

## Diabetes and COVID-19: A Review

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### Abstract

Coronavirus Disease 2019 (COVID-19) is an emerging disease and since its first identification in Wuhan, China, in December 2019, there has been a rapid increase in cases and deaths across the world. COVID-19 has been shown to have an immense impact in infected persons with diabetes, worsening their outcome, especially in elderly, smokers, obese, those having CVD, CKD, poor glycemic control and long duration of diabetes. In this review we summarize the current understanding of the impact of COVID-19 on diabetes and discuss the pathophysiological mechanisms and management of diabetes and its complication in this scenario.

**Key words:** Corona Virus, COVID-19, diabetes mellitus

### BACKGROUND

Globally, COVID-19 has impacted several millions of lives and is steadily increasing in number. The coronavirus has derived its name because of resemblance of its shape to a crown or solar corona when imaged using an electron microscope. So far three deadly human respiratory coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV) and coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) which causes COVID-19 (Coronavirus Disease-2019), have been detected.

Human coronavirus (HCoV) have long been considered inconsequential pathogens, causing the "common cold" in otherwise healthy people. However, in the 21st century, 2 highly pathogenic HCoVs - severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality.

In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019-nCoV), was recognised in Wuhan, China, and has spread currently to almost more than 130 countries resulting in a pandemic and caused serious illness and death.<sup>1</sup>

Across the world, COVID-19 has become most critical public health emergency and as per recent reports 15% of

the cases are severe cases.<sup>2</sup> The incubation period varies from 2 to 14 days (average 5.2 days) and the symptomatic phase varies between 6 to 41 days (average 14 days).

Diabetes has been reported as one of the most common comorbidities and is correlated with higher mortality and is significantly worsened with increasing age and longer duration of uncontrolled diabetes. Depending on the report, pre-existing co-morbid conditions of COVID-19 patients range between 25% to 50%.<sup>3</sup> The Case Fatality Rate (CFR) has varied significantly between countries and age-groups. Patients with diabetes have 7.3% CFR as compared to 2.3% in the general population. Subjects with diabetes and SARS-CoV-2 infection exhibit enhanced disease severity due to compromised innate immune response. Multiple organ failure is the final cause of death because of acute respiratory distress syndrome and septic shock among patients with COVID-19.

This article summarizes the current understanding of the impact of COVID-19 on diabetes and discusses the pathophysiological mechanisms and management of diabetes and its complication in this respect.

### COVID-19 AND OTHER CORONA VIRUS: SIMILARITIES AND DISIMILIARITIES

Like any other flu, COVID-19 is characterised by a wide spectrum of symptoms including fever, sneezing, coughing, myalgia and respiratory problems like respiratory distress due to viral pneumonia and in some cases, ultimately

**Table 1.** Comparison of Characteristics of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus Disease 2019 (COVID-19)\*

Characteristics	Severe Acute Respiratory Syndrome	Middle East Respiratory Syndrome	Coronavirus Disease-2019
First patients reported	Guangdong, China, November 2002	Zarga, Jordan, April 2012 and Jeddah, Saudi Arabia, June 2012	Wuhan, China, December 2019
Virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Type of coronavirus	betacoronavirus	betacoronavirus	betacoronavirus
Host cell receptor	Angiotensin converting enzyme 2	Dipeptidyl peptidase 4	structural analysis suggests Angiotensin converting enzyme 2 receptor
Incubation period			
Mean (95% CI: days)	4.6 (3.8-5.8)	5.2 (1.9-14.7)	5.2 days (95% confidence interval [CI], 4.1 to 7.0); 95 <sup>th</sup> percentile of the distribution was 12.5 days
Range (days)	2-14	2-13	2-14
Time from illness onset until hospitalization	2-8 days	0-16 days	12.5 days (mean)(95% CI, 10.3 to 14.8) - onset before January 1 9.1 days (mean); 95% CI, 8.6 to 9.7 January 1-11
Patient characteristics			
Adults	93%	98%	Nearly all reported patients are adults
Haematological abnormalities			
Leukopenia	25-35%	14%	9-25%
Lymphopenia	65-85%	32%	35-70%
Thrombocytopenia	40-45%	36%	5-12%
Mortality			
Mortality Rate	9.6%	34.4%	2.3%

\*Modified from Rasmussen et al.,<sup>11</sup> Wan Y et al.,<sup>12</sup> Li Q. et al.,<sup>13</sup> Lu R et al.,<sup>14</sup> Shen KL et al.<sup>15</sup>

respiratory failure. But unlike the common flu, the number of hospitalizations due to severe respiratory distress are much higher and can lead to death.<sup>4-9</sup> What is most disturbing is that a large number (81%) of infected people are without symptoms (yet remain infectious) or have only mild symptoms.<sup>10</sup>

SARS and COVID-19 have many similarities from the virus homology to the origin and transmission routes, but there are several clinical differences which have emerged. Many more patients with COVID-19 compared to SARS have mild symptoms that contribute to spread because these patients are often missed and not isolated. Also, COVID-19 has higher transmissibility than SARS (Table 1).

## PATHOPHYSIOLOGY OF COVID-19

COVID-19 is classified under the orthocoronavirinae subfamily with the subgenus sarbecovirus and also represents the seventh member of the coronavirus family and is sufficiently different from SARS-CoV.<sup>16</sup> COVID-19 is also classified by the World Health Organisation (WHO) as a  $\beta$ CoV of group 2B.<sup>17</sup> One study shows ten genome sequences exhibited 99.98% sequence identity which has been obtained from a total of nine patients infected with COVID-19.<sup>14</sup>

A few articles already confirm that SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE2), just like SARS-C, as a receptor to enter host cells.<sup>18</sup> The pathogenesis of infection is determined by the binding of the virus with host cell receptors.

Spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes are the four structural genes which encode SARS-CoV-2 membrane structural proteins.<sup>19,20</sup> In SARS-CoV-2 *orf1ab* is the largest gene which encodes the pp1ab protein and 15 nsps. When the SARS-CoV-2 binds with the host receptor, it leads to a structural change in S protein which, through the endosomal pathway, facilitates viral envelope

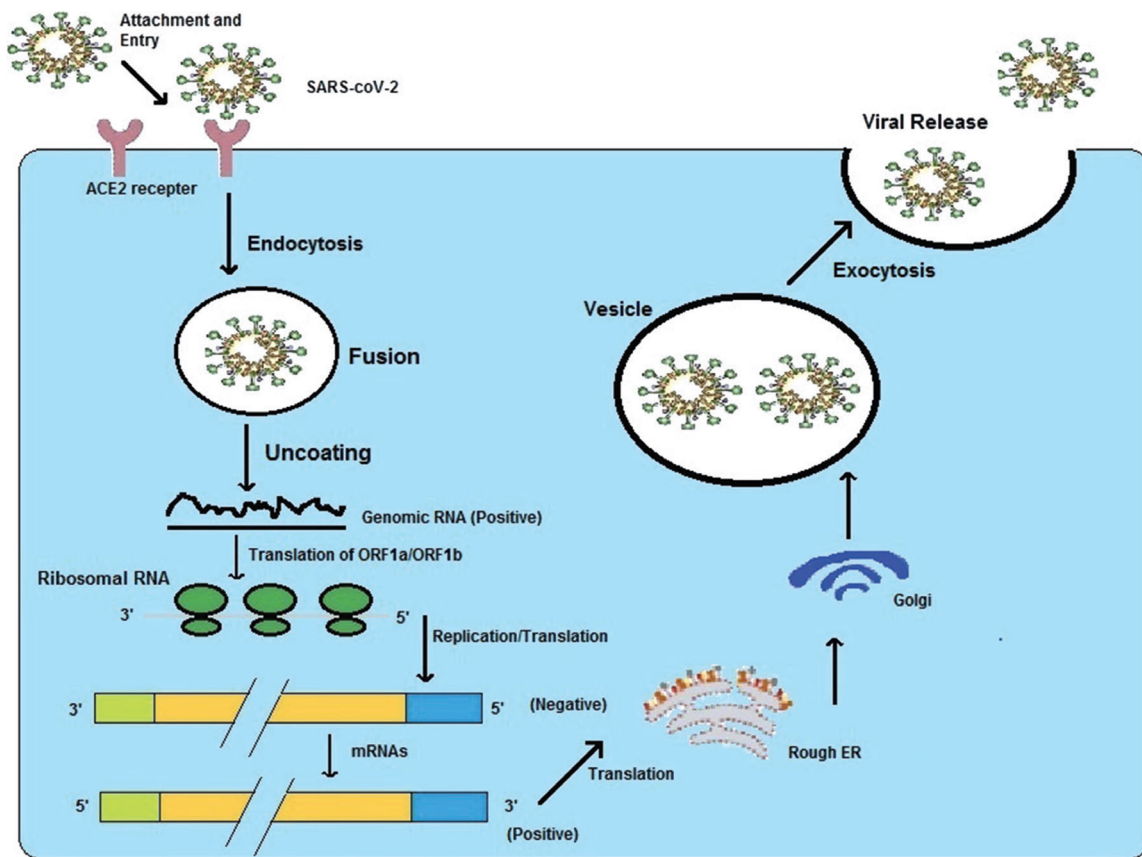
fusion with the cell membrane (Figure 1). The RNA of SARS-CoV-2 is then released into the host cell and is finally translated into relevant viral proteins. Subsequently, in the endoplasmic reticulum (ER) the genome mRNA and viral proteins are assembled into virions and then transported via vesicles and released out of the cell (Figure 1).

In the respiratory system, angiotensin II degrades to angiotensin 1-7 by ACE2. When ACE2 is inhibited and as a consequence ACE1 activity is increased, there is a substantial increase in aldosterone secretion because that intact angiotensin II acts via the angiotensin 1 receptor (AT1R) or AT2R to exert pro-inflammatory responses.<sup>21</sup> Thus, during infection with COVID-19, blood pressure increases due to the stimulated aldosterone secretion and potentially causes hypokalemia which leads to an increased risk of respiratory distress syndrome. Severe COVID-19 patients have an imbalance in angiotensin system with an increase in the activation of AT1R and AT2R which further worsens in T2DM, hypertension and insulin-resistant states.

In patients with COVID-19 infection significantly high blood levels of chemokines and cytokines were noted which included IL7, IL8, IL9, IL10, IL1- $\beta$ , IL1RA, IFN $\gamma$ , IP10, basic FGF2, GCSF, GMCSF, PDGFB, TNF $\alpha$ , MCP1, MIP1 $\alpha$ , MIP1 $\beta$  and VEGFA. High levels of pro-inflammatory cytokines including IL2, IL7, IL10, MCP1, MIP1 $\alpha$ , GCSF, IP10 and TNF $\alpha$  that are thought to promote disease severity were observed in some of the severe cases that were admitted to the intensive care unit.<sup>22</sup>

## CLINICAL PRESENTATION AND DIAGNOSIS OF COVID-19

The symptoms of COVID-19 appear after an incubation period of approximately 5.2 days.<sup>23</sup> The period from the onset of COVID-19 symptoms to death ranges from 6 to 41 days with a median of 14 days.<sup>24</sup> It is shorter among patients who are more than 70 years of age.<sup>25</sup>



**Figure 1.** The life cycle of SARS-CoV-2 in host cells.

The clinical diagnosis of COVID-19 is mainly based on clinical manifestations, epidemiological history and some auxiliary examinations, such as nucleic acid detection (RT-PCR) from nasal and preferably nasopharyngeal swab, immune identification technology (Point-of-care Testing) (POCT) of IgM/ IgG, enzyme-linked immunosorbent assay (ELISA), chest CT scan and blood biochemistry. The clinical symptoms and signs include cough, fever, dyspnea, while other symptoms include sputum production, haemoptysis, tightness of chest, dysgeusia, diarrhoea, abdominal pain, anosmia, headache, dizziness, myalgia, encephalopathy, stroke, seizures, arrhythmias and heart failure. The blood biochemistry profile includes lymphopenia, thrombocytopenia, leucopenia; increased Hs-CRP, IL-6, ferritin, D-Dimer and prothrombin time.<sup>26-28</sup> A chest CT scan generally reveals ground-glass opacities.<sup>29</sup> Both systemic and localized immune response causing increased inflammatory flare, leads to multiple peripheral ground-glass opacities in subpleural regions of both lungs.<sup>30</sup>

It is important to note that in COVID-19 and earlier betacoronavirus features such as dyspnoea, dry cough, fever and bilateral ground-glass opacities share similar features in the symptoms and chest CT scans. However, some unique clinical features present with COVID-19 which include the targeting of the lower airway as evident by relatively low incidence of upper respiratory tract symptoms like sore throat, sneezing and rhinorrhoea.<sup>31,32</sup> Increasing dyspnea with hypoxemia with infiltrates in the upper lobe of the lung is also observed on chest radiographs.<sup>33</sup> Gastrointestinal symptoms like GI distress and diarrhoea can also develop in patients infected with COVID-19.<sup>34-36</sup>

Fever, pulmonary complications (including ARDS), cytopenias and hyperferritinemia are cardinal features of sHLH (secondary Hyperphagocytic Lymphoreticulosis-Hyperinflammatory) syndrome which is triggered by viral infection and sepsis.<sup>37</sup>

## IMPACT OF COVID-19 ON DIABETES

Elderly people are at a higher risk of COVID-19 infection due to their decreased immunity and body reserves, as well as multiple associated co-morbidities like diabetes, hypertension, chronic kidney disease and chronic obstructive pulmonary disease. Moreover, the course of the disease tends to be more severe in elderly, possibly due to aging, resulting in higher mortality (CFR-15% above 80 and 8% in 70 to 79-year-old patients).<sup>38</sup> The CFR in persons with diabetes is 7.3% whereas it is around 6% in hypertensives and chronic pulmonary disease patients increasing to 10.5% in patients with CVD.<sup>39</sup>

In COVID-19 infected patients, diabetes is the one of the major risk factors specially when it is uncontrolled with significant blood glucose variability. Wu et al., in a study among 52 intensive care subjects, found that diabetes was a comorbidity in 22% of 32 non-survivors.<sup>2</sup> In one study of 173 patients, 16.2% patients were with diabetes and severe symptoms of the disease. Zhang et al., found 12% of 140 hospitalized patients with COVID-19 have diabetes.<sup>6,7</sup> A recent study also reveals a twofold increase in the incidence of patients in intensive care having diabetes, when compared to intensive care and non-intensive care patients with COVID-19.<sup>40</sup> This study also confirmed that

the mortality rate almost increased up to three folds in subjects with diabetes compared with the general mortality of COVID-19 in China.

Several aspects of immune response to viral infection are affected by uncontrolled diabetes and can lead to the high chance of bacterial secondary infection in the lungs.<sup>41,42</sup> Obesity in type 2 Diabetes (T2DM) is also a risk factor for severe infection.<sup>43,44</sup>

In addition, there is a direct link of coronavirus infection in T2DM patients. In the pancreas when SARS-CoV-2 binds with the ACE 2 receptor, it damages islets and reduces insulin release.<sup>40</sup> Yang et al., found that more than 50% of patients became diabetic during hospitalization for the SARS-CoV infection and only 5% of patients remained diabetic after 3 years of recovery. T2DM patients might be particularly vulnerable to the insult from a coronavirus infection due to increased expression of ACE2 in the pancreas, as demonstrated in mice.<sup>41</sup>

Subjects with diabetes and infected with SARS-CoV-2 might trigger stress and have increased secretion of hyperglycemic hormones, such as catecholamines and glucocorticoids which results in elevated glucose levels in blood, abnormal glucose variability and diabetic complications.<sup>47,48</sup> People with diabetes do face an increased risk of diabetic ketoacidosis (DKA) and or hypoglycemia.<sup>44</sup> DKA is commonly experienced by patients with type 1 diabetes.

Among hospitalised patients with COVID-19 infection the reported rates of chronic kidney disease appear to be low (1-3%) but this can increase if the patients have uncontrolled diabetes and hypertension as comorbidities. Sepsis is one of the dangerous systemic responses in persons who catch the new coronavirus. Check the patient's fluid and electrolyte levels and treat the sepsis. Uncontrolled diabetes with DKA cause electrolytes imbalance which can make sepsis harder to control. Highly elevated levels of inflammatory cytokines, termed as a cytokine storm, has been implicated in the multi-organ failure in patients with diabetes and infected with COVID-19.<sup>50</sup>

## IMPACT OF DIABETES ON COVID-19

In diabetes subjects, the immune system is in a compromised state due to metabolic inflammation and the body's ability to tackle the infection is reduced. As a consequence, recovery is prolonged by affecting the healing process.

An animal model demonstrated that due to immune dysregulation, MERS-CoV infection was enhanced in T2DM comorbid condition.<sup>46</sup> In this study, it was observed that human DPP4 expressed in mice resulted in susceptibility to MERS-CoV and showed altered cytokine profile following infection with increased expression of IL-17 $\alpha$ .

These data support the hypothesis that a more aggravated and prolonged lung pathology which occurs in patients with type 2 diabetes who were symptomatic with COVID-19, is mainly due to dysregulated immune response in this comorbid condition.<sup>47</sup>

Impaired immune-response mainly induced by abdominal obesity results in abnormal secretion of adipokines and

cytokines like TNF- $\alpha$  and interferon. Obese patients with uncontrolled diabetes also have an increased asthma risk and as well as reduced oxygen saturation of blood which leads to mechanical respiratory problems.<sup>48-49</sup> In individuals with uncontrolled diabetes, in response to lipopolysaccharide stimulation, secrete less interleukin-1 (IL-1) and IL-6 from their mononuclear cells and monocytes, and the reduced production is a consequence of an intrinsic defect in the cells.<sup>51,52</sup> There are several other studies which confirms that individuals with uncontrolled diabetes are more susceptible to respiratory infection than compared to individuals without diabetes.<sup>52-54</sup>

Hypertension is an important comorbidity of diabetes, which is linked to COVID-19.<sup>55-56</sup> With an estimated prevalence of 15%,<sup>6</sup> a recent Chinese article confirms that in 1099 patients, hypertension was the most frequent coexisting condition apart from diabetes and undoubtedly this comorbidity was much lower than other viral infections.<sup>57,58</sup> Coronavirus generally binds to target cells through angiotensin-converting enzyme 2 (ACE2) and these receptors are present at epithelial cells in the intestine, blood vessels and lungs.<sup>59,60</sup> In a study done in comparably small population, it was found that patients with COVID-19 have elevated levels of plasma angiotensin II<sup>47</sup> which were in turn correlated to degree of lung injury and total viral load.<sup>61</sup> It has also been observed that the expression of ACE2 is increased in patients treated with ACE and angiotensin II receptor blockers.<sup>62</sup> Therefore, it has been suggested that in patients with hypertension and diabetes, ACE2 expression may be increased, which could increase the risk of severe disease and fatality and facilitate infection with COVID-19.

Furthermore, corona virus pneumonia causes abnormal hemoglobin metabolism in humans. Patients with uncontrolled diabetes have higher glycosylated hemoglobin or deoxyhemoglobin. One very recent study done by Wenzhong Liu et al.,<sup>63</sup> has confirmed that heme on the beta chain of hemoglobin of host cell is attacked by orf1ab, ORF3a, and ORF10 of coronavirus and thus, patients with uncontrolled diabetes with high glycosylated haemoglobin are at higher risk of COVID-19 infection.

## TREATMENT OF TYPE 2 DIABETES WITH COVID-19

Maintaining good glycemic control with frequent monitoring of blood glucose levels is the most important and key factor to reduce the probability of not only being infected with COVID-19 but also the severity of the infection. As social distancing is one the major steps as per government mandate, it is currently difficult to exercise in gyms or in crowded places like parks, public gardens, play grounds, etc. Patients with diabetes must carry-on with their recommended physical activity in their respective homes. They should consume colorful fruits and vegetables, soy (antiviral effect-nicotianamine, anti-inflammatory effect-IRW), yogurt (promoting favorable gut microbiota) and stopping tobacco. It is important to have adequate sleep and reduce stress (ie., doing yoga).

Patients who are already on antibiotics and drugs like glucocorticoids need to be monitored with frequent blood glucose tests, and do proper dose adjustment accordingly. Patients who are moderately or severely infected with



COVID-19 should immediately discontinue metformin and SGLT2i (Sodium glucose transporter 2 inhibitor).<sup>64</sup> SGLT2i promotes renal ACE2 activity which has already proved in human studies. For patients with impaired kidney function linagliptin or other dipeptidyl peptidase 4 (DPP-4) inhibitors can be considered, as DPP4is do not alter ACE2 activity in diabetic mice and it might exert an overall anti-inflammatory role in human body.<sup>64</sup>

If patient's calorie intake is low, a high dose of sulphonylureas may induce severe hypoglycemia, so the doses of sulphonylureas have to be monitored carefully. Pioglitazone and liraglutide as shown in animal studies may be involved in upregulation of ACE2 in insulin sensitive tissues and pulmonary tissue, therefore use of this drug may theoretically be a concern during COVID-19 infection, however there is no data on human pulmonary ACE2 expression.<sup>64</sup>

Insulin is the preferred choice and should be initiated as early as possible to uncontrolled T2DM.<sup>64</sup> Rapid acting bolus insulin can be considered instead of basal insulin to reduce the chance of hypoglycemia.<sup>65</sup> In case of hospitalisation due to severe illness, the patient must be put on continuous insulin infusion and intravenous fluids as per standard protocols. No change in drugs is required in patients with diabetes who have not contracted SARS-CoV-2 infection. Animal studies done in diabetic mice have already established that insulin reduces renal ADAM-17 (a disintegrin and metalloproteinase-17 enzyme that cleaves and inactivates ACE2) expression thus further reducing urinary ACE2 shedding and increasing intrarenal ACE2 expression. There is still no human data regarding human use of insulin during COVID-19 pandemic.

Hydroxychloroquine (HCQ) deserves special mention. This drug (400 mg OD) has been approved in 2014 from the Drug Controller General of India (DCGI) as an adjunct to diet, exercise and two drugs (metformin plus sulphonylureas) to improve glycemic control in type 2 diabetes and it has shown promising results in COVID-19. Novel mechanism

of blood glucose lowering action with HCQ is observed as it offers post receptor inhibition of insulin degradation and reduces inflammatory loads.<sup>64</sup> Several studies has already confirmed HbA1c reduction of 0.87-3.3% along with significant reduction in fasting and post prandial blood glucose with HCQ in uncontrolled T2DM subjects.<sup>65-67</sup>

The 2018 Research Society for the Study of Diabetes in India (RSSDI) guidelines also have placed hydroxychloroquine as third line of drug indicated for the management of T2DM.<sup>68</sup> A recent study shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.<sup>69</sup>

Figure 2 depicts the probable mechanism by which hydroxychloroquine prevents COVID-19. An in-vitro study done by Yao et al., recommended hydroxychloroquine 400 mg BID at day 1 and 200 mg BID day-2 to day-5 for patients who are infected with COVID-19.<sup>71</sup>

The Indian Council of Medical Research (ICMR) has advised hydroxychloroquine prophylaxis in health care workers involved in the care of suspected or confirmed COVID 19 infected patients and contacts of confirmed cases.<sup>72</sup> Furthermore, HCQ is also one of the medications being evaluated as a treatment in these patients. Since it is likely that there could be many patients on this medication detailed drug interactions and precautions are also included in Table 2.

The dual benefit in terms of glycemic control as well as protection from COVID-19 makes HCQ a preferred add-on drug in uncontrolled persons with diabetes.

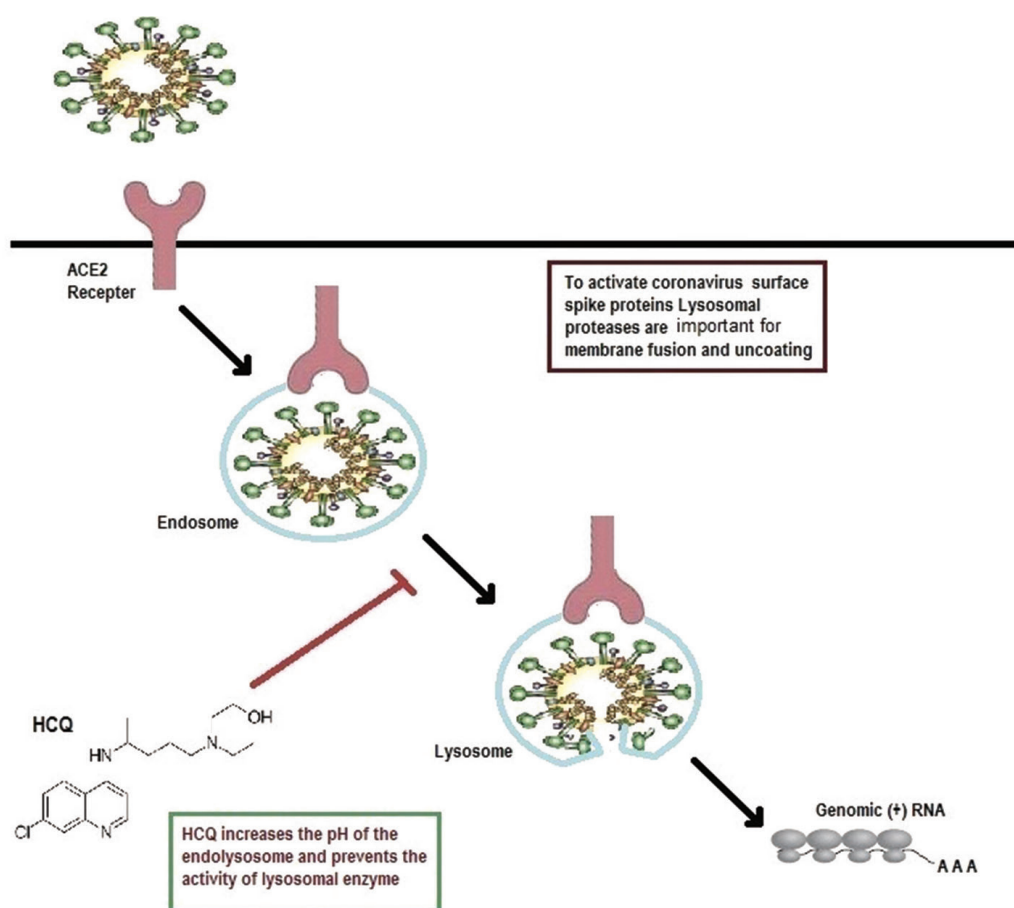
The American College of Cardiology and American Heart Association have recommended withholding the drug in patients with prolonged QT interval (like azithromycin).<sup>73</sup>

The European Medicines Agency (EMA) has approved trials with the following drugs: remdesivir, lopinavir/Ritonavir,

**Table 2.** Medications which have been used in various small clinical trials but are still not validated by any RCT's.\*

Drugs	Types	Mechanism of Action	Past Evidence
Chloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevent viral entry, transport and post-entry events.	Inhibits infection of cells by SARS-CoV-2 in vitro, approved for malaria treatment and prophylaxis.
Hydroxychloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevent viral entry, transport and post-entry events.	Inhibits infection of cells by SARS-CoV-2 in vitro, approved for malaria treatment and prophylaxis and autoimmune disease (e.g. rheumatic diseases). Approved for treatment of T2DM in India.
Azithromycin	Macrolide Antibacterial	Immunomodulatory mechanisms may include reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition of mucus hypersecretion, decreased production of reactive oxygen species, accelerating neutrophil apoptosis, and blocking the activation of nuclear transcription factors.	Used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
Remdesivir	Adenosine nucleotide analogues	Inhibits viral application	Effective against SARS and MERS. Several large clinical trials are underway.
Ribavirin	Nucleoside analogue	Inhibits viral replication	Mixed result against MERS
Ribavirin plus Interferon	Nucleoside analogue	Inhibits viral replication	Mixed result against MERS
Tocilizumab	Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody	inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors.	Preliminary data suggest tocilizumab may have clinical benefit as adjunctive therapy.
Lopinavir/Ritonavir	Protease inhibitors	Blocks viral cell entry	Effective against SARS-CoV-1 both in vitro and human studies, approved for HIV-1 treatment. Preclinical data suggested potential benefit; however, more recent data has failed to confirm.

\*Smith T et al.<sup>60</sup>



1. Hydroxychloroquine acts on host target respiratory cells by increasing the endosomal pH required for the virus-host target cell fusion.<sup>70</sup>
2. Hydroxychloroquine was found to interfere with the glycosylation of cellular receptor of the virus.<sup>57</sup>
3. Hydroxychloroquine acts as an inophonic agent for Zinc ions which adhere to the RNA dependent RNA polymerase enzyme of the virus and stops COVID-19 polymerization intracellularly.<sup>70</sup>
4. TNF alpha and IL6 production might be inhibited by HCQ and subsequently blocks the cascade of COVID-19 infection.<sup>57</sup>
5. Chloroquine could prevent gene expression (orf1ab, orf3a, and orf10) to attack the heme to form the porphyrin, and inhibit the binding of orf8 and surface glycoproteins to porphyrins to a certain extent.<sup>57</sup>

**Figure 2.** The mechanisms of action of hydroxychloroquine (HCQ) against COVID-19.

IL-beta1a, HCQ and immunoglobulin. The dosage of these drugs in the multi center/country DisCoVeRy trial in hospitalized patients is as follows: Remdesivir-100 mg/d IV for 10 days; Lopinavir-400mg/Ritonavir-100 mg orally every 12 hours for 14 days with or without IL-beta1a- 44 ug SC on D1, D3, D6; HCQ-400 mg (Ryles tube-600 mg) BD on D1 and 400 mg/d for 9 days.<sup>74</sup>

The other therapeutics under investigation include tocilizumab (IL-6 antagonist) in severe cases, ivermectin (inhibits viral replication affecting viral proteins), camostat (serine protease inhibitor acting on TMPRSS2 and restricting viral entry in host cell) and convalescent plasma.<sup>74</sup>

### TREATMENT OF TYPE 1 DIABETES WITH COVID-19

In patients with type 1 diabetes treated with basal bolus or insulin pump therapy, the insulin doses should be titrated using frequent glucose and ketone monitoring to avoid hypoglycaemia in patients with reduced food intake, and adding correctional boluses of rapid-acting insulin to avoid severe hyperglycaemia and ketoacidosis. In case

of illness, patients should not stop insulin but follow sick days rule and contact their health care provider. In case of hospitalisation due to severe illness, the patient must be put on IV insulin and fluids as per the standard protocol.<sup>75</sup> Acetaminophen can impact CGM sensor.<sup>76</sup>

### TREATMENT OF COVID-19 WITH DIABETES

The only approved preventive measures today for COVID-19 are social distancing and quarantine. General measures to prevent COVID-19 include thorough and proper hand washing with soap and water and/or alcohol-based hand rubs, practice of proper respiratory hygiene, minimising contact with affected individuals and avoiding nonessential travel to affected areas.

Until now, treatment is available only for affected cases who are severely symptomatic. To treat or control novel coronaviruses, no specific effective drugs and vaccines are available.<sup>77</sup> However, in the latest clinical treatments, several old drugs have been found to inhibit some viral pathology, for example, chloroquine/hydroxychloroquine phosphate has a definite effect on the novel coronavirus pneumonia.<sup>78,79</sup>

As coronavirus pneumonia might be closely related to abnormal hemoglobin metabolism in humans, scientists suggest the therapeutic effect of chloroquine/HCQ phosphate on this infection<sup>57</sup>

### Plasma Therapy

One small study from China showed convalescent plasma therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases.<sup>81</sup>

### Vaccines

For reducing disease severity, viral shedding and transmission, effective SARS-CoV-2 vaccines are essential to help prevent and minimize coronavirus outbreaks. For animals with SARS-CoV and MERS-CoV several vaccination strategies have been applied including a live-attenuated virus, inactivated virus, viral vectors, subunit vaccines, recombinant DNA, and proteins vaccines.<sup>82</sup> SARS-CoV-2 vaccines are in various stages of development. But it requires months and years to develop vaccines for human use.<sup>83</sup>

### Special Precautions

There are also several suggested measures for patients with diabetes and COVID-19 infection. These include notifying the appropriate health authorities when there is a clinical suspicion for COVID-19, isolating for 14 days or until symptoms resolve, and maintaining hydration and symptomatic treatment. Patients with type 1 diabetes should measure blood glucose and urinary ketones frequently in case of fever with hyperglycemia. Antihyperglycemic treatment should be adjusted to avoid hypoglycemia and volume depletion and patients should follow sick days guidelines. In severe cases when patients are hospitalized, it is recommended to frequently monitor blood glucose and discontinue oral agents, especially metformin and sodium-glucose cotransporter-2 inhibitors, as insulin is the preferred treatment modality in this scenario.

Few preclinical works have pointed out that ACE2 expression increases by RAAs inhibitors which put a question regarding their safety in patients with COVID-19. The beneficial effect of RAAS inhibitors on heart failure, myocardial infarction and associated cardiovascular complications is well established<sup>84</sup> and the abrupt withdrawal of these drugs may result in clinical instability and current evidence is not strong enough to recommend discontinuing these medications.<sup>85</sup>

A recent article mentioned a few cases where the use of non-steroidal anti-inflammatory drugs causes severe adverse events in COVID-19 infected patients who had no other comorbid conditions.<sup>86</sup>

## CONCLUSIONS

Infection with COVID-19 is associated with significant morbidity especially in patients with comorbid conditions like diabetes, hypertension, chronic kidney disease, etc. On the other hand, uncontrolled diabetes subjects have increased chance of being infected with COVID-19 and have significant morbidity and mortality. Thus, although COVID-19 is primarily not a metabolic disease, good glycaemic control is the key to reduce the probability of

infection with COVID-19 and reduce the chance of acute metabolic decompensation in patients who are already infected and symptomatic. However, a specific and mechanistic approach which reduces the local inflammatory response and blocks viral entry into cells and prevent and ameliorate the acute effects of this virus is warranted.

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### Author Disclosure

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