

Assessment and Management of Diabetic Patients During the COVID-19 Pandemic

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Abstract: COVID-19 has become a great challenge across the globe, particularly in developing and densely populated countries, such as India. COVID-19 is extremely infectious and is transmitted via respiratory droplets from infected persons. DM, hypertension, and cardiovascular disease are highly prevalent comorbidities associated with COVID-19. It has been observed that COVID-19 is associated with high blood-glucose levels, mainly in people with type 2 diabetes mellitus (T2DM). Several studies have shown DM to be a significant risk factor affecting the severity of various kinds of infection. Dysregulated immunoresponse found in diabetic patients plays an important role in exacerbating severity. DM is among the comorbidities linked with mortality and morbidity in COVID-19 patients. Chronic conditions like obesity, cardiovascular disorders, and hypertension, together with changed expression of ACE2, dysregulated immunoresponse, and endothelial dysfunction, may put diabetic patients at risk of greater COVID-19 severity. Therefore, it is important to study specific characteristics of COVID-19 in diabetic people and treat these comorbidities along with COVID-19 infection, mainly among old individuals who are already suffering from serious and critical infections. This review will be helpful in understanding the mechanisms involved in COVID-19 and DM, the role of ACE2 in COVID-19 pathogenesis, management of DM, and associated complications in COVID-19 patients.

Keywords: COVID-19, diabetes, hypertension, cardiovascular diseases, India

Introduction

SARS-CoV2 causes COVID-19.¹ It is an enveloped virus and has ssRNA, which generally infects the upper respiratory tract in humans.² COVID-19 is highly contagious and is transmitted via respiratory droplets from infected persons.³ It enters the human body via upper respiratory mucous membrane and thereafter affects the lungs.⁴ In most cases, COVID-19 infection is a minor disease; however, some individuals develop serious characteristics of infection through compromised respiratory function (SpO₂ <93%; pulmonary infiltrate, >50% of lung field during radiology, respiration rate ≥30 breaths per minute, PaO₂:FiO₂ <300).⁵ Few people have developed dangerous or life-threatening coronavirus infection through multiple-organ failure.⁶ Information related to COVID-19 patients has suggested that most of them had comorbidities. Diabetes (DM), hypertension, and cardiovascular disease (CVD) are highly prevalent comorbidities associated with COVID-19. Data from COVID-19 patients have revealed that COVID-19 is linked with high blood-glucose level, mainly in people with type 2 DM (T2DM).⁷ Due to high DM prevalence, it is very important to study specific characteristics of SARS-CoV2 in diabetic people.⁸

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Several studies have also reported that immunocompromised COVID-19 patients, including those with HIV, pregnant women, and cancer patients, could be at higher risk of severe COVID-19 symptoms.^{9–12} Nations with high HIV-infection rates, such as India and South Africa, tend to have more COVID-19 patients.¹¹ Sahu et al suggested that COVID-19 infection in pregnant patients requires extra management with special care.¹² The UK National Health Service found that some groups, including blood cancer patients and those undergoing radio- or chemotherapy for lung cancer, were particularly susceptible to severe COVID-19 infection.¹⁰

At the time of writing, COVID-19 cases are increasing day by day with >91 million confirmed cases, 1,986,871 deaths worldwide,¹³ and >10.5 million confirmed cases with 151,918 deaths in India.¹⁴ In 2019, around 77 million were living with DM in India, and this number will increase to 101 million by 2030 and 134.2 million by 2045. After China, India has the second-highest number of diabetic patients across the globe.¹⁵ In India, about 12.1 million people aged ≥ 65 years had DM in 2019.¹⁶ According to an International DM Federation report, India had the greatest number of children and adolescents (age 0–14 years) living with type 1 DM in 2019. There are around 15.9,000 new type 1 DM cases reported annually in children and adolescents.¹⁶ T1DM and T2DM are two types of DM.¹⁷ Both types intensify the risk and complications related to the infection.^{18,19} Viral and bacterial diseases in the respiratory system are common infections associated with DM, and disrupted humoral immunoresponse, neutrophil dysfunction, and decreased T-lymphocyte responses contribute to the infection.^{5,20} Increase risk of mortality and morbidity after pneumonia is linked with DM, and people with high blood glucose (>200 mg/dL) have more pneumonia complications than those with normal glucose levels.^{21,22} At the time of the SARS epidemic (2002–2003), DM remained an autonomous interpreter of risk of mortality (OR 3, 95% CI 1.40–6.30; $p=0.005$).²³ During the MERS-CoV epidemic (2012), comorbidities like DM influenced the risk of mortality (adjusted HR 3.74 per year, 95% CI 2.57–5.56).²⁴ Studies also reported that among all comorbidities, DM had the greatest influence on risk of mortality in people with MERS-CoV.²⁵ Furthermore, similar results were observed during H1N1 infection (2009), where DM intensified intensive care unit (ICU) admission of young patients with H1N1 (OR 4.72, 95% CI 1.81–12.3).²⁶ In this review, we discussed the mechanisms involved in

COVID-19 and DM, the role of ACE2 in COVID-19 pathogenesis and management of DM, and associated complications in COVID-19 patients.

COVID-19 Characteristics

Incubation Time

The period between infectivity and onset of disease is known as incubation time. A study involving 1,099 people infected with COVID-19 reported that average incubation time for symptomatic SARS-CoV2 was 4 days.²⁷ Another study on 181 COVID-19 patients from China confirmed an average incubation time of 5 days for SARS-CoV2, and in 97.5% of patients, symptoms of infection developed within 12 days.²⁸ On the basis of the incubation time of SARS-CoV and MERS-CoV, the US Centers for Disease Control and Prevention (CDC) projected that COVID-19 symptoms would arise 2–14 after infection. As such, 14 days (quarantine) is the period used for examining and limiting the movement of individuals at risk.²⁹

Modes of Transmission

Most of the original people infected with COVID-19 had a history of direct contact with a wholesale market for wildlife and seafood in China, signifying the exposure of zoonotic virus as a major transmission mode of COVID-19.³⁰ Analysis of virus-sequencing data revealed that COVID-19/COVID-19 found in bats and SARS-CoV2 may have a common ancestor, though this Chinese wholesale market does not sell bats.³¹ After some time, COVID-19 infections were found in health-care personnel and other individuals with no contact with wildlife or travel history in Wuhan, China, indicating individual-to-individual transmission or spread of COVID-19.³⁰ Numerous studies have suggested that SARS-CoV2 could be transmitted via aerosols, drops, and direct contact with infected persons (Figure 1). Respiratory drops spread infection from one individual to another through sneezing and coughing. This happens because respiratory drops from an infected individual get into the air and are inhaled by healthy individuals nearby (within 2 m). Individuals can get COVID-19 infection via contacting contaminated objects or surfaces infected with COVID-19 and then touching their eyes, mouth, or nose.³² Studies have revealed that COVID-19 can stay viable within aerosols for up to 3 hours and spread in a closed system if inhaled breathed into the respiratory tract.^{32,33} As such, transmission of COVID-19 through the air has been made possible due to aerosol-producing processes like cardiopulmonary

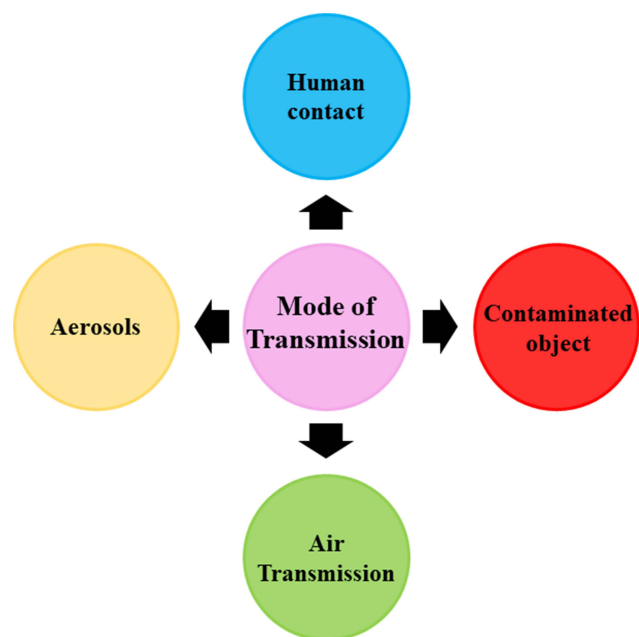


Figure 1 Mode of transmission of novel COVID-19.

resuscitation, bronchoscopy, tracheostomy, endotracheal intubation, and noninvasive positive-pressure ventilation.¹³

Pathogenesis

SARS-CoV2 infection can be differentiated into three phases: phase 1 is the initial infection stage, phase 2 the pulmonary stage, and phase 3 the hyperinflammation stage.^{34,35} In the early phase of infection, patients show symptoms like headache, fever, and dry cough. Clinical signs involve increased lymphopenia, high IL6, D-dimer, and prothrombin, and mild level of lactate dehydrogenase. In the pulmonary stage, some patients show abnormal chest images, breathlessness, and increased levels of transaminases. In the more serious stage, some develop cytokine storm, which leads to other complications involving shock, multiorgan failure, acute respiratory distress syndrome, and death. Elevated clinical inflammatory markers, such as lactate dehydrogenase, ferritin, D-dimer, IL6, troponin, CRP, and N-terminal (pro-brain natriuretic peptide) are hallmarks of this stage. These results are in line with MERS and SARS in that the incidence of cytokine storm and lymphopenia may play an important role in COVID-19 pathogenesis.^{36–38} Therefore, disease intensity in COVID-19 patients is due both to the virus and the response of the host.³⁹

Infectivity Period

It is not known how long it takes for a COVID-19 patient to recover from infection. The infectivity period is estimated by detecting the virus or its ssRNA in respiratory

tract samples. Though, presence of ssRNA of virus does not approve the contagious virus occurrence. Reports suggest that transmission of the virus may occur in the early stage of COVID-19 infection, as high virus loads are found in respiratory samples shortly after the onset of symptoms.⁴⁰ The period of shedding of the virus changes with the seriousness of the infection. About 90% of COVID-19 individuals with mild symptoms show an absence of virus or give negative tests on nasal swabs after 10 days of onset of infection, whereas in serious and critical cases, nasal swabs are positive.⁴¹ Studies have also revealed that the virus load found in asymptomatic individuals was similar to the virus load found in symptomatic patients.⁴⁰

Diagnosis

To manage COVID-19 outbreaks in communities and hospitals, several diagnostic tests have been utilized. Real-time fluorescence-based quantitative PCR is considered the standard test for diagnosis of COVID-19. In this method, ssRNA of COVID-19 is detected in respiratory swabs, lower respiratory secretions, and sputum.^{29,42}

RT-PCR Test

Real-time PCR is an important and widely used method for diagnosis of COVID-19 where RNA is converted into cDNA using reverse transcriptase, which is quantified using different primer sets, as recommended by the World Health Organization and using RNase P as an internal control.⁴³ Different regions in the genome have been identified, which has served as the template for primer design, with primers targeting E gene, N gene, and RNA replicase or RdRp possessing the highest sensitivity.^{43,44} Beside this, a number of multiplex assays have been developed that can target multiple genes together, eg, RdRp/He1, S, and N.⁴⁵ Multiplexing offers improved sensitivity in cases of degraded virus-RNA samples and development of putative mutations, with sensitivity >95%. However, false-positive tests might be obtained through primer cross-reactivity with other coronaviruses like SARS-CoV.⁴⁶

The isothermal method does not require thermal cycling as a conventional RT and amplifies DNA at a particular temperature, but delivers sensitivity similar to PCR.⁴⁶ Variations of isothermal amplification have been developed, such as HAD,⁴⁷ NASBA,⁴⁸ LAMP,⁴⁶ SDA,⁴⁹ and RPA.⁵⁰ RT-LAMP uses four to six pairs of primers corresponding to distinct regions in the genome,

which imparts the assay very high specificity.^{51–53} This test involves an SD polymerase and primer binding, as well as amplification, and occurs at 60°–65°C. The reaction occurs in a single Eppendorf tube, and the DNA product is identified through its turbidity, color, or fluorescence, depending on the type of reagent added.⁵⁴ The assay offers several advantages, such as ease of operation, less background signal, and higher sensitivity, in comparison to conventional RT-PCR.⁵¹ However, its major drawback is the requirement for extensive optimization of the primers. RT-LAMP can be multiplexed using polymeric beads with unique signatures and barcodes,⁵⁵ which increases the amount of information gained through a single reaction.⁵⁶ Multiplexing allows us to measure different biomarkers in a single reaction with improved specificity and sensitivity. These barcoded bead-based assays still need thorough optimization before being introduced into the clinical setup. However, barcoded bead-based assays are still available for the diagnosis of cystic fibrosis and respiratory diseases.⁵⁷

Rapid Antigen-Detection Test

This test can qualitatively determine the occurrence of COVID-19 antigen and provide results in much less time, which provides the opportunity for better management of the disease. However these tests suffer from poor sensitivity, as observed with influenza viruses.^{58–61}

ELISAs can detect specific antibodies among respiratory and blood samples of an infected person. Antibody-mediated immunity against virus can be determined by measuring generated IgG and IgM. IgM is produced on the basis of the initial humoral response against the virus, while IgG is produced after 7 days of infection and stays thereafter, mediating the acquired immunoresponse.^{62,63} Detection of COVID-19 in patients by detecting the antigen is difficult compared to other developing methods that identify NAbs, as it requires production of purified monoclonal antibodies.

Immunodetection can also be used in identifying recovered patients whose convalescent plasma can be utilized for the treatment of critical patients.⁶⁴ Proteins that mediate virus entry into host cells by interacting with ACE2 receptor are the key target for developing diagnostic antibodies.⁶⁵ Other targets include the N protein and virally encoded repressor.⁶⁶ ELISAs are an easy and appropriate method for rapid recognition of antibodies generated against COVID-19 in a short period in the same patient. Receiver-operating characteristic analysis has revealed that the sensitivity of IgG- and IgM-based ELISAs 88.9% and 48.1%, respectively, whereas

specificity was 90.9% and 100%. The lower sensitivity associated with IgM is due to the fact that the response occurs early and then gradually decreases with time,⁶⁷ which can be improved by the incorporation of novel labels like gold-labeled Ig.⁶⁸

Comorbidities Associated with COVID-19

Many studies have revealed that life-threatening and critical cases of COVID-19 are found among old patients or in persons with comorbidities, specifically DM, hypertension, CVD, cancer, and chronic renal and lung disorders.^{27,37,38,69} Table 1 shows the prevalence of comorbidities among COVID-19 patients.⁸ One meta-analysis from China on 1,527 infected individuals reported that the highly prevalent comorbidities associated with SARS-CoV2 were hypertension (17.1%, 95% CI 9.9–24.4), DM (9.7%, 95% CI 6.9–12.5) and cerebrovascular disorders (16.4%, 95% CI 6.6–26.1). This meta-analysis showed that COVID-19-infected people with hypertension or DM had double the severity of infection or ICU admission, whereas patients with cerebrovascular disorders showed triple the disease severity.³⁶ A comprehensive review and meta-analysis reported that older age and associated comorbidities, such as DM, hypertension, heart disorder, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and chronic liver disease enhanced the risk of progression to critical disease and death among COVID-19 patients.⁷⁰ Moreover, it has been observed that COVID-19 causes more neurological complications than MERSCoV or SARS-CoV.⁷¹ A comprehensive evaluation reported that hypertension is more common than T2DM in patients with COVID-19.⁷² Another study reported that blood type influenced prognosis in COVID-19 patients with hypertension.⁷³ A study conducted on COVID-19 patients with hypertension found significantly higher values on prothrombotic indices and high rates of cardiac damage and mortality in non-O blood-group patients in comparison with O blood-group patients. This study also suggested that endothelial dysfunction level in non-O blood-group patients can be increased by prothrombotic status.⁷³ Lip reported that endothelial dysfunction in patients with hypertension can trigger stroke and cardiac injury through thromboembolism.⁷⁴ It has been recommended that modified immune-system, anti-inflammatory, and anti-hypertensive treatments may inhibit poorer prognosis and increase clinical consequences in hypertensive patients with COVID-19.⁷⁵ Furthermore, antihypertensive drug treatment, including ACEIs and ARBs did not

Table I Prevalence of comorbidities among COVID-19 patients

Source	Region	Subjects, n	DM (%)	Smokers (%)	CKD (%)	COPD (%)	CLD (%)	Htn (%)	CVD (%)	Reference
CCDCP	China	20,982	5.3	—	—	2.4	—	12.8	4.2	152
Liu et al	China	61	8.2	6.6	—	8.2	—	19.7	1.6	153
Gupta et al	India	21	14.2	—	—	0	—	—	0	80
Chen et al	China	274	17.0	7.0	1.0	7.0	—	34.0	8.0	154
Guan et al	China	1099	7.4	12.6	0.7	1.1	—	15.0	3.8	27
Zhou et al	China	191	19.0	6.0	1.0	3.0	—	30.0	8.0	38
Huang et al	China	41	19.5	7.3	—	2.4	2.4	14.6	15.0	82
Zhang et al	China	140	12.1	—	1.4	1.4	—	30.0	8.6	155
Chen et al	China	99	12.1	—	—	1.0	—	—	40.0	156
Yang et al	China	52	17.0	4.0	—	8.0	—	—	23.0	157
Wang et al	China	138	10.1	—	2.9	2.9	2.9	31.2	19.6	35
Wu et al	China	201	10.9	—	1.0	2.5	3.5	19.4	4.0	158
Liu et al	China	137	10.2	—	—	1.5	—	9.5	7.3	159
Guo et al	China	187	15.0	9.6	3.2	2.1	—	32.6	11.2	160
CDC COVID-19 Response Team	USA	7162	10.9	3.6	3.0	9.2	0.6	—	9.0	161
Bhatraju et al	USA	24	58.0	22.0	21.0	4.0	—	—	—	162
COVID-19 Surveillance Group	Italy	481*	33.9	—	20.2	13.7	3.7	73.8	30.1	88
Onder et al	Italy	355	35.5	—	—	—	—	—	42.5	81

Notes: *Deaths from COVID-19. Data from Singh et al.⁸

Abbreviations: CCDCP, Chinese Center for Disease Control and Prevention; CKD, chronic kidney disease; CLD, chronic liver disease; Htn, hypertension; CVD, cardiovascular disease; CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease.

influence the prognosis among patients with COVID-19. As a result, it was suggested that hypertensive patients with COVID-19 infection undergoing antihypertensive drug therapy should continue their treatment to manage hypertension and prevent severe complications.⁷⁵ Several studies have identified stroke in COVID-19 patients.^{71,76–78} Mechanisms involving endothelial dysfunction and immunomediated injury cause stroke and lead to hypoxia-induced injury and cytokine storm.⁷¹ Yang et al reported that chronic kidney–disease patients with COVID-19 exhibited poor prognosis, high prevalence of neutrophilia, and in-hospital deaths and also that dialysis patients are more susceptible to COVID-19 infection.⁷⁹ A study from India reported that 14.2% of 21 COVID-19 patients had DM.⁸⁰ Of 355 COVID-19–infected people who expired in Italy, only three were had no comorbidities.⁸¹ A couple of studies have revealed that along with the lungs, SARS-CoV2 can also harm the kidneys, heart, and/or liver.^{35,82} There is a need to treat these comorbidities along with COVID-19 infection, especially among old-age individuals who already have serious and critical infections.

COVID-19 and Diabetes

Mechanisms and Common Factors

DM is a major cause of morbidity and mortality across the globe. This disease is linked with numerous complications

that affect disease severity.⁸³ Diseases like pneumonia and influenza commonly found in old people with T2DM.^{84,85} Studies have reported that high blood glucose and DM play a vital role in death and severity of infection in individuals with infectious virus, such as MERS-CoV, H1N1 (influenza A), and SARS-CoV.^{23,86,87} Several studies have reported that people with diseases like DM and CVD are at greater risk of serious and critical illness from COVID-19.^{27,81,88} Chen et al also observed that older diabetic patients were more susceptible to death due to COVID-19. They reported that COVID-19 infection in diabetic patients was associated with higher CRP and older age.⁸⁹ COVID-19 disease in diabetic people may trigger excessive stress and high secretion of hyperglycemia-related hormones like catecholamine and glucocorticoid. These hormones cause irregular variability of glucose in blood and increase blood-glucose (Figure 2).⁹⁰

Resistance of insulin and high blood glucose encourages production of oxidative stress inhibits the production of glycosylation and proinflammatory cytokines. It also influences the synthesis of adhesion molecules, which facilitate tissue inflammation. The process of inflammation comprises an underlying system that increases tendency toward infection and results in serious and life-threatening consequences in diabetic patients with COVID-19.^{91–93} Uncontrolled or poorly managed DM has been found to be

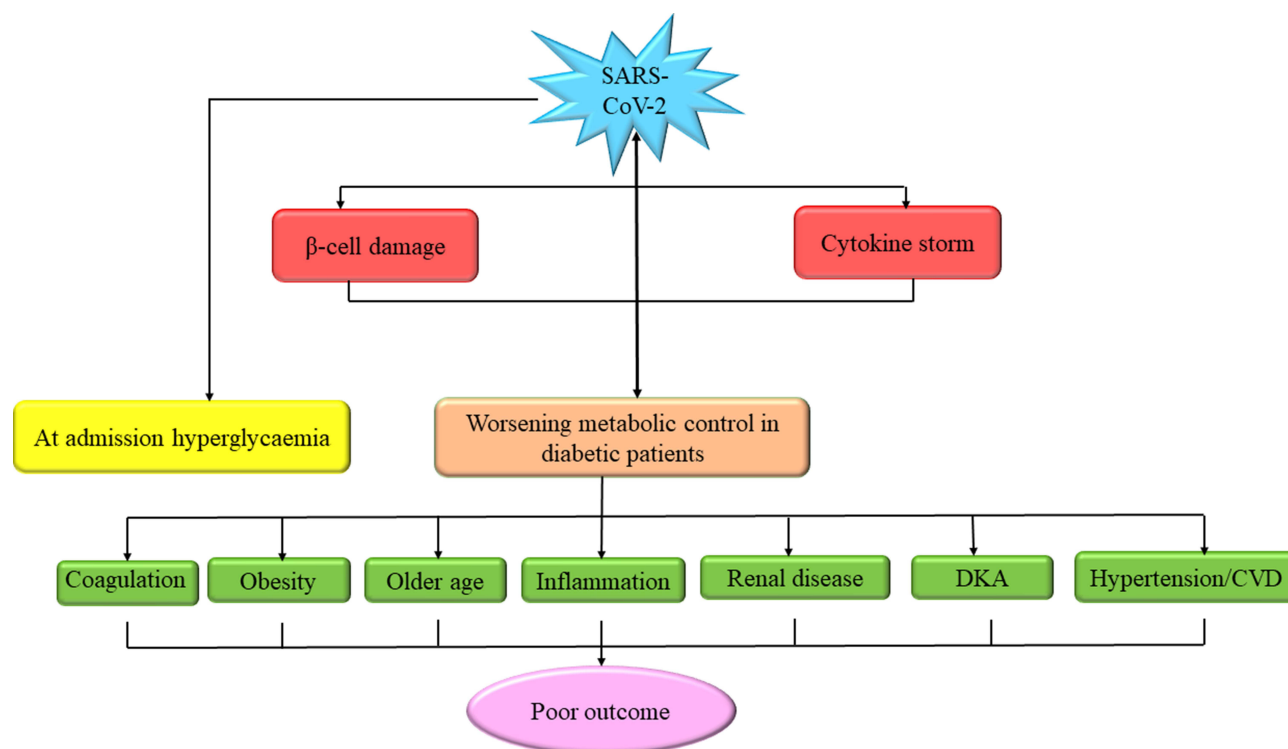


Figure 2 Reciprocal effects of COVID-19 and DM. Diabetic patients with COVID-19 infection face severe consequences due to various associated conditions that enhance the risk. Due to its tropism for β -cells, SARS-CoV2 may sustain hyperglycemia at admission to hospital. β -cell damage, cytokine storm, and counterregulatory hormone response may cause critical metabolic disorders, such as DKA. Hyperglycemia at admission and critical metabolic disorders may exacerbate COVID-19 consequences.

Note: Data from Apicella et al.⁹³

Abbreviations: CVD, cardiovascular disease; DKA, diabetic ketoacidosis.

associated with reduced lymphocyte-proliferative responses to different stimuli and also decreased function of neutrophils and macrophages.⁹² Raoufi et al study showed that chest-severity scores and clinical outcomes were alike in COVID-19 patients with well-controlled DM and poorly controlled DM in an Iranian population.⁹⁴ Dysfunctional activation of complement and irregular delayed hypersensitivity have been observed in diabetic people.^{95,96}

Dysregulated Immunoresponse and Cytokine Storm

Diabetic patients have chronic low-level inflammation, leading to exaggerated monocyte, macrophage, and T-cell recruitment, thereby promoting inflammation in a feedback loop. Excess production of proinflammatory cytokines may ultimately damage the infrastructure of the lungs. As a result, cytokine storm may activate the coagulation system. In all types of viral infections, effective clearance of virus load strongly depends upon the combined action of adaptive and innate immunity.³⁹ High blood glucose may repress the antiviral response.⁹⁷ It has been observed that diabetic patients undergo changes in components of innate immunity. For instance, primary cell

events to identify and destroy pathogens like phagocytosis and chemotaxis are impaired in diabetic patients.^{98,99} More proinflammatory M1 macrophages are present among T2DM patients, whereas natural killer-cell activity is reduced in patients with DM.^{100,101} Moreover, activity of T cells is distorted. Diabetic patients are in a low chronic proinflammatory phase with T_H1 – T_H2 imbalance.^{102,103} Irrespective of endothelial cell participation, primary delay in response of $IFN\gamma$, along with hyperinflammatory responses in diabetic patients may worsen the cytokine storm and increase the severity of COVID-19 infection.³⁹

Endothelial Dysfunction

Virus infection induces pyroptosis and is related to inflammation and vascular injury, as seen in SARS-CoV patients.¹⁰⁴ It has been observed that destruction by COVID-19, MERS, and SARS is not restricted to the lungs only, appearing in other organs, such as the kidneys and heart, which suggests that SARS-CoV2 can infect blood vessels and spread to other body organs.¹⁰⁵ Monteil et al showed that SARS-CoV2 can directly infect

vascular endothelial cells in engineered human capillary organoids.¹⁰⁶ Another study demonstrated the occurrence of viral accumulation and elements of inflammatory cells in the blood vessels of patients with COVID-19.¹⁰⁷ These studies suggest that SARS-CoV2 infection may induce endothelial inflammation among other organs and that pyroptosis may play a key role in host inflammatory responses and endothelial cell damage. High blood pressure, kidney disorders, DM, venous and arterial thromboembolism, and neurological diseases in COVID-19 patients signify that SARS-Cov-2 affects the endothelium.⁷² Endothelial dysfunction is associated with microvascular complications in patients with T1DM or T2DM.¹⁰⁸

Diabetes, SARS-CoV2, and ACE2

The receptor-binding domain of SARS-CoV2 uses host-cell ACE2 to bind membranes of host cells and virus.¹⁰⁹ ACE2, type 1 glycoprotein, is abundantly expressed in the lungs, kidneys, heart and endothelium.¹¹⁰ ACE2 upregulation provides more receptors for entry of viruses and causes more viruses to enter host cells.¹¹¹ ACE2 transforms angiotensinogen I into angiotensinogen (1–9) and angiotensinogen II into angiotensinogen (1–7) (Figure 3). These have cardio-protective and anti-inflammatory effects, and later function as vasodilators. Under normal circumstances, many studies

have demonstrated reduced expression of ACE2 in lung cells and tissue.^{112,113} However, injury in lungs upregulates ACE2 expression. Studies on human and animal subjects have reported that ACE2 can be used as a therapeutic agent in the treatment of inflammatory acute lung injury.^{114,115} Moreover, SARS-CoV seems to down-regulate the expression of ACE2 in virus-infected cells.¹¹⁶

People infected with SARS in 2003 showed high blood glucose in comparison to patients with pneumonia without SARS infection, regardless of premorbid blood-glucose levels or disease severity.⁵ Consequently, SARS-CoV combined with ACE2 in islet cells of the pancreas and injures them, which increases blood glucose. It also contributes to increased mortality rates in patients with/without DM.¹¹⁷ A similar process may occur in SARS-CoV2 infection and contribute to high blood glucose and related complications, as well as a high rate of mortality. Though few features of ACE1 and ACE2 are similar, but ACEIs does not inhibit ACE2.¹¹⁸ The expression of ACE2 is upregulated by ARBs and ACEIs. As such, ARBs or ACEIs may help SARS-CoV2 infection, which leads to disease severity.¹¹⁹ Moreover, polymorphism in the *ACE2* gene is associated with elevated DM and CVD risk, which can cause vulnerability to COVID-19, whereas upregulation of ACE2 increases angiotensinogen (1–7)

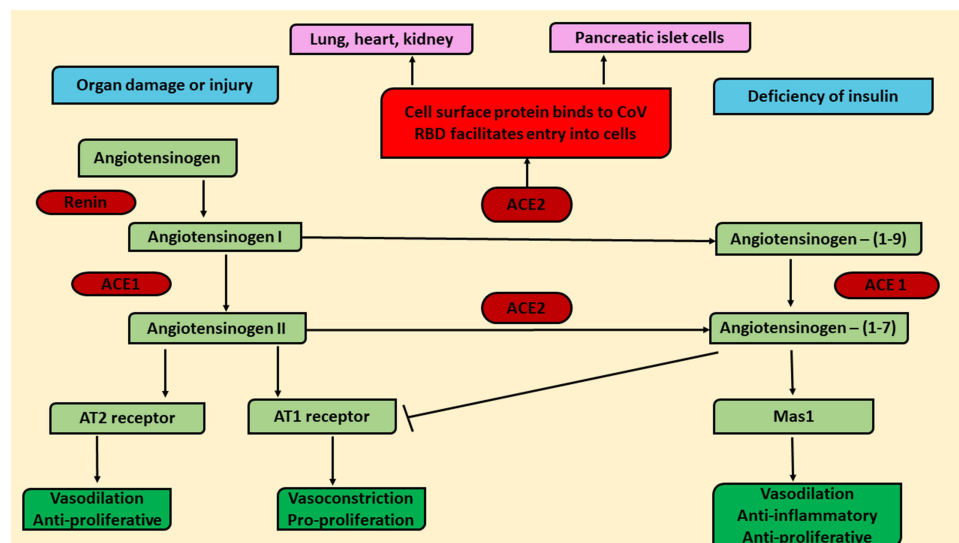


Figure 3 ACE2 role in COVID-19 pathogenesis. ACE2 transforms angiotensinogen I into angiotensinogen (1–9) and angiotensinogen II into angiotensinogen (1–7). ACE2 poses as a mediator for COVID-19 entry into cells and is expressed in the pancreas, lungs, heart and kidneys. Angiotensinogen-I level increases due to ACE1 use which upregulate the expression of the *ACE2* gene. It causes overload entry of virus into cells, which leads to deficiency of insulin and organ damage or injury and contributes to high blood-glucose levels (hyperglycemia). After upregulation, ACE2 converts angiotensinogen II into angiotensinogen (1–7) and causes anti-inflammatory and antiproliferative effects by acting on Mas1 receptors and also inhibit the AT₁ receptor to trigger vasoconstriction. Coronavirus infection downregulates the expression of ACE2 and reduces levels and anti-inflammatory effects of angiotensinogen (1–7), and organs become more vulnerable to infection.

Note: Data from Katulanda et al.⁵

Abbreviations: RBD, receptor-binding domain; AT, angiotensin; CoV, coronavirus.

levels, which leads to increased anti-inflammatory effects. However, COVID-19 infection downregulates the expression of ACE2 and reduces the level of angiotensinogen (1–7), which decreases the anti-inflammatory effects of angiotensinogen (1–7), and thus organs become more vulnerable to infection.¹¹³

India's Situation During the COVID-19 Pandemic

There are many people currently living with DM in India. Around 18 million diabetics aged ≥ 65 years are specifically susceptible to mortality because of COVID-19 pandemic.¹²⁰ This huge number is a major challenge in the assessment, management, and prevention of COVID-19 in India.²⁷ Poverty, illiteracy, overpopulation, a distressed health-care system, and unplanned towns are the main obstacles in the fight against COVID-19 in India.¹²¹ During lockdown, diabetics have raised their carbohydrate intake and also reduced physical exercise, which results in gain in body-weight gain and destabilization of blood-glucose levels in the body.¹²² A study examined the link between the period of lockdown in India and loss of glycemic control and subsequent complications. The projected increase in HbA_{1c} from base-line was 2.26% after 30 days of lockdown and 3.68% after 45 days of lockdown. The projected increase in complication rate was 2.9% for peripheral neuropathy, 2.8% for diabetic retinopathy, 0.5% for stroke, 0.9% for heart attacks, and 14.2% and 9.3% for proteinuria and microalbuminuria, respectively.¹²³ This represents an increase in the number of people with DM and its complications. Pal et al reported that 72% of all T1DM patients complained of high blood glucose based on self-monitored blood-glucose records during the nationwide lockdowns in India.¹²⁴

Trained immunity provided by bacillus Calmette–Guérin (BCG) vaccination may offer some protection from the deleterious effects of COVID-19.¹²⁵ In fact, lower mortality and disease burden were found in the primary weeks of the COVID-19 pandemic among countries that had a universal BCG-vaccination policy.¹²⁶ However, several variations from this general finding have also been found. For instance, in Israel a study reported that people born after or during the universal BCG-vaccination policy did not exhibit any deviation in mortality or infection rate for COVID-19, though the study was limited to younger age-groups.¹²⁷ Similarly, Brazil

also had a universal BCG-vaccination policy for a long time, but also witnessed a rise in mortality and COVID-19 infection.¹²⁸ Iran began universal vaccination in 1984, but did not exhibit the same protection from high mortality as seen in nations like India, which started universal BCG vaccination much earlier.^{129,130} As such, BCG vaccination may provide ethnicity-specific protection against viral microbes among South Asian populations, though the role of other factors needs to be examined.

Management of Diabetes and Associated Complications in COVID-19 Infection

COVID-19 with comorbidities leads to a fierce circle of high mortality and vast morbidity in infected patients. SARS-CoV2 exposure among people with comorbidities like CVD (reduced immunity and function of heart), DM (high expression of ACE2 and lung inflammation) are detrimental to the heart, liver, kidneys and lungs. These complications result in adverse impacts on the patient due to ARBs, shock, multi-organ failure, renal and heart failure, and ultimately death.¹³¹ The US National Institutes of Health (and the World Health Organization) have released suggestions on the basis of expert advice and clinical evidence for optimum care of COVID-19 patients.¹³² Though COVID-19 patients mostly develop minor symptoms, around 20% require hospital care, 5%–8% develop serious diseases and require critical care and ICU admission.³⁷ Variation in ICU-admission rates in different nations depends on admission requirements and clinical practice in the particular region. Furthermore, the rate of ICU admission is also influenced by factors like comorbidity and age. Disorders like CVD, hypertension, DM, asthma, and malignancy have been found to be key risk factors of serious conditions in COVID-19 patients and increased mortality rate. As such, special attention should be paid to these patients. A pilot study observed that continuous glucose monitoring is needed even in non-critically ill diabetic patients with COVID-19 infection.¹³³ Many COVID-19 patients die due to preexistent comorbidity, and thus correct assessment is needed at the time of admission to hospital.¹³⁴ It is important to segregate COVID-19 patients with and without comorbidities into two distinct groups, and separate recommendations must be considered for these patients.¹⁰⁵ People with comorbidities must adhere strictly to personal care routines, especially physical/social distancing and hand-washing.¹³⁵ Diabetic patients must increase their metabolic control as required, as it is a primary preventive step of

COVID-19 infection.⁷ Influenza vaccination decreases pneumonia risk by 43%–55% among people with DM, and can be applied to distinguish symptoms of COVID-19 and influenza.¹³⁶ Because of reduced immunity among patients with comorbidity, it is recommended that if a patient is experiencing minor symptoms that can be regulated at home, they should live in isolation. Additionally, physician consultations must be augmented for managing COVID-19 infection in patients with comorbidities.¹³⁴ Sardu et al reported that during hospitalization, optimal glycemic control was linked to reduced risk of serious conditions and death in COVID-19 patients. They found that during hospitalization, D-dimer and IL6 levels were substantially higher in hyperglycemic patients than normoglycemic patients ($P < 0.001$).¹³⁷ In T2DM patients, altered glucose homeostasis and insulin resistance cause interstitial lung disease and alveolar capillary microangiopathy via conditions like overinflammation.¹³⁸ This suggests that COVID-19 patients with hyperglycemia are at higher risk of disease severity during hospitalization. Overactivation of innate immunity might be a poor outcome of COVID-19 infection in hyperglycemic patients, including those treated with tocilizumab, which is an IL6 inhibitor.¹³⁹ Despite complete treatment with antivirals, oxygen therapy, and hydroxychloroquine, hyperglycemic patients with COVID-19 infection have poorer prognosis.¹⁴⁰ These data suggest that early management of glycemia may be a potential therapeutic method to reduce poor outcomes among hospitalized hyperglycemic COVID-19 patients with/without prior diagnosis of DM.¹⁴¹

Mostly, T2DM patients have other elements of metabolic disorders like dyslipidemia and hypertension. As such, continuous treatment is suitable for lowering lipids and hypertension in people with T2DM. Use of ARBs and ACEIs in treatment may enhance ACE2 expression, which facilitates virus entry into host cells (Figure 4).¹⁴² SARS-CoV2 may damage ACE2- and Mas1-receptor pathways and increase harmful AT2 action, as they can provide a safeguard against lung injury after COVID-19 infection. A recent study reported that ACEI and ARB prescriptions benefited COVID-19 patients in terms of reducing mortality and hospital stay.^{143,144}

Studies from the European Society of Cardiology, American College of Cardiology, American Heart Association, and Heart Failure Society of America have recommended that T2DM patients continue with hypertension treatment, which should include ARBs and ACEIs.^{7,145} Drugs, particularly statin, can fix the reduced ACE2 caused by high levels of lipids, such as low-density lipoprotein.¹⁴⁶ Anti-inflammatory effects of statins contributed into upregulation of ACE2. Table 2 shows pharmacotherapies used during COVID-19 infection for DM and associated complications.⁵ Due to the close association between CVD and DM, the researchers recommended the management of concentration of lipids in COVID-19 patients. People who have undergone kidney, islet, or pancreas transplantation and those on immunosuppressive treatment are at high risk of COVID-19 infection.⁷

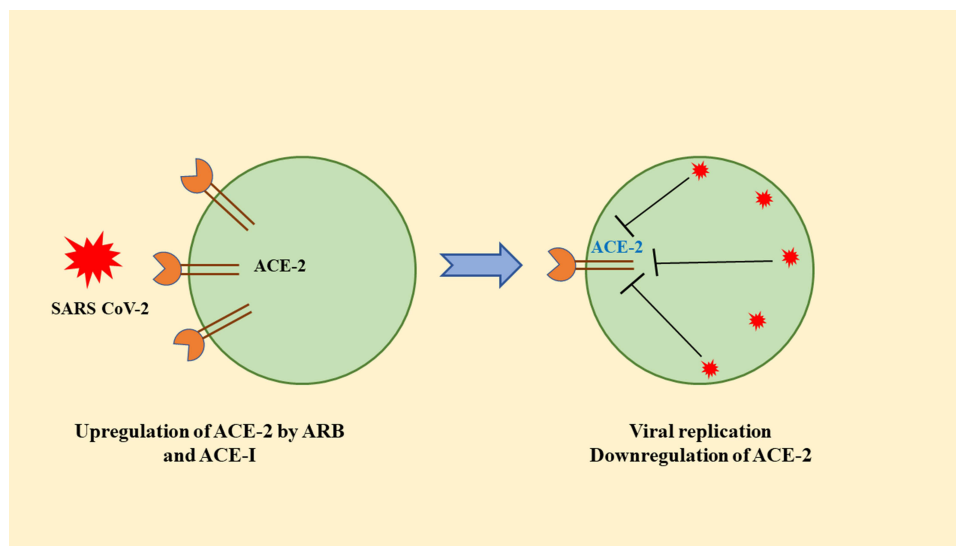


Figure 4 Interactions among SARS-CoV2 and pneumocytes. SARS-CoV2 enters cells through ACE2. ACE2 gets upregulated by ARB and ACEI. After entering host cells, the virus replicates and downregulates ACE2. This causes a decrease in angiotensin II and results in more aldosterone secretion and renal wasting of potassium.

Note: Data from Pal and Bhansali.¹⁶³

Abbreviation: ARB, angiotensin receptor blocker.

Table 2 Pharmacotherapies used during COVID-19 infection for DM and associated complications

Considerations for use	
Statins	Elevated myositis and transaminitis risk
Sulfonylureas	Risk of low blood-glucose level in cases of oral ingestion or in association with chloroquine/ hydroxychloroquine
Aspirin	CVD risk higher with COVID-19 infection
DPP4 inhibitors	Risk of low blood-glucose level is low, may use for several renal dysfunction
ACEI/ARBs	Risk of increased infection susceptibility and benefited in inflammatory injury
SGLT2 inhibitors	Elevated risk of euglycemic DM ketoacidosis and dehydration
Insulin	Regular monitoring is required
GLP1RAs	Aspiration risk and gastrointestinal side effects
Pioglitazone	Edema and fluid-retention risk, contraindicated during hemodynamic instability
Metformin	Lactic acidosis risk in conditions of hypoxia and acute infection

Note: Data from Katulanda et al.⁵

Data show that most T2DM patients are obese or overweight. BMI is a vital factor of oxygenation, lung volume, and respiratory mechanics at the time of automated ventilation in the body, particularly in a horizontal posture. Therefore, obese diabetic patients can be at higher risk of ventilation failure and problems at the time of automated ventilation.¹⁴⁷ India has developed several national strategies and policies, such as the National Cancer Control Programme, National Trauma Care Programme and National Programme for Prevention and Control of Diabetes, Cardiovascular Disease, and Stroke, to carefully tackle the chronic disorder burden.¹⁴⁸ SARS-CoV2 may cause long-term metabolic disorders in infected people. Similar results were observed in individuals infected with the SARS virus.¹⁴⁹ There is a need for regular and constant cardiometabolic examination of people who have survived severe and critical SARS-CoV2 infections.⁷ COVID-19 is highly prevalent among health-care professionals with DM, who administer care to COVID-19 patients. Therefore, wherever possible, these workers must not work around sick people or they should use high-level safety protocols.^{7,150} Dorjee et al suggested that appropriate management of modifiable risk factors like DM and hypertension may decrease mortality and morbidity due to COVID-19.⁷⁰

Recommended Steps for Good Health in Diabetic Individuals During the COVID-19 Pandemic

People with DM must exercise regularly. Exercises like stationary running, cycling, resistance training, and treadmill are helpful, and everyone can easily follow this exercise routine in India.

- Diabetic people should maintain consistency in their regular meals. They must eat healthily, with a balanced quantity of fibers and proteins. A limited amount of fat in food is vital to control blood-glucose levels.
- It is important to regularly take prescribed medicines or antidiabetic drugs and insulin on time.
- Patients should keep their feet clean to prevent problems linked to the feet.
- Old people should know the ambulance number (102) for emergency situations.
- Diabetic people should visit hospital immediately in emergency conditions, such as chest pain, altered senses, shortness of breath, drowsiness, weakness in the limbs, and vomiting.^{8,151}

Conclusion

SARS-CoV2 is extremely infectious and transmitted via respiratory droplets from infected persons. Severe cases of COVID-19 have been observed in people with comorbidities, particularly CVD, hypertension, and DM. An increasing number of studies have shown DM to be a vital risk factor affecting the severity of various other kinds of infection. Dysregulated immunoresponse found in diabetic patients plays an important role in exacerbating severity. DM is among the comorbidities linked to mortality and morbidity due to COVID-19. Chronic conditions like obesity, CVD, and hypertension together with changed expression of ACE2, dysregulated immunoresponse, and endothelial dysfunction may put diabetic patients at greater risk of COVID-19 infection. The awareness and opinions of people are likely to impact the great amount of protection methods and eventually affect the results of clinical research. Therefore, it is important to study specific characteristics of COVID-

19 in diabetic people and treat comorbidities along with COVID-19 infection, mainly among old individuals who are already suffering from serious and critical infections.

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Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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