Research Article

Asymptomatic Transmission of Acute Respiratory Syndrome Sars-Cov-2 Effect on Diabetes Mellitus Management in Patients

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Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia quickly became a newly recognized illness that was spreading rapidly throughout Wuhan (Hubei province) to other provinces in China, and continues to spread around the world. Some diseases, for instance diabetes, are continuously suggested as a risk factor which contributes to the severity and mortality of COVID-19. However, to date, there are no comprehensive studies aiming to explain the exact relationship between diabetes and COVID-19. Thus, this study aims to summarize the evidence about diabetes and COVID-19 outbreak through a systematic review and meta-analysis approach. We have performed an extensive literature search for articles in PubMed, Science direct, MedRxiv, EMBASE and Google Scholar databases till September 15, 2020. Some studies suggest that there were no significant differences in symptoms between patients who suffered from both diabetes and COVID-19 and those who only suffered COVID-19. In the subsequent meta-analysis 14.5% of the subjects were diabetic patient. An optimized glycemic control should be pursued in patients with diabetes and SARS-CoV-2 infection in order to reduce the risk of severe COVID-19 course.

Keywords:
Diabetes mellitus, COVID-19, SARS-CoV-2, comorbidity
INTRODUCTION:
In 1985, 30 million people suffered from diabetes, and by 2010 that figure increased to 285 million. According to the latest global estimate from the International Diabetes Federation that number of affected patients in 2019 stands at 463 million. It is estimated that by 2045, around 700 million people will suffer from diabetes.\(^1,2\) Diabetes is the leading cause of end-stage renal disease, adult-onset blindness, and non-traumatic lower extremity amputations.\(^3\) Diabetic complications cause more disability, and at extreme threat disorders.\(^4\)

Patients with diabetes are vulnerable to infection because of hyperglycemia; impaired immune function; and comorbidities such as hypertension, dyslipidemia, and cardiovascular disease. In addition, angiotensin converting enzyme 2 (ACE2) is a receptor for SARS-CoV-2 in the human body.\(^5\) Hence, the use of angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB) and high level of angiotensin II in patients with diabetes requires attention. In fact, it was reported that the overall proportion of diabetics with COVID-19 was 5.3–33.9% in China,\(^6\) Italy,\(^7\) and the USA.\(^8\) The severity and mortality from COVID-19 was significantly higher in patients with diabetes than in those without.\(^9\) Even though there are differences in the pattern and intensity of transmission ranges between different countries, the similar finding was that the elderly; those with comorbidities including hypertension, diabetes, cardiovascular disease, chronic lung disease, immune compromised state, severe obesity, chronic kidney disease treated with dialysis, and liver disease; and people in nursing homes or long-term care facilities were at a high risk of fatal outcomes from COVID-19.

While type 1 diabetes (T1D) is characterized by autoimmune mediated destruction of insulin b-cells, type 2 diabetes (T2D) results from a combination of insulin resistance and b-cell insulin secretory defect, in the long-term resulting b-cell exhaustion and eventually destruction. Diabetes is the leading noncommunicable, chronic pandemic disease worldwide and is associated with complications. Over time, high blood glucose can damage tiny and large blood vessels, causing an increased risk for microvascular and macrovascular complications.\(^10\) A research study with more than 1.3 million participants showed that 98% of adults with type 2 diabetes have at least one comorbid chronic disease and almost 90% have at least two.\(^11,12\) The most common conditions in patients with T2D included hypertension (82.1%), overweight/obesity (78.2%), hyperlipidemia (77.2%), chronic kidney disease (24.1%), and cardiovascular disease (21.6%).\(^12\) Poorly controlled diabetes increases the risk for skin, bone, eye, ear, gastrointestinal, urinary tract, and respiratory infections, among others, with significantly increased hospitalization and mortality rates. Thus, the patients with diabetes should take precautions during the COVID-19 pandemic. In addition, knowledge of the molecular mechanism of viral entry and replication can direct the treatment strategies and future research on targeted antiviral drugs and vaccines. Therefore, we review the current knowledge of COVID-19 including the global and western-Pacific regional epidemiology, virology, impact of diabetes on COVID-19, treatment of COVID-19, and standard of care in the management of diabetes during this critical period. We searched all the articles in PubMed, Science direct, MedRxiv, EMBASE and Google Scholar databases till 11 September, 2020.

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia quickly became a newly recognized illness that was spreading rapidly throughout Wuhan (Hubei province) to other provinces in China, and continues to spread around the world.\(^13\) The World Health Organization (WHO) pronounced the official name of SARS-CoV-2-induced disease as the coronavirus disease 2019 (COVID-19). In Fig-1: A graphical representation demonstrates the symptoms of Covid-19.
Diabetes with COVID-19

The prevalence of diabetes among people with COVID-19 and severity of COVID-19 in patients with diabetes varies, depending on the location and age of the patients and severity of the pandemic. We summarized the prevalence, severity, and mortality of diabetes among patients infected with COVID-19. In China, the prevalence of diabetes in patients with COVID-19 is similar to the nationwide prevalence of diabetes mellitus in China (approximately 10.9%).[9] Therefore, patients with diabetes do not seem to be more susceptible to COVID-19. The severity and mortality of patients with diabetes was higher than those of patients without diabetes infected COVID-19. A previous early large observational study found that the incidence of diabetes was higher in patients with severe illness (16.3%) than in patients with non-severe illness (6.9%).[14] Other single center observational studies showed similar results, i.e., higher (13.8–22.2%) proportion of diabetes in severe COVID-19 cases than in non-severe cases (4.5–11%).[13,15-20]

Several early single-center retrospective studies in Wuhan showed significantly higher prevalence (15.6–31%) of type 2 diabetes among non-survivors than among survivors (7.8–14%). The COVID-19 mortality in the presence of diabetes rose up to 7.3% (80/1102), which is significantly higher than the COVID-19 mortality without any comorbidities (0.9%, 133/15,536) and an overall fatality rate of 2.3% in the largest epidemiological investigation from the Chinese Center for Disease Control (CDC).[6,19-23]

Epidemiology of Diabetes

The latest meta-analysis from China states that among 46,248 patients infected by COVID-19, most of the patients have pre-existing disease background. Hypertension remains on top (17 ± 7, 95% confidence interval (CI) 14–22% followed by diabetes (8 ± 6, 95% CI 6–11%), cardiovascular diseases (5 ± 4, 95% CI 4–7%) and respiratory diseases (2 ± 0, 95% CI 1–3%), which unexpectedly arises much later than the components of metabolic syndrome. Patients suffering from the severe disease were 2.36 times more probable to have hypertension (95% CI 1.46–3.83), 2.46 times expected to have respiratory disease (95% CI 1.76–3.44) and 3.42 times likely to have underlying cardiovascular disease (95% CI 1.88–6.22), as compared to those with the mild disease who do not require any hospitalization.[24] In a cohort of 54 severely ill patients admitted with COVID-19 pneumonia in China, 44.4%, 24.1% and 14.8% of patients had preexisting hypertension, diabetes and coronary heart disease, respectively. In which 44.4% of patients were complicated with myocardial injury as demonstrated by elevated cardiac enzymes, and N-terminal pro-B-type natriuretic peptide. These patients are having a profile of very high mortality of 48.1%.[25] In another cohort study of 131 patients with COVID-19 infection admitted at a hospital in Wuhan, hypertension was the most common associated comorbidity (30%), followed by diabetes (19%) and coronary artery disease (8%).[23]

Investigation of Diabetes

In the case of type 1 diabetes, the immune cells of the body begin to destroy β-cells, which are solely liable for the production of insulin hormone in the pancreas. Data from various studies as well as coronavirus infected patients indicates that the novel virus destroys insulin producing β-cells, which is further resulted as hyperglycemia.[26] Different viruses, including one that causes SARS, were related to autoimmune conditions, including such as type 1 diabetes.[27] There are multiple organs involved behind the regulation of blood sugar in the body and also consists of different
proteins like ACE2, and coronavirus further uses it to infect the cells). Blood sugar and ketones are seen in higher levels in COVID-19 infected patients. If the body is unable to produce an adequate level of insulin to breakdown the blood sugar, it utilizes ketone as another source of fuel, which further leads to diabetic ketoacidosis. In the pancreas, β-cells produce blood sugar-lowering hormone insulin, and α-cells make the glucagon hormone that increases blood sugar. SARS-CoV-2 may infect α- and β-cells; as a result, few of them get destroyed. The virus can also induce some protein production (chemokines and cytokines), which can trigger an immune response that can also kill the specific cells and alter insulin secretion. In obese people, insulin resistance (IR) may be a crucial aspect of the incidence of COVID19. ACE2 is the potential link between IR and COVID-19 since the virus enters the host body via ACE2. ACE2 helps in the maintenance of RAAS and abnormality of the same leads to IR and cardiovascular dysfunction. Degradation of angiotensin 2 results to the reduction of IR by decreasing oxidative stress, improving insulin signaling and enhanced insulin transport. It is important to normalize the blood glucose and insulin level, thereby reducing the expression of ACE2 and eventually COVID-19 severity. It is assumed that insulin production and SARS-CoV-2 are interconnected to each other. Low levels of insulin contribute to hyperglycemia, and patients with COVID-19 exacerbates the situation. Therefore, additional care and treatment are also required for patients with low insulin levels.

**Diabetes Management**

Persons affected with the virus must inform the healthcare persons about their diabetic profile when they admitted to hospital for their better treatment management; especially people dealing with type 1 diabetes and those who depend on adrenal corticosteroids/mineralocorticoids for survival. If patients are not in a condition to take the oral tablets or are unable for subcutaneous insulin, they must give them intravenously. The management of diabetes itself a unique challenge, particularly for those who are on non-insulin depended diabetes mellitus (NIDDM) or type 2 diabetes. In cases with uncontrolled hyperglycaemia, it would be pragmatic to intensify insulin dosing, relatively than other oral drugs. Present data give an idea that hydroxychloroquine (HCQ) is the drug of choice for the patient affected with Coronavirus due to its antiviral properties. Still, there are not enough pieces of evidence present to support the uses of hydroxychloroquine as an ideal drug for the management of diabetes complicated by COVID-19 infection. Healthcare professions must alert the potential endocrine and adverse metabolic effects of the drugs, which are in use. Like corticosteroids, able to cause dysglycaemia, however long-term antiretroviral therapy may be associated with metabolic syndrome. Apart from the lack of specific therapies and knowledge about potential therapeutic targets, it is challenging to treat a disease along with other comorbidities. The drug repurposing for SARS-CoV-2 also found to be an exciting option to combat with this novel virus infection for diabetic patients. Nearly all patients accepted oxygen therapy, and the WHO recommends extracorporeal membrane oxygenation (ECMO) to patients with refractory hypoxemia. Because the elderly and those with underlying disorders (i.e., hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease) progressed rapidly into ARDS, identification of high-risk factors and management of comorbidity are very important.

**Glucose control of COVID-19 patients**

Recently, acute hyperglycemic crisis such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) were reported in patients with diabetes. As ACE2 is expressed in the human endocrine pancreas, SARS-CoV-2 might enter the islets cells and cause acute beta-cell dysfunction. Acute hyperglycemic crises can be precipitated by COVID-19 and result in catastrophic outcomes in patients with diabetes and poor glycemic control. Therefore, timely adequate strategies for glucose control should be emphasized in patients with diabetes during the COVID-19 pandemic. Active cooperation of diabetologists and protocols for glucose control are needed. Even after discharge, adequate blood glucose level should be maintained continuously and patients...
need to be cautious of infectious diseases due to their low immune response. Long-term follow-up is very important for patients with diabetes to reduce diabetes related complications and mortality.

Many countries now use telemedicine programs that allow clinicians to see patients at their home. Telemedicine has been very helpful and useful during the COVID-19 pandemic. With the aim of preventing person-to-person transmission, a variety of online services of glucose management have been implemented widely for diabetic patients and the general population during COVID-19 pandemic around the world.

**Anti-diabetic medication for COVID-19 patients**

Treating with glucocorticoids to hyperglycaemic patients affected with COVID-19 come up with tremendous challenges to the medical professional. The problem associate with this novel virus infection results in loss of glycaemic control due to unstable food intake and intercurrent diseases like fever and others. To keep the glucose level optimum, frequent glucose monitoring in addition to continuous change in antidiabetic medications required. Patients having type 1 diabetes generally treated with basal-bolus or insulin pump therapy and the doses of insulin should be frequent and be monitored to avoid a situation like hypoglycaemia as well as severe hyperglycaemia and ketoacidosis mainly in patients with reduced food intake. Patients having a diabetic profile should follow some basic prevention instruction to dodge the novel coronavirus infection. This quickly spreading virus infection can stop since this is a communicable disease; several recommendations help to diminish the spread of the deadly virus. Patients are having a profile of type 2 diabetes, Sodium-glucose cotransporter-2 (SGLT2) inhibitors along with metformin, should be stopped to control moderate to severe illness. Chances of dehydration and diabetic ketoacidosis during infection is there, so additional precaution requires to be taken by the patients to avoid such incidences. Inhibitors like Dipeptidyl peptidase-4 (DPP4) linagliptin can be useful in the cases of impaired kidney function without risk of hypoglycaemia. Drugs class, like sulphonylureas, consider as one of the reasons for inducing hypoglycaemia in patients having a low-calorie intake, so before taking this class of drug, proper guidance should be followed. Uses of drugs like long-acting glucagon-like peptide-1 (GLP-1) receptor agonist should not be discontinued without the proper consultation of a physician. Patients having a profile of Type 2 Diabetes Mellitus, insulin treatment is better and vital to be started. Treatment of patients in the case of intercurrent disease a time-involved process, which is a serious issue. A drug like pioglitazone a thiazolidinedione should be avoided; it may trigger the severity of the disease. Although anti-diabetic medication has been found to have an effect on immune-modulation, there was no strong evidence on the effect of anti-diabetic medication on the outcome of COVID-19 patients. Good glycemic control is important to improve the outcomes of patients with COVID-19. Therefore, anti-diabetic medications that effectively control the blood glucose and have immune-modulating properties may have a beneficial effect on COVID-19 patients’ outcome. However, adverse reactions and contraindications of antidiabetic medications should be considered when hyperglycemia is treated in critically ill patients with diabetes.

**COVID-19: A threat to Diabetes patients**

Diabetes closely characterized by impaired immunity that assumed to lead an augmented susceptibility to COVID-19 contagion, particularly in those with an elevated level of blood glucose. Cardiovascular disease, collective comorbidity towards endocrine disease comprising diabetes, is a significant donor to COVID-19 morbidity. Prominent data of COVID-19 patients associating several other diseases such as hypertension, diabetes and CVD suggest that different studies have different prevalence rate globally, according to a report on comorbidities in COVID-19 patients by Singh et al., states that a pooled data from 10 Chinese studies (n = 2209) reported an occurrence of diabetes, hypertension and CVD in 11%, 21% followed by 7% separately. Due to less data availability, it is difficult to conclude that pre-existing diabetes in coronavirus affected patient increases the mortality rate. Liu et al. report a study that includes 61 patients in which 5 patients are having a pre-existing diabetic profile (8.2%). In that
report, 17.6% of cases are severe, whereas 4.5% of cases are non-severe.\[46]\ In another study, Guan et al. reports out of 1099 COVID-19 cases 81 patients also suffering from diabetes (7.4%), in which severe and non-severe cases are 16.2% and 5.7 respectively.\[47]\ Wu et al. state in a report that 14 patients out of 138 patients having diabetes (10.1%) as comorbidity, in which 5.9 cases are severe and 22.2% cases are non-severe.\[48]\ In addition to these reports, Zhang et al. report a study of a total of 201 patients in which 22 are diabetic (12.1%). That further states 19.2% and 5.1% of cases are severe and non-severe, respectively.\[49]\ Huang et al. in a study report that out of 41 total cases, 8.\[13]\ Remarkably, diabetes used to be a more significant risk factor for severe disease and mortality in the earlier SARS, MERS coronavirus infections along with severe influenza A H1N1 pandemic in 2009.\[50-52]\ Patients with type 2 diabetes tend to be obese, and obesity is another risk factor for severe infection. It was clarified from the period of influenza A H1N1 epidemic in 2009 that the disease was more severe and had a lengthier duration of approximately two-fold more patients with obesity who were then treated in intensive care units compared with a related population.\[52-54]\ 

**DISCUSSION**

More recently, a study conducted in England, has evaluated the risk of death in type 1 and type 2 diabetes (T2D) patients hospitalized with COVID-19. They found that those with T1D had a higher risk than those without diabetes and those with T2D. Cardiovascular comorbidities were taken into account and people with T1D were at a higher risk of in-hospital death after adjusting for age, sex, ethnicity, socioeconomic deprivation and region diagnosed cardiovascular comorbidities. Anxiety in people with T1D has been associated with less frequent BG monitoring and suboptimal glycemic control.\[55]\ Another factor that may have influenced the improvement in glycemic control is the fact that diabetes has been reported in the media as a risk factor for COVID-19 prognosis. This may have influenced patients’ awareness and self-management. In these studies, authors have also compared the infection risk between individuals with T1D and T2D and found that infection-related hospitalizations and deaths were higher in individuals with T1D.

It is well documented that diabetes increases the severity of the COVID-19 disease. However, the pathology is not clear. Understanding the interaction between diabetes and COVID-19 could open a window for therapeutic measures, but there is a paucity of data on this issue. The results of a study on MERS and diabetes concluded virus replication, and clearances are not influenced by diabetes.\[56]\ For treatment of patients with both diabetes and COVID-19, HCQ is suggested because it is safe in diabetes, and was useful for COVID-19 patients.\[57,58]\ It can be administered with zinc supplements to enhance the clinical efficacy. A retrospective analysis showed reduced rates of death and intubation in patients with viral pneumonia who were continued on ACE inhibitors.\[59]\ But theoretically, it could increase the risk of infection with COVID19, especially for diabetic patients.\[60]\ Further study must be conducted for more information.

**DECLARATION OF CONFLICTING INTERESTS**

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