Review Article

# COVID-19 and Diabetes Mellitus: Prevalence and Precautions

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**Abstract**

**Background and Aims:** Diabetes Mellitus (DM) is a chronic metabolic disorder complicating multiple organs in the human body. Diabetes may be associated with a severe form of Coronavirus Disease 2019 (COVID-19). We performed a systematic review and analyzed available data to investigate the association between DM and the severity of disease in patients with COVID-19.

**Methods:** We systematically searched the PubMed, WHO database, and Google Scholar databases until 20 May 2020 using the keywords "COVID-19", "comorbidities," "diabetes mellitus." Relevant full-text articles accessed and data retrieved.

**Conclusion:** DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19. We have also identified the problems of diabetes self-management in the current scenario of lockdown and mobility restrictions and suggested possible solutions to overcome those.

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**Keywords** | COVID-19, SARS-CoV-2, Comorbidities, Diabetes mellitus, hypertension, Cardiovascular disease.

## Introduction

Infectious diseases have been a significant threat to human civilization, causing catastrophic effects on the entire population. Most of these conditions were bacterial or viral in origin. December 2019 witnessed the emergence of a disease called Coronavirus Disease 2019 (COVID-19) from China, caused by the novel Coronavirus (SARS CoV- 2). In January 2020, the WHO declared this disease as a Public Health Emergency of International Concern and, on 12th February 2020, officially named the disease as coronavirus disease 2019 COVID-19).[1,2] Ever since its inception, COVID-19 has become a medical emergency, and a global crisis threatening to wipe out a significant part of the human population from across more than 227 countries. On 11 March 2020, the World Health Organization (WHO) declared COVID-19 as a andemic.[3] Since December 2019 and as of May 20, there were 4,897,567 cases of COVID-19, including 323,286 deaths. There are 2,885,651 active cases, and 1,688,630 recoveries, can be shown in Figure-1.

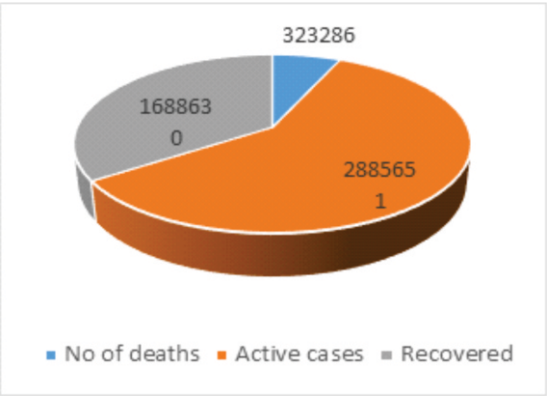



**Figure-1:** *No. of Covid-19 Cases and Recoveries.*

Diabetes Mellitus is another condition with high

prevalence across the globe. According to WHO, currently, more than 422 million adults are suffering from Diabetes mellitus in the world. In this context, it becomes imperative to understand the association between Diabetes Mellitus and Coronavirus disease in 2019. Furthermore, strategies adopted by different nations to contain the spread of COVID-19, like mobility restrictions, have made the diabetic population more vulnerable to the severe outcome of this disease.

## Aims of this Work

1. This work aims to collect the available data of COVID-19 infection and Diabetes Mellitus.
2. It specifically looks into the associated comorbidities and mechanism of interaction between SARS-CoV- 2 and Diabetes Mellitus.
3. Finally, the work also tries to emphasize the guidelines to prevent COVID-19 in diabetic patients.

## Methods

We systematically searched the PubMed, WHO database, and Google Scholar databases till 20th May 2020 using the keywords "COVID-19", "comorbidities," "diabetes mellitus."

We accessed relevant full-text articles and retrieved the data.

## History of Viral Pandemics

The last two decades have witnessed viral pandemics such as Influenza A (H1N1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2009 and in 2016 respectively. In both these conditions, a strong association with comorbidities such as Diabetes and hypertension was observed.[4] During both these pandemics, Diabetes Mellitus, as comorbidity, was responsible for the development of fatal complications.[5]

A meta-analysis carried out by Badawi et al. reported the prevalence of Diabetes in H1N1 and MERS-CoV and made a comparison in its frequency between the two viral conditions. The overall incidence of Diabetes in H1N1 was 14.6%, a 3.6-fold lower than in MERS-CoV 54.4%.[6] Assiri et al., in a study of 47 patients with MERS-CoV disease in Saudi Arabia, reported that 68% had Diabetes, and 34% had hypertension as comorbidity.[7,8] In another study of 281 MERS-CoV positive Saudi subjects, there was a strong association of both hypertension and Diabetes with increased mortality.[9] Since these viruses belong to the same family, they may share a common or related pathophysiology.

## Pathophysiology of COVID-19 and Diabetes Mellitus

The family Coronaviridae is a family of viruses, with several pathogenic strains. Some members of this family in the past have caused diseases in human beings such as MERS (Middle East respiratory syndrome) and SARS (Severe Acute Respiratory Syndrome). SARS-CoV-2 is a new strain of the Coronavirus, responsible for the COVID-19 pandemic. It has a single strand of RNA, roughly around 70–90 nm in size.[10] The viral envelope consists of a lipid bilayer. There are four structural proteins encoded in the genome of SARS-CoV-2. These proteins are Spike protein (S), the Envelope protein (E), Membrane protein (M), and Nucleocapsid protein (N), which make the complete virus particle, as shown in Figure-2.

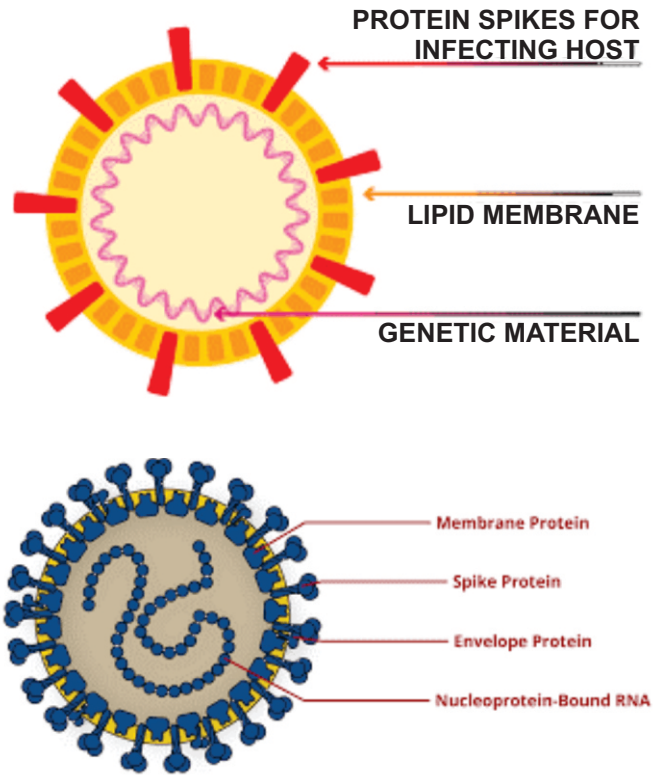



**Figure-2:** *The Viral Surface Proteins*

## Angiotensin-Converting Enzyme 2 (ACE2) Receptors

The ACE2 receptors are mainly present on the alveolar cells in the lungs. These receptors are also present on the cells of intestinal tract, renal cells and cells of the cardio-vascular system [11]. The S protein (S) of the virus attaches to the host receptors and facilitates the entry of the virus. In a way, the S protein is the entry point for the entry of coronaviruses into target cells. Entry into the host cell depends on the binding of the S protein to a cellular receptor and priming by cellular enzyme proteases. SARS-CoV-2 engages ACE2 as the entry receptor.[12] Previous studies have shown that the SARS-CoV-2 S protein attaches to the ACE2 receptors with higher affinity as compared to the SARS.[13]

Virus replication starts with the entry of the virus into the host cell. This is followed by a period of immunological reactions in the host cell over the next few days.[14] The virus replication causes an influenza-like illness with mild symptoms due to the toxins released by the virus. Gradually the immune system takes over, and the overall viral levels decline due to the antibodies neutralizing the virus. However, in some patients, a large number of inflammatory cytokines are released, which causes massive tissue destruction and clinical deterioration. This cytokine storm explains why some patients who were relatively well initially suddenly deteriorate, as shown in Figure-3.

## Dipeptidyl Peptidase IV (DPP-4) Receptors

Dipeptidyl peptidase IV (DPP-4) receptors may be responsible for COVID-19 infection in patients with Diabetes Mellitus. In a study on diabetic mouse models, Kulcsar et al, showed the expression of the DDP-4 receptor on the alveolar cells of the lungs. This study helped to understand the relation between Diabetes Mellitus and MERS infection severity. They observed inflammatory infiltrates by macrophages in the alveolar tissue. Similar pathological features were also seen in the disease associated with Diabetes Mellitus.[15]

## Morbidity and Mortality in Diabetics with COVID-19

Many comorbidities such as Diabetes, hypertension, and immunodeficiency conditions can complicate the clinical picyure of COVID-19. These conditions can cause an increase in the severity of illness, the use of assisted ventilation, an increase in the length of the Intensive Care Unit (ICU) stay, and an increase in the mortality rate.

People who have Diabetes are at increased to bacterial and viral infectious diseases, primarily affecting lower airways.[16,17] However, there is a lack of under-

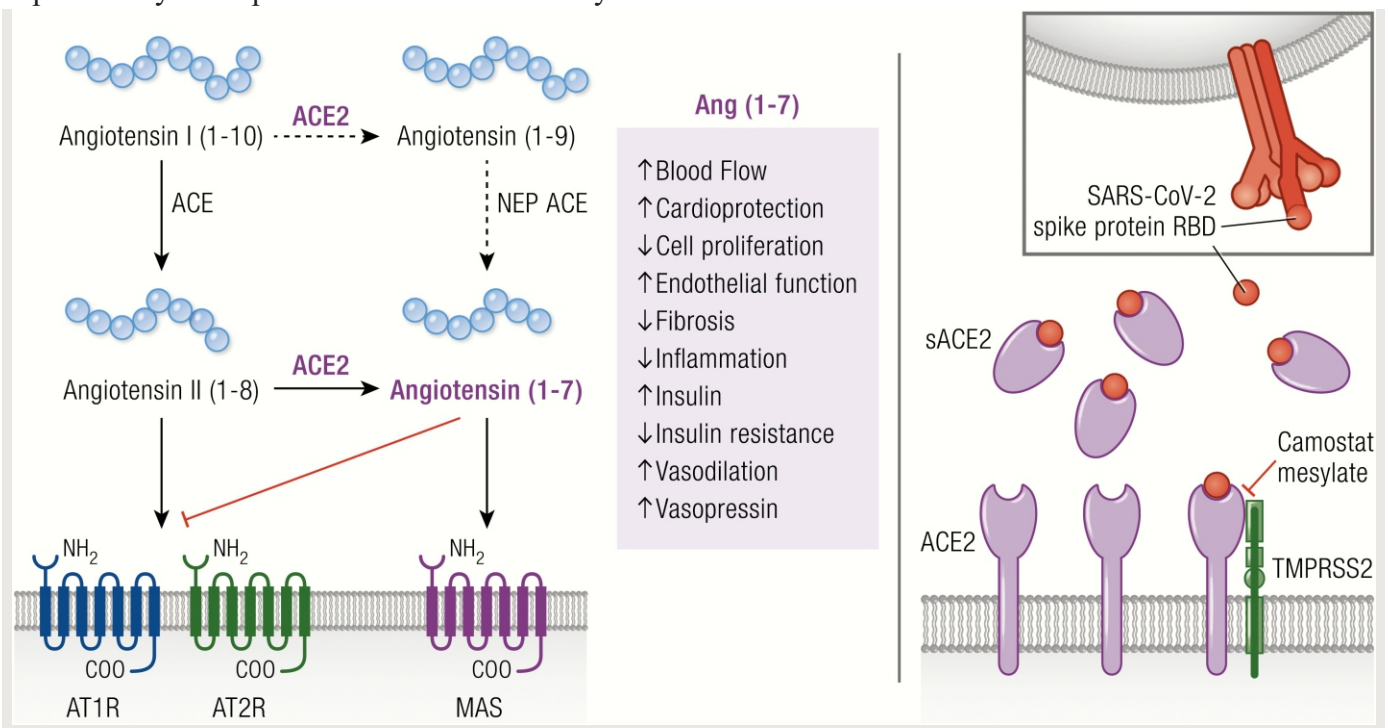



**Figure 3:** *Metabolism of angiotensin I by ACE and ACE 2 to yield different bioactive angiotensin peptides.*

standing of the pathophysiological mechanism behind this vulnerability. In Hyperglycemia, the normal anti-bacterial function of the neutrophils is impaired. Besides, the chronic complications associated with Diabetes Mellitus come in to play.[5] Long-term complications such as micro-angiopathic changes can occur in the respiratory lining of diabetics, thus compromising the exchange of and lung compliance.

The COVID-19 disease mainly affects male population and older people with accompanying conditions such as respiratory disease, hypertension, and diabetes mellitus[18]. Data from China showed that 22% of infected people suffered from cerebrovascular diseases, 24 to 12% from hypertension, and 22 to 12% from Diabetes Mellitus. Patients who were previously on medications with ACE inhibitors were found to be at higher risk for severe forms of infection. The pathogenic coronavirus bind to target cells through ACE2 receptors, which are expressed mainly on epithelial cells of the lung, intestine, kidney, and blood vessels.[19] Arterial hypertension is a common chronic complication of Diabetes Mellitus and, consequently, an increased expression of ACE2, receptors were observed in these patients, especially those on medications with either ACE inhibitors or angiotensin two receptor blockers.[19] People with increased blood pressure and on treatment with ACE inhibitors exhibited a similar phenomenon [20,21&22].

Patients of COVID-19 with accompanying diabetes mellitus have a higher risk when compared with those with normal blood glucose levels.[23,24] The anxiety and fear of corona virus infection and the use of steroids to combat the stress during hospitalization may be the cause of higher glycemic spikes.[25] The sequence of events increases the chances of infection due to the increased concentration of intracellular toxins.[26,27] Moreover, during a severe illness, the expression of glucose transporters on the cell mem-brane is increased, causing glucose overload and damage to the cells.[28,29,30&31] Decreased immunity, followed by the cytokine storm during severe infection, may attribute to the lung lesions and increased death rates.[32] The release of adhesion molecules by the pulmonary endothelial cells leads to the increased collection of inflammatory cells in the lung alveolus, further compromising the respiratory function.[33,34] Waxing and waning of glucose values during the hospital stay may increase these phenomena, worse-ning the prognosis[35]. Patients suffering from COVID- 9, showing high fluctuations in glucose value is predictive of high mortality [36].

## Statistical Analysis

In a study by Guan et al.[22], the mortality rate for hypertension was (15%) followed by Diabetes, which was (7.4%). The pathophysiological explanation to this could be the spike protein ACE- 2 receptor mechanism.

Singh et al.[37] studied pooled data of 2209 patients from ten Chinese studies on the different comorbidities in COVID-19. They reported a prevalence of 21% hypertension, 11% diabetes, and 7% CVD.

Yang et al. [38], in a meta-analysis of 46,248 COVID-19 patients from eight different trials has shown a prevalence of 17% hypertension, 8% Diabetes, and 5% CVD.

The CCDCP (Chinese Center for Disease Control and Prevention), analyzed the statistical data of 20, 982 COVID-19 patients. They reported hypertension, Diabetes, and CVD as 13%, 5%, and 4%, respectively.[39]

From a smaller sample of 355 Italian COVID-19 patients, Onder et al. reported an association of 36% Diabetes and 30% CVD.[40]

Bhatraju et al.,[41] in their study of 24 COVID-19 patients from the USA, reported Diabetes as a comorbidity in 58% of patients.

In another study by the Italian COVID-19 surveillance group involving 481 patients showed that 34% of patients had Diabetes. While the COVID-19 response team from the CDC, the United States reported that 11% had Diabetes.[42,43]

Data from Italy, Spain, Sweden, Switzerland, and the Netherlands showed that patients with accompanying comorbidities such as diabetes, chronic lung disease, cardiovascular diseases, and hypertension were at higher risk of having severe illness and death, as shown in Table 1.[52,53,54]

Table 1 summarizes the prevalence of these comorbidities in all available studies to-date in patients with

**Table 1:**

| S. no | Country | First Author | (n) | DM% | HTN% | CVD% | NSI | SI | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | China | CCDCP | 20982 | 5.3 | 12.8 | 4.2 | | | 39 |
| 2 | China | Guan et al | 1099 | 7.4 | 15 | 3.8 | 5.7 | 16 | 22 |
| 3 | China | Liu et al | 61 | 8.2 | 19.7 | 1.6 | 4.5 | 18 | 44 |
| 4 | China | Wang et al | 138 | 10.1 | 31.2 | 19.6 | 5.9 | 22 | 47 |
| 5 | China | Liu et al | 137 | 10.2 | 9.5 | 7.3 | | | 50 |
| 6 | China | Wu et al | 201 | 10.9 | 19.4 | 4 | 5.1 | 19 | 23 |
| 7 | China | Chen et al | 99 | 12.1 | | 40 | | | 46 |
| 8 | China | Zhang et al | 140 | 12.1 | 30 | 8.6 | 11 | 14 | 21 |
| 9 | China | Guo et al | 187 | 15.0 | 32.6 | 11.2 | | | 59 |
| 10 | China | Yang et al | 52 | 17.0 | | 23 | | | 18 |
| 11 | China | Chen et al | 274 | 17.0 | 34 | 8 | | | 51 |
| 12 | China | Zhou et al | 191 | 19.0 | 30 | 8 | | | 48 |
| 13 | China | Huang et al | 41 | 19.5 | 14.6 | 15 | 8 | 25 | 45 |
| 14 | Italy | Covid 19 surveillance group Italy | 481 | 33.9 | 73.8 | 30.1 | | | 42 |
| 15 | Italy | Onder et al | 355 | 35.5 | | 42.5 | | | 40 |
| 16 | Italy | Study from Lombardy | 1043 | 17.0 | 49 | 21 | | | 52 |
| 17 | Sweden | Study from Sweden | | 23.0 | 34 | 11 | | | 53 |
| 18 | Spain | Study from Spain | | 17.0 | | 30 | | | 54 |
| 19 | USA | Bhatraju et al | 24 | 58.0 | | | | | 41 |
| 20 | USA | CDC USA | 7162 | 10.9 | | 9 | 9.4 | 32 | 43 |

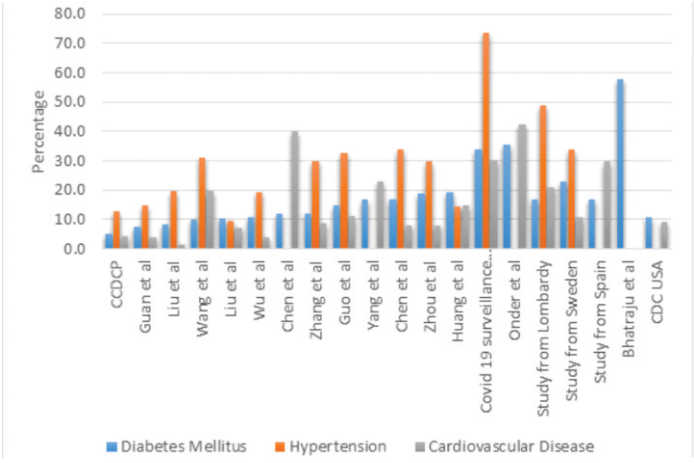
**(n)- No of Subjects in the study, DM- Diabetes Mellitus, HTN- Hypertension, CVD- Cardiovascular Disease, NSI- Non-severe illness, SI- Severe Illness, Ref.- References CCDCP - Chinese Centre for Disease Control and Prevention, CDC - Centre for Disease Control and Prevention, Empty cell represents unavailable data**

COVID-19[18,21,22,23]and[39–51]

The statistical analysis from the different studies on the severity of the disease ranged from 13.8% to 32.0%.

Zhang et al. reported 13.8% critically ill patients as against 32.0% by CDC COVID-19 Response Team, USA.[21, 22, 23, 43, 44, 45, 47] The statistical data is being shown in graphical form in Figure-4.

**Figure-4:** *Representations of Prevalence of DM, HTN & CVD in COVID-19 Patients*




The non-survival rate also varied from 21% to 31.0%. The highest survival rate reported by Zhou et al. and Chen et al. was 14% (Figure-5).

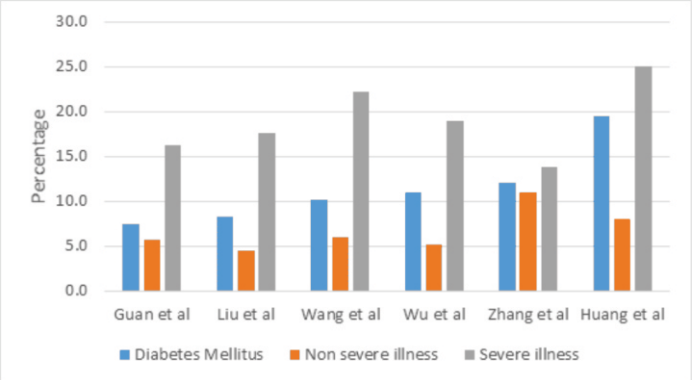



**Figure- 5:** *Graphical representation of Severity of illness in COVID-19 with DM*

**Prevention of COVID-19 in Diabetes Mellitus.**

The different studies on COVID-19, from around the globe, have clearly shown that the elderly population with Diabetes had issues in managing their blood glucose during this pandemic. Several factors may attribute to this like, social distancing, mobility restrictions, and lockdown strategies adopted by different governments to contain the virus.

Mobility restrictions and staying at home limited the physical activities and exercise routine of the people with Diabetes. Limitations in the food supply chain might compel the diabetic population to alter their habits and look for food with a reduced glycemic index. Lockdown measures also might make the situation difficult for them to procure their medical supplies. Last but not least, a routine medical check-up with their physicians may derail. In these situations, these elderly diabetics may experience long periods of uncontrolled hyperglycemia, making them more vulnerable to COVID-19.

The mental well-being of Diabetic people is also seriously challenged during this pandemic. The fear of coming in contact with the virus, not being able to meet their near and dear ones or participate in the social and religious gatherings, regularly plays on their psyche.

In the present scenario where countries are restricting movement, it becomes even more challenging to remain medically and mentally fit. During these stressful times, they should keep themselves hydrated, monitor their blood glucose levels, and strictly follow their treatment schedule.

**Diet:** A healthy and balanced diet should be taken. The food should be rich in fibers, protein, and some complex carbohydrates. Refined carbohydrates and juices should be strictly avoided. Fats should be less than 30% of the total calories/day with restricted salt intake. Unhealthy habits of smoking, drinking should be avoided.

- **Physical Activity and Exercise:** Exercise should be a part of the daily schedule of any individual, be diabetic or non-diabetic. During the lockdown periods, home-based exercises like treadmill, stationary jogging, and aerobic activities should be routinely followed without abstinence. A total of 60 minutes of moderate exercise per day is satisfactory.

- **Self-Blood Glucose Monitoring:** Self-monitoring of blood glucose should be done regularly to keep a check on the glycemic control.

- **Medications:** No patient should forget to take their conventional anti-diabetic drugs.

- **Telemedicine:** The concept of Telehealth delivery can be of immense help in these times. People with diabetes can consult their health care provider and follow instructions.

- **Managing Mental Fitness:** A handy way to manage mental stress is to stay away from watching, listening, or reading news, including social media, which are contributing a lot to anxiety and fear.

- They should visit the hospital urgently in emergencies like vomiting, drowsiness, shortness of breath, chest pain, weakness of limbs, altered sensorium, etc.

## Conclusion

COVID-19 patients with Diabetes Mellitus as comorbidity were associated with increased severity of the disease, higher mortality rates, and disease progression.

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