

Impact of Covid-19 on Diabetes

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Introduction

The coronavirus disease 2019 (COVID-19) outbreak, which originated in Wuhan, China, has now spread to 216 countries infecting more than seven million individuals of all ages. The prominent clinical manifestations are dry cough, dyspnea, fever, and bilateral lung infiltrates on imaging, and also various fatal complications including organ failure, septic shock, pulmonary edema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS) are reported.¹ On 7th January 2020, the causative agent was identified from throat swab samples by the Chinese Centre for Disease Control and Prevention (CCDC) and was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On February 11th the disease was designated as COVID-19 by the World Health Organization (WHO).²

Patients with underlying medical conditions like chronic lung disease or moderate to severe asthma, cardiovascular diseases, severe obesity (body mass index [BMI] of 40 or higher), diabetes, chronic kidney disease undergoing dialysis and chronic liver disease, if not controlled might be at higher risk for severe illness from COVID-19.³

People with diabetes have a higher overall risk of infection. It is currently undetermined why people with diabetes, hypertension or other chronic diseases are more severely affected by COVID-19. We are still in uncertain territory and day by day we are getting more and more depths in terms of vulnerability. One possible explanation is the involvement of angiotensin-converting enzyme 2 (ACE2). ACE2 is present in cardiac, kidney, lung, and intestinal tissue, and by converting angiotensin II to angiotensin 1-7, it

counteracts the effects of angiotensin II and promotes vasodilation. The etiology and pathogenesis of SARS-CoV-2 are similar to that of the SARS-CoV that caused Severe Acute Respiratory Syndrome (SARS). SARS-CoV-2 binds with human ACE2 on the surfaces of epithelial cells to bind and gain entry to infected cells thereby making it easier to spread. The binding intensity is 10-20 fold higher than the SARS-CoV-2.^{4,5}

COVID 19: An overview

The first coronaviruses found to infect humans in 1968 caused very mild infections until the outbreaks of a severe acute respiratory syndrome (SARS) in 2003, MERS (Middle Eastern respiratory syndrome) in 2012 and COVID-19 in 2019. The two possibilities of genomic and evolutionary evidence of the occurrence of COVID-19 outbreak is suggested to be the mutated form of either BatCoV RaTG13 or Pangolin-CoV, which showed 96% and 91.02% identical to SARS-CoV-2.⁶ This supports the theory that the origin of SARS-CoV-2 is from bats, which due to mutation can infect other animals and humans. Coronaviruses are single-stranded RNA viruses, about 120 nm in diameter. They are susceptible to mutation and are therefore highly diverse. The mortality rates for SARS-CoV-2 (2.3%) are relatively less when compared to SARS-CoV (10%) and MERS-CoV (35%).⁷ Most of the coronaviruses are covered by an envelope having spike protein, which contains a specific variable receptor-binding domain (RBD). The RBD has an affinity with angiotensin-converting enzyme-2 (ACE-2) receptor, especially those located in kidneys, heart, lungs, and gastrointestinal tract. This attachment facilitates the entry of the virus into target cells.⁸ COVID-19 affects different people in different ways. The most common

manifestations are fever, dry cough, tiredness and rare symptoms like aches, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, or discoloration of fingers or toes are recorded. Besides, the serious presentations are shortness of breath, chest pain, and loss of speech or movement.¹

Covid-19 severity due to associated comorbid conditions

It is proved that patients with comorbid conditions like diabetes, hypertension, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease and obesity showed higher mortality.⁹ At least one comorbidity was seen more commonly in severe cases than in non-severe cases (32.8%). Patients with at least one comorbidity were older, were more likely to have shortness of breath, nausea or vomiting and tended to have abnormal chest radiograph manifestations. Patients with two or more comorbidities had significantly escalated risks of reaching to the composite end-point compared with those who had single comorbidity, and even more so compared with those with no comorbidities.^{10,11}

A retrospective multi-center study showed patients with severe disease were older than those with a non-severe disease by a median of 7 years. Comorbidities were also more common among patients with severe disease (38.7%) including COPD (3.5%) diabetes (16.2%) hypertension (23.7%) and coronary heart disease (5.8%).¹² A Study compared with patients who did not receive ICU care (n = 102) with patients who required ICU care, were more likely to have underlying comorbidities. Compared with the non-ICU patients, patients admitted to the ICU were more likely to report pharyngeal pain, dyspnea, dizziness, abdominal pain, and anorexia.¹³ All the above study showed a significant increase in the severity of coronavirus infection when an underlying comorbid condition is manifested.

Why diabetes patients are at increased risk

Diabetes mellitus is an independent predictor of admission to intensive care unit or invasive ventilation or death in COVID-19.¹⁴ No clear distinction has however been made between type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), but both T1DM and T2DM are likely predictors of poor prognosis in COVID-19. The risk of developing pneumonia was reported to be 2.98 higher for Type 1 diabetes and 1.58 for Type 2 diabetes compared to the general population.¹⁵

In a similar study showed, Type 1 diabetes was at three and a half times the risk of in-hospital death with COVID-19, while people with Type 2 diabetes were at twice the risk, compared to people without a diagnosis of diabetes. Even with the additional risk associated with Type 1 diabetes or Type 2 diabetes, people under the age of 40 years with either type of diabetes were at the very low absolute risk of in-hospital death.¹⁶

There are several hypotheses to explain the increased incidence and severity of COVID-19 infection in people with diabetes. 1. Increased risk of infection because of defects in innate immunity affecting phagocytosis, neutrophil chemotaxis, and cell-mediated immunity; 2. Increased expression of ACE and Furin.^{17,18} Acute hyperglycemia has been shown to upregulate ACE2 expression on cells which might facilitate viral cell entry. However, chronic hyperglycemia is known to downregulate ACE2 expression making the cells vulnerable to the inflammatory and damaging effect of the virus.¹⁹

Potential Benefits and Harms of Novel Antidiabetic Drugs during COVID-19 Crisis

Most patients with type 2 diabetes have other components of metabolic syndrome including hypertension and dyslipidemia. Therefore, continuation with an appropriate antihypertensive and lipid-lowering regimen along with anti-diabetes agents in all these patients is of crucial importance.

Metformin tends to increase the ACE2 expression, as the pharmacological action of most of the metformin's showed 5'-AMP-activated protein kinase (AMPK) as a molecular effector. The potential role of AMPK is to regulate ACE2 expression and stability.²⁰ A retrospective analysis showed that antidiabetic treatment with metformin was associated with decreased mortality compared with those not receiving metformin.²¹ We need more such studies to confirm the mechanism of metformin in reducing mortality of people with diabetes. Metformin has shown fatal drug-to-drug interactions with Hydroxychloroquine an antimalarial drug, widely used in rheumatoid arthritis or systemic lupus erythematosus. The usage of which in the management of COVID-19 was still debated. The combination of CQ and metformin resulted in CNS neuronal damage after cardiac arrest in rats.^{22,23} The known adverse effect of metformin is dehydration and lactic acidosis, which can worsen the side effect caused by the coronavirus. Hence patients are recommended to discontinue metformin and start insulin to manage diabetes.

Human dipeptidyl peptidase 4 (DPP-4) inhibitors act as a functional receptor for MERS-CoV (MERS-Coronavirus). Although SARS-CoV-2 does not require DPP4, the potential anti-inflammatory role of DPP4i raises questions as to whether DPP4 modulation might help offset the cytokine-mediated acute respiratory complications of COVID-19. Nonetheless, DPP4i does not alter ACE2 expression as shown in diabetic mice. They are well-tolerated and so can be continued with caution.^{24,25} Among sodium-glucose co-transporter (SGLT)2 inhibitors, canagliflozin, dapagliflozin and empagliflozin have shown cardio-renal protective effects and suggested to be the preferred choice in patients with heart failure considering the clear benefits of these agents in this population. However, SGLT2 inhibitors, have been associated with increased risk of DKA, therefore patients receiving such treatments should be well-instructed on

recognizing early signs and symptoms of DKA.²⁶ Glucose lowering agents, such as (SGLT)2 inhibitors, glucagon-like peptide 1 receptor agonists (GLP1RA), or dipeptidyl peptidase (DPP)4 inhibitors, which are associated with extremely low risk for hypoglycemia, especially when used in monotherapy.²⁷

It is crucial to prevent hypoglycemia in patients with diabetes in general, but specifically in older patients and those prone to hypoglycemia. Hypoglycemia would increase the risk for hospitalization during a pandemic with limited available hospital resources and exposing patients to a higher risk for infection by SARS-CoV2.

Diabetes condition may lead to the suspicion that the excessive expression of ACE2 aids the entry of SARS-CoV-2 into the host cells resulting in COVID-19. Since diabetes mellitus and hypertension conditions are treated with ACE2 increasing drugs. There forth, it became controversial whether COVID-19 affected patients who are predisposed with diabetes mellitus should be resumed with their treatment with ACEi and ARBs or not. Also, if the medication is abruptly ceased, there are chances that the patient may die due to hypertension instead of COVID-19. For this reason, it has been suggested that there is no need to stop the medication of a diabetic patient even though if he is affected by COVID-19 because there is no scientific evidence available conducted on human subjects regarding whether to use ACEi and ARBs.²⁸ Implications of these findings in the current context of COVID-19 and its relation to anti-diabetic drugs is not yet fully clear.

Management of diabetes patient infected with SARS-CoV2

American Association of Diabetes Educators (AADE) has described seven self-care behaviors of a patient as reliable outcome measures of diabetes self-management education, namely, being active, healthy eating, taking medication, monitoring, solving problems, reducing risks and healthy coping.²⁹

Like everyone people with diabetes can also get infected with the coronavirus even when trying their best to prevent it. So being prepared and knowing what to do if you get sick is very important. There are few rules to be followed on the sick days being at home, but also talk to your doctor about the best way to handle being sick if it happens.

Sick day rules for acutely ill patients with diabetes infected with coronavirus disease 2019

- Monitor home blood glucose every 2-4 h
- Monitor ketones (blood or urine) every 2-4 h for patients with Type 1 diabetes
- Stop metformin, SGLT2i, and GLP-1RA
- Consume carbohydrates as a meal replacement
- Drink fluids (water or sugar-free) 100 ml every hour
- Continue basal insulin (dose may need adjustment according to glucose levels)
- Meal insulin is adjusted according to glucose values and corrective algorithm as advised by the treating physician
- Contact the medical team or seek immediate medical assistance if
 - Persistently high glucose levels (>13 mmol/L)
 - Persistently high ketones
 - Unusual symptoms (such as dyspnea, vomiting, or chest pain)
 - Symptoms of hyperglycemia (if glucose monitoring is not available) as polyuria, polydipsia, or tiredness³¹

Hyperglycemia (with or without diabetes) is a double-edged sword: it depends on the acute illness and by itself negatively contributes to a more severe prognosis. A stable blood glucose concentration below 10 mmol/L is the recommended target and a clinical priority in hospitalized patients.

Blood glucose should be measured in all newly admitted patients with COVID-19 and ketones in all with known diabetes or admission glucose >12 mmol/L. However, one must keep in mind that shortness of breath can also result from metabolic acidosis. It is advised to discontinue sodium-glucose co-transporter 2 inhibitors (SGLT2is) in all admitted patients. It may be noted that the glucose can be <11 mmol/L if the patient is on SGLT2i, is pregnant, and/or has severe COVID-19.³⁰

Never stop basal insulin in individuals with type 1 diabetes. Patients who are very sick with the inability to eat should be on Intravenous Insulin Infusion along with usual basal subcutaneous (SC) insulin.³² In a case report study, the successful use of MINIMED 670G to obtain a glucose control in a Patient with T1DM and COVID-19 was noted.³³

Specific Measures in Patients with Diabetes

People with diabetes must maintain good glycemic control through regular monitoring of blood glucose. A survey showed that only 28% of the participants were checking their blood glucose levels regularly during the lockdown period in India.³⁴ Continuous glucose monitoring (CGM) and flash glucose monitoring systems are useful and allow remote monitoring by healthcare providers. For patients with type 1 diabetes, monitoring of ketone levels (particularly for people who are persistently hyperglycaemic) and vigilance for the development of symptoms of DKA are important. People with diabetes and co-existing heart disease or kidney disease need special care and attempts should be made to stabilize their cardiac/renal status.

Routine clinic visits and overcrowding in hospitals should be minimized to reduce disease spread, measures such as Telephone consultation, Video consultation and Emails can be incorporated. Various other strategies and innovative ways are needed to support and deliver good quality care to those who are unable to come to routine face-to-face appointments. Novel glucose monitoring technology, with cloud-based

access to glucose and insulin data, supports virtual consultations. It also allows services to identify those at highest risk and provide targeted care, as well as enhancing the quality of interaction.

During this time of uncertainty, fear, helplessness and strong emotions may increase stress in some patients. It is important to ensure psychological wellbeing, as stress may adversely affect glycaemic control. Maintaining a healthy diet may be challenging because of limited access to appropriate food. Attention to nutrition and adequate protein intake is important. Any deficiencies of minerals and vitamins need to be taken care of.

Adopting a regular exercise plan might not be feasible owing to social distancing, restrictions on outdoor activities and concerns over the high risk of disease spread in gyms and sports centers. Activities such as indoor walking, gardening and stationary high-intensity activities may be suitable alternatives to maintain an active lifestyle.

Priority		Conditions	Site of care
1	Critical	IDSA severe infections, Gas gangrene, sepsis and acute limb-threatening ischemia.	Hospital
2	Serious	IDSA is mild to moderate infections, chronic limb-threatening ischemia, Dry gangrene, Active Charcot foot.	Outpatient clinic/ Podiatrist office
3	Guarded	Improving foot ulcers.	Podiatrist office/ Home / Telemedicine
4	Stable	Recently healed foot ulcer, diabetic foot risk assessment.	Home/ Telemedicine

It is important to take influenza and pneumonia vaccinations. The latter may decrease chances of secondary bacterial pneumonia after a respiratory viral infection, however, data in the present viral epidemic is not available.^{35,36}

Lastly, the care of feet should be emphasized to avoid foot-related complications. There are telemedicine temperature mats that can screen for inflammation without having to visit the clinic. The patients who show inflammation can then be called to the clinic.³⁷

Podiatrists have quickly adapted the new pandemic system of care and changed to provide services in new and unique ways. By strongly implementing a triage system for lower-extremity wounds and diabetic foot problems.³⁷

Conclusion

Diabetes patients are prone to a severe clinical course of COVID-19 and significantly increased mortality. Hence, people with diabetes and with other comorbidities must be urged to comply with social isolation and other preventive measures for COVID 19 infection. There are many unanswered questions like a patient with controlled diabetes who are at risk of getting infected with COVID-19? Is there any specific diet or supplement which could help patients of diabetes and COVID-19? Many more unanswered doubts yet to be resolved, due to limited data regarding diabetes associated with COVID-19. Overall, the COVID-19 pandemic crisis should be used to establish innovative management strategies for patients with diabetes. Early isolation, early diagnosis, and early management might collectively contribute to better control of the disease and outcomes.

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