID-19) started becoming more clear. In this article, we asked the question whether people with diabetes are more prone to COVID-19 and whether they also are likely to get more severe form with the disease and have worse outcomes than people without diabetes. We also discussed the mechanisms by which diabetes worsens COVID-19 and also possible changes to the treatment of diabetes in the presence of COVID-19. Finally, we discuss preventive strategies that need to be taken in people with diabetes to prevent COVID-19.

Keywords: Coronavirus disease-2019 (COVID-19), diabetes, drugs

INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic is one of the most unprecedented in the recent history of mankind. Already, millions have been affected in all continents of the world (except Antarctica) and hundreds of thousands have died due to COVID-19. There is convincing evidence that diabetes, hypertension, and cardiovascular disease are associated with more severe outcomes and higher mortality in COVID-19.

This article will deal with the connection between diabetes and COVID-19 and will try to answer the following questions:

1. Are people with diabetes more prone to COVID-19?
2. Are they likely to get more severe form of the disease and are outcomes worse in those with diabetes?
3. What are the mechanisms by which diabetes worsens COVID-19?
4. Are any changes to the treatment of diabetes to be made if they develop COVID-19?
5. And finally, what special precautions should people with diabetes take to prevent COVID-19?

Access this article online

Quick Response Code:

Website:
www.journalofdiabetology.org

DOI:
10.4103/jod.jod_36_20

ARE PEOPLE WITH DIABETES MORE PRONE TO CORONAVIRUS DISEASE-2019?

It is well known that individuals with diabetes are more susceptible to viral, bacterial, and fungal infections as compared to those without diabetes. This is mainly because those with diabetes (especially uncontrolled diabetes) have a less robust immune function. With respect to respiratory infections, it has been recognized that although people with diabetes are more prone to lower respiratory infection, there is no such increased predisposition when it comes to upper respiratory infection such as rhinitis, sinusitis, and pharyngitis. Therefore, it is probably not surprising that there is no evidence to suggest that people with diabetes are more prone to COVID-19 (which starts off as an upper respiratory infection in most cases). The American Diabetes Association (ADA) has also issued

Address for correspondence: Dr. Ranjit Unnikrishnan, Madras Diabetes Research Foundation and Dr. Mohan's Diabetes Specialities Centre, No. 4, Conran Smith Road, Gopalapuram, Chennai 600086, Tamil Nadu, India.
E-mail: drranjit@drmohans.com

How to cite this article: Unnikrishnan R, Saboo B, Kesavadev J, Deshpande N, Aravind SR, Joshi S, *et al.* Diabetes and coronavirus disease-2019 (COVID-19). J Diabetol 2020;11:52-6.

statements that people with diabetes are not more prone to COVID-19 than the general population.[1]

ARE THEY LIKELY TO GET MORE SEVERE FORM OF THE DISEASE AND ARE OUTCOMES WORSE IN THOSE WITH DIABETES?

If individuals with diabetes do get COVID-19, they are at increased risk for developing more severe or advanced stages of the disease.[2] Recent data from Wuhan, China confirm that approximately 20% of intensive care unit (ICU) admissions due to COVID-19 have diabetes as a comorbidity.[3] Data from Italy also showed similar findings in that more than two-thirds of those who died due to COVID-19 had diabetes.[4] Another retrospective study from Wuhan revealed that of 41 patients with COVID-19, 32% of them had an underlying disease among which diabetes accounted for 20%.[5] A retrospective study focusing on outpatients at Fujian Provincial Hospital, China included 135 elderly patients and concluded that those with type 2 diabetes (T2D) had worse outcomes. According to reports from India, of the first 125 deaths on COVID-19, 56% had diabetes, 47% had hypertension, and over a third had both diabetes and hypertension.[6]

A large observational report from China including 1099 patients with confirmed COVID-19 infection indicated that in 173 patients with severe disease, comorbidities such as hypertension (23.7%), diabetes mellitus (16.2%), coronary heart diseases (5.8%), and cerebrovascular disease (2.3%) were seen.[7] In another study of 140 patients who were admitted to a hospital with COVID-19, 30% had hypertension and 12% had diabetes.[8]

A summary report from the Chinese Centre for Disease Control of 72,314 cases across the country showed an overall fatality rate of 2.3% but this increased to 10.5% in people with cardiovascular disease and to 7.3% and 6%, respectively, for people having diabetes or hypertension.[9]

Another worrying finding is that people with diabetes potentially have milder early symptoms of COVID-19, which makes the subsequent rapid deterioration much more difficult to predict and prevent.[10]

WHAT ARE THE MECHANISMS BY WHICH DIABETES WORSENS CORONAVIRUS DISEASE-2019?

T2D is a chronic, low-grade inflammatory disease characterized by long-term immune system imbalance, metabolic syndrome, or nutrient excess associated with obesity.[11,12] Also, in individuals with diabetes, there is an exaggeration of pro-inflammatory cytokine response, notably interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-α). This may be further exaggerated in response to a stimulus, as seen in patients with COVID-19 complicated by acute respiratory distress syndrome. Prolonged hyperglycemia alters the host immune system.

Dysfunctions in leukocytes, monocyte and macrophage chemotaxis and phagocytosis, and damaged specific immunity have also been reported in subjects with diabetes.[13,14] Moreover, diabetes shares the common features promoting disease progression with infectious disorders such as the pro-inflammatory state and endothelial dysfunction.[15]

Role of angiotensin-converting enzyme 2 in diabetes and coronavirus disease-2019

Angiotensin-converting enzyme 2 (ACE2) is a type-1 integral membrane glycoprotein that is constitutively expressed by the epithelial cells of the lungs, kidney, intestine, and blood vessels. In normal physiology, ACE2 breaks down angiotensin-II and to a lesser extent, angiotensin-I to smaller peptides, angiotensin 1–7, and angiotensin 1–9, respectively.

ACE2/Ang (1–7) system plays an important anti-inflammatory and antioxidant role protecting the lung against acute respiratory distress syndrome (ARDS); indeed, ACE2 is protective against lethal avian influenza A (H5N1) infection. ACE2 expression is reduced in patients with diabetes possibly due to glycosylation; this might explain the increased predisposition to severe lung injury and ARDS with COVID-19.[16]

Drugs such as ACE inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) are widely used in diabetes as hypertension and albuminuria are common in people with diabetes. ACE2 is the receptor to which the spike (S1) protein of the virus binds to gain entry into the respiratory tract epithelial cells. When ACEi or ARBs are used, expression of ACE2 is markedly increased in patients with diabetes. This is likely an adaptive response to counteract the elevated levels of Ang-II and Ang-I. It is believed that ACE2 receptor stimulation might facilitate the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the pneumocytes and thus results in severe outcomes in patients with diabetes.

One study from China by Chen *et al.*[2] claimed that viral clearance is delayed by diabetes, hypertension, male gender (perhaps because the gene for ACE2 is on the X chromosome), and old age, which may worsen the prognosis of COVID-19 infection, likely due to the increased expression of ACE2. The authors recommended that the use of ACE inhibitors be carefully considered in such populations, as it may lead to upregulation of ACE2. However, there is another school of thought that ACE2 overexpression may help as it converts angiotensin-2 into angiotensin 1–7, which has effects exactly opposite to that of angiotensin-2, meaning that it can balance angiotensin-2 in the body so that it is potentially useful to protect against ARDS and the cytokine storm.[2] Therefore, ACE 2 seems to attract the virus into the pneumocytes, but on the contrary, perhaps also equips the cells against a cytokine storm. Thus, some authors have contended that blockage

of the renin–angiotensin–aldosterone system (RAAS) by ACE inhibitors or angiotensin receptor blockers can be beneficial in protecting against COVID-19.[17]

Current evidence does not support the discontinuation of ACE inhibitor treatment due to concerns regarding Coronavirus infection.[18] Moreover, the European Society of Cardiology, Council on Hypertension; ACC/AHA/HFSA (American College of Cardiology, the American Heart Association, and the Heart Failure Society of America); and the American Society of Hypertension have released policy statements, strongly recommending that patients should continue treatment with their usual antihypertensive therapy because there is no clinical or empirical scientific evidence to suggest that treatment with ACE inhibitors or angiotensin receptor blockers should be discontinued because of the COVID-19 infection.

Some studies found that pioglitazone and liraglutide were also associated with upregulation of the ACE2 in animals.[19,20] It is not clear whether these drugs should be discontinued in COVID-19 but pioglitazone is not favored in COVID due to the chances of fluid retention.

MANAGEMENT OF DIABETES

Glycemic control is the first and foremost factor in diabetes management; otherwise, complications associated with long-term hyperglycemia are not only frequent causes of premature mortality but also virtual drivers of indirect costs. Some studies have shown that the glucose concentration in the airway secretion is directly proportional to the blood glucose concentration.[21]

CAN ALL ANTIDIABETIC DRUGS BE CONTINUED?

There is as yet no direct evidence on the effects of the various categories of antidiabetic medications on the risk of developing COVID-19 infection or on the adverse outcomes of the same.[22]

In those with mild or well-controlled diabetes

In general, patients with type 2 diabetes who have mild symptoms of COVID-19 and asymptomatic patients can continue their usual dose of medications, with appropriate titration if necessary to maintain good glycemic control. If the control is inadequate, the addition of insulin would be warranted. There are no data on whether the use of metformin, sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitors alpha-glucosidase inhibitors, or insulin influences outcomes of COVID-19 over and above their effects on glycemic control.[16] As regards the other classes of antidiabetic agents:

➢ Sodium-glucose co-transporter-2 (SGLT2) inhibitors are best avoided in severely symptomatic and hospitalized patients with COVID-19, primarily on account of the risk of dehydration and diabetic ketoacidosis (DKA). Also, these agents are known to upregulate renal ACE2, although the implications of this upregulation in the context of COVID-19 are unknown.

➢ As discussed earlier, pioglitazone and liraglutide are associated with ACE2 upregulation in animals.

➢ Hydroxychloroquine, approved as a third-line antidiabetic agent in India, also seems to have beneficial effects in COVID-19, and has been approved for prophylaxis of COVID-19 among healthcare professionals treating patients with COVID-19 and for asymptomatic close contacts of such patients.

➢ Many patients with COVID-19 infection report loss of taste and smell sensation and hence have a poor appetite. Many also have gastrointestinal (GI) symptoms such as nausea, diarrhea, and vomiting. The antidiabetic drug regimen should be closely titrated to account for fluctuations in food intake caused by these symptoms.

In those with severe diabetes or in hospitalized patients and those in intensive care unit

Patients with severe COVID-19 infection can experience deterioration in their glycemic control and some (especially those with type 1 diabetes) may go into DKA on account of the excessive outpouring of counterregulatory (stress) hormones. In all such severe cases or hospitalized patients, insulin would be the antidiabetic agent of choice. Treatment with basal–bolus insulin regimens or intravenous (IV) insulin infusion will usually be needed in such cases. However, the treatment has to be individualized on a case to case basis.

Role of antidiabetic drugs in coronavirus disease-2019

➢ **Metformin**
  ✤ Has antiproliferative and immunomodulatory effects—protective[23]
  ✤ Decreased mortality in lower respiratory infections[24]
  ✤ Risk of lactic acidosis
➢ **Thiazolidinediones (TZDs)**
  ✤ Seen to increase risk of pneumonia compared to sulphonylureas[25]
  ✤ Increase ACE2 expression[26]
  ✤ Therefore, to be avoided in COVID-19
➢ **Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (liraglutide)**
  ✤ Also increases ACE2 expression in lungs[27]
  ✤ Best avoided
➢ **DPP 4 inhibitors**
  ✤ In Middle East respiratory syndrome coronavirus (MERS-CoV): Reduced viral entry
  ✤ Increased upper respiratory infection with DPP-4 inhibitors known, but no increased risk of pneumonia

✤ No evidence for or against the use of DPP-4 inhibitor in COVID-19
➢ **SGLT2 inhibitors**
  ✤ Better to discontinue because of the risk of dehydration and euglycemic ketosis.
➢ **Sulphonylureas and insulin**
  ✤ The dose may have to be adjusted based on blood glucose levels.

CONCLUSION

People with diabetes are not more prone to COVID-19 than the general population. However, if they get COVID-19, they are at increased risk for developing more severe or advanced stages of the disease. Hence, glycemic control is of primary importance. Any infection is likely to increase the blood sugar levels and uncontrolled diabetes can further lead to worsening of the infection. The following precautions can help people with diabetes to protect themselves from COVID-19.

Precautions to be advised for patients with diabetes

1. It is important to keep blood sugars under good control. Do not stop any of your regular medications unless asked to do so by your doctor.
2. Increased testing of the blood glucose levels with a capillary blood glucose meter or continuous glucose monitoring may be necessary.
3. If the blood sugar levels are found to go very high, the physician should be consulted at the earliest to bring the sugars under control as quickly as possible. If directly consulting the doctor in person is not possible due to the lockdown, one can take recourse to telemedicine modalities such as telephone or video or e-mail consultation. Video consultations are considered closest to that of in-person consults. It helps physicians keep connected with patients during this pandemic. In many countries including India consultations via social media platforms are also now legalized.
4. Unless one has type 1 diabetes or severe insulin-requiring T2D, where the sugar levels tend to go very high and signs of ketosis or DKA develop, it is not necessary to get admitted into the hospital.
5. Follow all the usual precautions such as washing hands with soap and water regularly and "social distancing," that is, keeping a distance from people who are likely to be infected.
6. Although spreading the infection through a needle used for blood glucose testing or insulin injections is highly unlikely, it is better not to share your blood testing lancet or insulin needles with anybody else.
7. A proper diet, regular exercise, yoga, and meditation might help in strengthening immunity. However, there are no scientifically proven data, which shows that yoga and meditation could boost immunity.

Financial support and sponsorship

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. American Diabetes Association. Available from: https://www.diabetes.org/coronavirus-covid-19/how-coronavirus-impacts-people-with-diabetes. [Last accessed on 2020 May 4].
2. Chen X, Hu W, Ling J, Mo P, Zhang Y, Jiang Q, *et al*. Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. Available from: https://doi.org/10.1101/2020.03.22.20040774. [Last Accessed on 2020 Apr 20].
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors formortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohortstudy. Lancet 2020;395:1054-62.
4. Remuzzi A, Remuzzi, G. COVID-19 and Italy: What next? Lancet 2020;395:1225-8.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-9.
6. Infection rate falling in Chennai, 12 Tamil Nadu districts. Times of India. April 19, 2020. Available from: https://timesofindia.indiatimes.com/city/chennai/Infection-rate-falling-in-Chennai-12-Tamil-Nadu-districts/articleshow/75229137.cms. [Last Accessed on 2020 Apr 20].
7. Guan W, Ni Z, Hu Y, Liang W-H, Ou C-Q, He J-X, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; Published online 2020 Feb 28.
8. Zhang JJ, Dong X, Cao YY, Yuan Y-d, Yang Y-b, Yan Y-q, *et al*. Clinical characteristics of 140 patients infected by SARS-CoV- 2 in Wuhan, China. Allergy 2020;1-12.
9. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA2020;323:1239-42.
10. Hussain A, Bhowmik B, Moreira NCDV. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract 2020;162:108142.
11. Guzman-Flores JM, Lopez-Briones S. Cells of innate and adaptive immunity in type 2 diabetes and obesity. Gac Med Mex 2012;148:381-9.
12. Shu CJ, Benoist C, Mathis D. The immune system's involvement in obesity-driven type 2 diabetes. Seminimmunol 2012;24:436-42.
13. Rajagopalan S. Serious infections in elderly patients with diabetes mellitus. Clin Infect Dis 2005;40:990-6.
14. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: Convergence of two epidemics. Lancet Infect Dis 2009;9:737-46.
15. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): A systematic review and meta-analysis. Int J Infect Dis 2016;49:129-33.
16. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: The conundrum, Diabetes Research and Clinical Practice. 2020;162:108132.
17. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med 2020;382:1653-9.
18. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic: At present there is no evidence to abandon renin-angiotensin system blockers. Hypertension 2020;75:1382-5.
19. 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:e21.
20. Romanı´-Pe´rez M, Outeirin˜o-Iglesias V, Moya CM, Santisteban P, Gonza´lez-Matıas LC, Vigo E, *et al*. Activation of the GLP-1

receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology 2015;156:3559-69.

21. Morra ME, Van Thanh L, Kamel MG, Ghazy AA, Altibi AMA, Dat LM, *et al*. Clinical outcomes of current medical approaches for middle East respiratory syndrome: A systematic review and meta-analysis. Rev Med Virol 2018;28:e1977.

22. RSSDI Guidance for Healthcare Professional on COVID-19. Available from: https://rssdi.in/newwebsite/rssdi-guidance-for-healthcare-professionals-on-covid-19.php. [Last accessed on 2020 Apr 20].

23. Kajiwara C, Kusaka Y, Kimura S, Yamaguchi T, Nanjo Y, Ishii Y, Udono H, Standiford TJ, Tateda K. Metformin mediates protection against legionella pneumonia through activation of AMPK and mitochondrial reactive oxygen species. J Immunol 2018;200:623-31.

24. Mendy A, Gopal R, Alcorn JF, Forno E. Reduced mortality from lower respiratory tract disease in adult diabetic patients treated with metformin. Respirology 2019;24:646-51.

25. Gorricho J, Garjón J, Alonso A, Celaya MC, Saiz LC, Erviti J, *et al*. Use of oral antidiabetic agents and risk of community-acquired pneumonia: A nestedcase-control study. Br J Clin Pharmacol 2017;83:2034-44.

26. Zhang W, Xu YZ, Liu B, Wu R, Yang YY, Xiao XQ, *et al*. Pioglitazone upregulates angiotensin converting enzyme 2 expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. Sci World J 2014;2014:603409.

27. Romaní-Pérez M, Outeiriño-Iglesias V, Moya CM, Santisteban P, González-Matías LC, Vigo E, *et al*. Activation of the GLP-1 receptor by liraglutide increases ACE2 expression, reversing right ventricle hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats. Endocrinology 2015;156:3559-69.