

**Review article/Meta analysis**

**“Elucidation of the Shared Pathophysiology between Diabetes and COVID-19”**

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**Abstract**

**Background:** COVID-19 is a rapidly spreading communicable disease worldwide. It varies widely in its spectrum of manifestations, from being mild self-limiting disease, to fulminant disease, often leading to complications and death. Diabetes is an important co-morbidity linked to severity of infection by SARS-CoV-2, which predisposes them to severe pneumonia. Poor glycaemic control is associated with worse outcomes. The disease burden of COVID-19 is continuously increasing, and with a high prevalence of diabetes, it is all the more important to understand the vital aspects of COVID-19 infection in diabetic population. Hence, we try to provide close insights into its pathophysiology, clinical characteristics, recommendations on management and prevention and possible avenues for improving disease outcomes.

**Methods:** PubMed database and Google Scholar were searched using the key terms ‘COVID-19’, ‘SARS CoV- 2’, ‘Corona’ and ‘diabetes’. Full texts of the retrieved articles were accessed and referred. Three main mechanisms which influence COVID-19 disease manifestation in diabetics include: (a) Entry of virus via ACE-2 receptors (b) Action through Dipeptidyl-peptidase-4, and (c) Elevation of glucose concentration in airways by elevated blood glucose. ACE-2 is expressed in alveolar epithelial cells, heart, renal-tubular and intestinal epithelia and pancreas. S-Glycoprotein on the surface of SARS-CoV-2 binds to this ACE-2 and undergoes a conformational change. This allows its’ proteolytic digestion by host cell proteases TMPRSS2 and Furin, leading to internalization of virus. Viral entry into cells triggers an inflammatory response by T-helper-cells and at times, a ‘cytokine storm’, resulting in organ damage. Apart from diminishing neutrophil chemotaxis and reducing phagocytosis, by which diabetes predisposes individuals to infections, there are several specific factors with respect to SARS-CoV2: (i) Increased ACE-2 expression (ii) Raised Furin (iii) Diminished T-cell functioning, and (iv) Increased IL-6 levels. Movement restrictions, increased stress due to social isolation and lack of physical activity further complicates the issue. It is therefore, much essential to raise awareness among front-line workers. Finally, the current situation emphasizes the need for more clinical investigation and define best practices for optimum outcomes.

**Keywords:** COVID-19; Diabetes; Epidemics; Pandemics; outcome; glycaemic control; ACE-2; DPP-4; cytokine storm; comorbidity; prevention

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**Introduction:**

COVID-19 (Coronavirus Disease-2019), a disease caused by Coronavirus (SARS-CoV), has emerged as a rapidly spreading communicable disease affecting almost all countries. The disease severity varies

from mild self-limiting flu-like illness, to fulminant pneumonia, respiratory failure and death.<sup>1,2</sup> The spread of this novel virus has reached pandemic proportions and it represents a threat by its increased morbidity and mortality, globally.<sup>3</sup>

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### **Increased incidence of COVID-19 in patients with Diabetes:**

In most regions, increased morbidity and mortality associated with COVID-19 is particularly seen in older individuals and in those presenting with one or the other co-morbidities, such as diabetes, obesity, hypertension, cardiovascular disease, cerebrovascular disease, chronic kidney injury, chronic liver disease.<sup>6-9</sup> High prevalence of diabetes makes it a very important co-morbidity among these in patients with COVID-19.<sup>1-5</sup>

### **Importance of glycaemic control in diabetic patients with Covid-19 infection:**

Diabetes is a primary risk factor and is one of the most important co-morbidities linked to the severity of infectious disease caused by respiratory pathogens. Depending on the global region, 20–50% of patients in COVID-19 pandemic had associated diabetes. It predisposes individuals to infections such as influenza and severe pneumonia.<sup>10,11,1</sup> Similar evidence of high risk among diabetic patients have also been reported for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome<sup>3</sup> (MERS-CoV).<sup>12</sup> Poor glycaemic control in patients with COVID-19 and pre-existing diabetes is associated with worse outcomes, due to increased need for medical interventions, ARDS, multiple organ injuries and high rate of mortality.<sup>2,4</sup> COVID-19 infected diabetic individuals are at an increased risk for complications because of suppressed immune functions. The disease burden of COVID-19 has been continuously increasing,<sup>13</sup> and with a high prevalence of diabetes, it is important to understand the vital aspects of COVID-19 infection in people with diabetes.<sup>3,5</sup>

Hence, in this review, we try to provide close insights, by revealing the possible mechanistic links, into the biochemical basis and pathophysiology behind increased susceptibility of patients with co-morbidities, especially diabetes mellitus, for infection and severity of the disease caused by this novel corona virus. We also present clinical characteristics of COVID-19 patients with pre-existing diabetes, practical recommendations on its management / prevention, an insight into the differing needs of several patient groups and possible avenues for improving the disease outcomes.

### **Methods**

PubMed database and Google Scholar were searched using the key terms ‘COVID-19’, ‘SARS CoV- 2’, ‘Corona’ and ‘diabetes’. Full texts of the retrieved articles were accessed and referred.

### **Observations And Discussion**

#### **Link between Diabetes and COVID-19 infection:**

Three main mechanisms are thought to influence the interplay between diabetes and Covid-19 infection: (a) Initial entry of SARS-CoV-2 virus into host cells through its spike protein, via ACE-2 receptors (plays crucial role in blood pressure regulation, metabolism and inflammation<sup>14</sup>, where it attacks the endocrine pathway (b) It's action through Dipeptidyl peptidase-4 (DPP-4) enzyme (one of the pharmacological targets in those with type 2 diabetes). DPP4 are tissue oligopeptides that control the activity of growth factors, chemokines, bioactive peptides and T-cell activation besides regulating glucose metabolism<sup>15</sup> and (c) Elevation of glucose concentration in airways by elevated blood glucose<sup>16</sup> This hyperglycaemia may increase viral replication<sup>17</sup>, by disrupting the defensive capacity of airway epithelia and suppressing anti-viral immune response. Hyperglycaemia might exacerbate virus induced respiratory dysfunction too. Diabetes in animal models is associated with several structural changes in lung, such as increased vascular permeability and a collapsed alveolar epithelium<sup>16</sup>.

#### **Special aspects of Pathophysiology of diabetes**

As mentioned above, CoV utilises ACE-2 as receptor for cellular entry.<sup>18</sup> ACE-2 is expressed in type I and II alveolar epithelial cells of lungs and upper respiratory tract, heart, endothelium, renal tubular epithelium, intestinal epithelium and pancreas. S-Glycoprotein on the surface of SARS CoV-2 binds to this ACE-2 and undergoes a conformational change in itself, which allows its' proteolytic digestion by host cell proteases TMPRSS2 and Furin, ultimately leading to internalization of the virus particle.<sup>19</sup> Viral entry into the cell triggers an inflammatory response by T-helper cells by producing interferon gamma and then other inflammatory cells, thus leading to a ‘cytokine storm’, resulting eventually in organ damage and multi-organ failure.

Diabetes is associated with poor outcomes in COVID-19. Apart from the common mechanisms of diminished neutrophil chemotaxis and reduced phagocytosis, by which diabetes predisposes

individuals to infections, there are several specific factors liable for increased risk and severity of SARS CoV2 infection in patients with diabetes such as: (i) Increased expression of ACE-2 (ii) Raised Furin, the host cell protease (iii) Diminished functioning of T-Cells, and (iv) Increased levels of Interleukin-6.

### **Special considerations on the use of Anti-diabetes drugs:**

Although optimising glycaemic control to reduce the risk of severe COVID-19 disease is important, specific considerations around treatment modality should be made. Lactic acidosis associated with metformin usage, or euglycemic/moderate hyperglycaemic diabetic ketoacidosis associated with SGLT-2 inhibitors are rare instances; however, it is recommended that these drugs Should be discontinued in patients with severe symptoms of COVID-19 in an attempt to reduce the risk of acute metabolic decompensation.<sup>20</sup>

### **Management of hyperglycaemia and associated Metabolic conditions:**

People with diabetes should intensify their metabolic control by adopting suitable lifestyle modification protocols in addition to pharmacologic therapy. Most patients with type 2 diabetes have other components of Metabolic Syndrome i.e., hypertension (using drugs not acting through ACE-2), dyslipidaemia, etc. Hence, continued treatment using an appropriate antihypertensive and lipid-lowering agent is highly recommended. Treatment with ACE inhibitors or AT2 blockers is discouraged since they could increase the expression of ACE2 and facilitate viral entry into cells.<sup>21, 22</sup>

### **Challenges associated with achieving optimal metabolic control in COVID-19 affected diabetic patients:**

In spite of knowing the importance of maintaining optimal blood glucose levels in current situation of COVID-19 pandemic, certain hindrances have to be overcome to achieve it practically. It is therefore important to raise awareness regarding the significance of glycaemic control among the front-line workers. The optimal treatment of these patients should consist of a multidisciplinary approach by doctors from emergency medicine, infectious diseases, pulmonary medicine, endocrinology, nutritionists and exercise rehabilitation specialists, especially

during prolonged periods of hospitalization.

### **Measures in Diabetic Patients infected with COVID-19:<sup>1,4</sup>**

- Majority of patients have mild disease and can be managed at home
- If the patient develops fever, cough, running nose or dyspnoea, notify the appropriate health authority and seek immediate medical help
- Isolate the patient for 14 days or till the symptoms resolve (whichever is longer)
- Hydration should be well maintained
- Symptomatic treatment with acetaminophen, steam inhalation etc. will be helpful
- Patients with type 1 diabetes should measure blood glucose and urinary ketones frequently
- Avoid Anti-hyperglycaemic agents which can cause volume depletion or hypoglycaemia
- Adjust the dose of oral anti-diabetic agents
- Severely diseased and hospitalised patients need frequent blood glucose monitoring.
- Oral Anti-diabetic agents like metformin and SGLT-2 inhibitors need to be stopped to reduce the risk of acute metabolic decompensation.<sup>20</sup>
- Insulin is the preferred agent for control of hyperglycaemia in sick patients

### **Unproven therapies and future directions:**

- In the absence of specific antiviral drug, anecdotal use of drugs like lopinavir, ritonavir, interferon-1b, Remdesivir (RNA polymerase inhibitor) and chloroquine has been reported
- Regular supplementation with Zinc and Vitamin C is quite essential
- A definitive vaccine can be a major tool to contain this viral epidemic<sup>23</sup>

### **Preventive Measures**

Following measures are suggested for prevention of this disease in patients with diabetes:<sup>1,5</sup>

#### **A. Specific Measures in Patients with Diabetes**

- More frequent monitoring of blood glucose levels (to lessen chances of superadded bacterial pneumonia as well) using Glucometer

preferably (to lessen the exposure)

- Regular intake of antidiabetic medication – Telemedicine can be very helpful
- Stabilise the co-existing cardiac/renal disease
- Balanced and adequate nutrition with good intake of proteins and fibre, together with limited intake of saturated fats is very much recommended
- Home based Exercise (cycling, treadmill, stationary jogging and resistance exercise with small weights) has been shown to improve immunity
- Care of feet should be emphasized
- Patients need to be educated about the need to visit the hospital immediately in emergency situations like vomiting, drowsiness, shortness of breath, chest pain, weakness of limbs, altered sensorium etc.

### **B. General Preventive Measures:**

- Thorough handwashing with soap and water
- Practise proper respiratory hygiene with covering of mouth and nose
- Contact with an affected person needs to be minimised – Usage of face mask is highly recommended
- Non-essential travel to affected areas to be avoided

### **Conclusion**

Diabetes is associated with increased incidence and severity of COVID-19. There is experimental evidence on the effect of diabetes on viral entry into cell and inflammatory response to the infection. It is therefore important to control blood glucose in patients infected with COVID-19. As a result, increased vigilance and testing in diabetes and general medicine clinics for COVID-19 and a lower threshold for hospitalization of these patients is imperative.

Due to the challenges associated with restriction on movement, an increasing number of diabetic patients are cancelling their routine visits to diabetes clinics. This development along with the increased stress associated with social isolation and lack of physical activity provides a fertile ground for worsening of glycaemic status and blood pressure control, further predisposing these vulnerable patients to COVID-19 infections.

As suggested by American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE), it is much essential that we alert the health care community and the public regarding the increased risks of this progressing pandemic in diabetic patients. Also, adherence to CDC (Centers for Disease Control and Prevention) guidance regarding social isolation is very important in persons with diabetes. Finally, the current situation emphasizes the need for more clinical investigation as the pandemic unfolds to fully characterize the problem and define best practices for optimum outcomes.

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### **Authors' Contribution:**

- Data gathering and idea owner of this study: Dr Nagalakshmi CS
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- Writing and submitting manuscript: Dr Nagalakshmi CS
- Editing and approval of final draft: Dr Nagalakshmi CS, Dr Shaheen B Shaikh, Dr Santhosh NU

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