

# Effect of glycemic regulation in diabetes mellitus on COVID-19 infection management

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**ABSTRACT**

A newly identified disease termed as COVID 19 that emerged from Wuhan in China has rapidly spread across most of the nations worldwide since the end of 2019. The infection that caused pneumonia and even deadly lung failure was the severe acute respiratory syndrome corona virus (SARS-CoV-2). Novel coronavirus has stalled the world and badly affected India with 9,11,871 confirmed cases and top 24,309 deaths as of July 15, 2020 ranking India third most affected country in the world. India, a nation already been the diabetes capital of the world, is significantly associated with increased mortality risk of COVID 19 along with severe presentations like ARDS, ICU requirements and longer duration of stay in hospital. Various theories have been postulated for the poor outcomes of SARS-CoV 2 infection in diabetes. In this light, the current study was designed to assess the relationship between glycemic control in diabetes mellitus patients and COVID-19 progression and prognosis in patients admitted to the RMCH Medical College and Hospitals in Bareilly, India. The researchers wanted to see if there was a link between clinical presentation, disease severity, care, and outcome in diabetic patients with uncontrolled and controlled blood sugar levels.

**KEY WORDS:** COVID 19, diabetes mellitus, pneumonia, severe acute respiratory syndrome corona virus

**INTRODUCTION**

A newly identified disease termed as COVID 19 that emerged from Wuhan in China has rapidly spread across most of the nations worldwide since the end of 2019. The infection that caused pneumonia and even deadly lung failure was the severe acute respiratory syndrome coronavirus (SARS-CoV-2) Novel coronavirus has stalled the world and badly affected India with 9,11,871 confirmed cases and top 24,309 deaths as of July 15, 2020, ranking India third most affected country in the world. India, a nation already been the diabetes capital of the world,

is significantly associated with increased mortality risk of COVID 19 along with severe presentations such as ARDS, ICU requirements, and longer duration of stay in hospital. Various theories have been postulated for the poor outcomes of SARS-CoV2 infection in diabetes mellitus.

1. Diabetes mellitus is associated with impaired immunity. Both short-term and long-term hyperglycemia alters the complement fixation with subsequent phagocytosis
2. Diabetes mellitus can lead to pro-inflammatory state with increased levels of IL-6 and TNF-alpha which is associated with multi-organ failure in patients with SARS-CoV2
3. ACE-2 receptor is up-regulated in patients with DM promoting virus to infect cells
4. COVID-19 infects endocrine pancreas cells via their expression of ACE-2 receptors resulting in impaired insulin secretion
5. Hyperglycemia increases glucose concentration in airway secretions making lung cells prone to viral infection and replication.

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## METHODS

The current retrospective observational study involved 80 COVID-19 patients admitted to RMCH Medical College and Hospital in Bareilly, Uttar Pradesh, India, who had type 2 diabetes mellitus (T2DM) and were already using antidiabetic medications. The Institutional Ethical Committee, RMCH, BIU, gave its approval to this study. The Ethical Committee decided to forego written informed consent. All patients with T2DM were divided into two groups based on their glyceemic control. T2DM patients in Group 1 had poorly regulated blood sugar levels, as shown by HbA1c levels of higher than 8%. Patients in Group 2 had T2DM and HbA1c levels less than 8%, indicating that their blood sugar levels were under control. Age, gender, and the absence of any comorbidities were all matched in both of these groups. COVID-19 was diagnosed based on the World Health Organization interim advice, which stated that confirmed cases of COVID-19 were positive on reverse transcriptase-polymerase chain reaction (RT-PCR) assays of nasal and pharyngeal swab specimens.<sup>[1]</sup> Patients with T2DM were divided into two groups based on their glyceemic control after other comorbidities were ruled out. Hemograms, C-reactive protein (CRP), ferritin, fibrin degradation product (FDP), D-dimer, and interleukin-6 (IL-6) were used to make the laboratory findings (IL-6). To infer radiological results, the average visual score from a digital chest radiograph (rated from 0 to 4 based on visual assessment of the affected lung area),<sup>[2]</sup> the average severity score from a USG chest, CT severity score from HRCT chest,<sup>[3]</sup> and the proportion of patients with CT severity scores >10/25 were used. The data of patients with diabetes complications, particularly diabetic ketoacidosis (DKA) and septic shock, was collected. Treatment with hydroxychloroquine, lopinavir-ritonavir combination therapy (LPV/r), ICU care, and non-invasive ventilation (NIV) was also gathered for both groups. The number of recovered COVID-19-infected patients, the length of seroconversion (the time between the first positive RT-PCR for COVID-19 and the first negative RT-PCR for COVID-19), and the length of hospital stay.

### Statistical Analysis

The mean and standard deviation were used as descriptive statistics for quantitative data, whereas proportions were used for qualitative data. The parameters were compared using the chi-square and z-score tests to see if there were any significant differences between the groups.  $P < 0.05$  was used to determine the degree of significance.

## RESULTS

In the current study, 22 patients in group 2 (27.50 percent) had poorly regulated blood sugar levels, with HbA1c levels less than 8%. T2DM patients infected with SARS-CoV-2 had an average age of 61.45 years. (95 percent confidence interval: 61.45 5.08, standard deviation = 11.59.) People with uncontrolled diabetes had a mean age of 63.2 years (95 percent confidence interval: 63.2 4.35, SD = 4.96), while those with controlled diabetes had a mean age of 60.86 years (95 percent confidence interval: 60.86 6.67, SD = 13.18), and the difference was not significant. There were no significant variations in gender across the groups ( $P = 0.301$ ). Other COVID-19 comorbidities have not been examined in order to fully comprehend the impact of COVID-19.

### Clinical Presentation

A total of 24 individuals (30.00 percent) presented with symptoms. When compared to group 2, Group 1 (50.00 percent) had considerably more symptomatic presentation (22.41 percent). Cough (16.25 percent), fever (15.00 percent), shortness of breath (11.25 percent), and sore throat were the most common symptoms in COVID-19-infected T2DM patients (8.75 percent). A small percentage of patients also experienced headaches (5.00%), chest pain (3.75%), and symptoms (5.00%) such as abdominal pain, vomiting, diarrhea, and altered sensorium. Cough (31.82 percent in group 1 vs. 10.34 percent in Group 2) and shortness of breath (22.73 percent in group 1 vs. 6.90 percent in Group 2) were shown to be more common in people with uncontrolled diabetes than in people with controlled diabetes.

### Laboratory Findings

The total leukocyte counts (TLC) of both groups were normal, with an average TLC of 7.48 10<sup>9</sup>/L 4.23, platelet count of 2.12 Lac/1 0.64, and neutrophil/lymphocyte (N/L) ratio of 3.15 1.98. Uncontrolled diabetes, on the other hand, had a greater TLC and N/L ratio, with values of 9.01 10<sup>9</sup> and 3.98, respectively, when compared to the managed group, which had values of 7.01 10<sup>9</sup> ( $P = 0.0403$ ) and 3.00 ( $P = 0.0495$ ). The following laboratory parameters were also taken into account: CRP, ferritin, FDP, D-dimer, IL-6. The biochemical parameters of the two patient groups were found to be considerably different. In comparison to Group II patients, FDP levels were 43.22 g/L compared 24.69 g/L ( $P = 0.0433$ ), D-dimer levels were 6.78 g/L vs. 4.05 g/L ( $P = 0.047$ ), and IL-6 levels were 78.52 pg/mL versus 50.32 pg/mL ( $P = 0.0256$ ).

## RADIOLOGICAL FINDINGS

Digital chest radiographs (CXR) of all patients, USG chest of 16 patients (20.00%), and HRCT chest of 30 patients (37.50%) were available for the assessment of lung involvement in the sample population. In 20 patients (25.00%), CXR represented classic for COVID-19 images, with an average visual score of 0.78 0.90 out of 4. The severity score of the USG was 16.14 11.32 out of 42. The average CT severity score was 7.4 6.75 out of

25, with 12 individuals having a CT severity score of > 10/25. (40.00 percent). Group 1 (1.12) had a substantially higher CXR average visual score ( $P = 0.0439$ ) than Group 2. (0.68). Uncontrolled diabetes group (11.96) had a significantly higher CT severity score ( $P = 0.0489$ ) than controlled diabetes group (6.1), with a CT severity score > 10/25 in 75.00 percent and 27.27 percent patients in respective groups ( $P = 0.0182$ ).

### Diabetic Complications

DKA struck six individuals (7.50%), and septic shock struck nine patients (11.25%). When compared to the controlled diabetes group, patients with uncontrolled diabetes (18.18 percent) developed DKA more frequently ( $P = 0.0257$ ). (3.45 percent). Septic shock was seen in 22.73 percent of uncontrolled diabetes patients, but only 6.90 percent of those with controlled diabetes.

### Outcome

In total, 80 patients were considered; 40 patients (50.00%) recovered, 14 patients (17.50%) succumbed to COVID-19, and the other patients were still receiving treatment at the time this study was completed. When compared to individuals with controlled diabetes, the average length of stay in the hospital was substantially longer ( $P = 0.0479$ ) in patients with uncontrolled diabetes (16.94 days) (13.91 days). According to the gathered data, the average recovered patients in the uncontrolled diabetes group were relatively low (36.36%) when compared to Group 2. (55.17 percent). Not only that, but uncontrolled diabetic patients had considerably greater COVID-19-related mortality (31.82 percent vs. 12.07 percent).

## DISCUSSION

Uncontrolled diabetes has a significant impact on biochemical markers, as well as a worsening prognosis, according to our findings. Diabetes mellitus predisposes a person to a certain type of infection and mortality,<sup>[4]</sup> including COVID-19, albeit its risk as a co-morbidity in COVID-19 needs to be further researched. T2DM affects 7.3 percent of the population in India,<sup>[5]</sup> putting

a large percentage of the population at risk for COVID-19 and its effects. Type 2 diabetes mellitus, which develops as a result of metabolic syndrome and obesity, impairs immunity by raising inflammatory and chemokine levels.<sup>[6,7]</sup> SARS-CoV-2 invasion in human cells has been connected to ACE2, which has anti-inflammatory properties, and its expression has been discovered to be reduced in diabetic individuals, probably due to glycosylation.<sup>[8]</sup> This could explain why COVID-19 patients with diabetes mellitus have a higher risk of severe acute lung damage and ARDS. When comparing islet tissue to exocrine pancreatic tissues, immunostaining indicated an increased staining characteristic for ACE2, implying a possible involvement for coronavirus in islet destruction.<sup>[9]</sup> As a result, COVID-19 may cause a significant change in blood glucose levels in diabetes patients, potentially impacting the disease's many clinical manifestations.

Clinical presentation was more prominent in the uncontrolled diabetes group than in the controlled diabetic group in the current investigation. Cough and shortness of breath were more common in people with uncontrolled diabetes, and the underlying cause could be early and extensive lung involvement in COVID-19 infection as a result of glyceemic fluctuation. Furthermore, a high CT severity score suggested severe lung damage in people with uncontrolled diabetes. In uncontrolled diabetes patients, the aforementioned clinical image, which was verified by radiological data, revealed a severe pneumonia, but in controlled diabetic patients, the aforementioned clinical picture revealed a mild pneumonia. Uncontrolled diabetes was shown to have a higher average TLC, which could be due to an enhanced secondary inflammatory response in these patients. The neutrophil to lymphocyte ratio was also raised in the peripheral blood of uncontrolled diabetes patients, most likely due to neutrophilia or a relative lymphocytopenia as a result of COVID-19 infection. Furthermore, serum levels of inflammatory biomarkers such as IL-6, ferritin, and CRP were alarmingly high in the uncontrolled diabetes group. IL-6 is a predictor of disease severity and prognosis,<sup>[10]</sup> and Huang *et al.* found that levels of IL-6 were higher in patients with SARS-CoV-2 infection, concomitant with a significantly lower lymphocyte

Characteristics	Total no./mean value	Group 1 (HbA1c>8)	Group 2 (HbA1c<8)	P-value
Male	46	12	34	0.301
Female	34	10	24	
Symptomatic patient	24	11	13	0.0164
Others	4	2	2	0.3030
CT severityscore	12	6	6.1 ± 6.21	0.0489
DKA	6	4	2	0.0257
Septic shock	9	5	4	0.0455
Insulin therapy	38	15	23	0.0226
Lopinavir	11	5	6	0.1498
ICU care	5	3	2	0.0929
NIV	4	3	1	0.0292
Recovered patients	40	8	32	0.1336
Death	14	7	7	0.0375

count.<sup>[11]</sup> The activation of the monocyte-macrophage system, which contributes considerably to the inflammatory storm associated with COVID-19,<sup>[12]</sup> is indicated by an abnormally high ferritin level. In the current study, increased ferritin levels were found in patients with uncontrolled diabetes, implying that these individuals are more susceptible to an inflammatory storm, which leads to rapid deterioration owing to COVID-19. Hypoxia caused by inflammation may activate thrombin, resulting in the unfolding of the exogenous coagulation pathway.<sup>[13]</sup> Inflammatory storm in COVID-19 is linked to a considerable increase in D-dimer levels, and a similar pattern was shown in our investigation, where uncontrolled glyceemic patients had considerably higher D-dimer levels than diabetic patients who were under control. In such patients, this data indicates a hypercoagulable state, possibly even disseminated intravascular coagulation. During the natural course of COVID-19, patients with uncontrolled diabetes mellitus were more likely than those with controlled diabetes to acquire diabetic complications. Diabetic complications such as DKA and diabetic retinopathy developed in patients with uncontrolled diabetes. Patients with uncontrolled diabetes needed more active pharmacological and supportive treatments than those with well-controlled diabetes, as evidenced by the need for insulin therapy in Group I. Uncontrolled diabetic patients also had a higher need for supporting therapy such NIV and ICU care.

## CONCLUSION

We looked at 80 COVID-19-infected T2DM patients and described them using biochemical, radiological, and other clinical criteria in this retrospective investigation. Uncontrolled diabetes mellitus may predispose a person to a severe and lethal COVID-19 infection, according to the findings. The severity of COVID-19 in diabetics may be attributed to a defective immune system, which is vulnerable to viral infection while also experiencing a cytokine storm, an overactive immune response. In diabetics, having such a high level of immunity makes it easier for viruses to survive and recover. COVID-19 patients with uncontrolled diabetes require more pharmacological and supportive care than COVID-19 patients with well-controlled diabetes. Because of the high prevalence of T2DM in India, a considerable part of the population is predisposed to COVID-19 and its consequences. A HbA1c of more than 8% should be considered a risk factor for a higher overall susceptibility to COVID-19 infection and severity in terms of symptomatic presentation, inflammatory storm, rapid

pulmonary invasion, the need for more intensive treatment, and a poor outcome in patients with uncontrolled diabetes mellitus. As a result, patients with underlying DM should take extra precautions to avoid COVID-19.

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