

## Disease Severity and Pathophysiology of COVID-19 in Type 2 Diabetes Mellitus Patients

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### ABSTRACT

The world is facing COVID 19 pandemic which has created a chaos among the mankind. It has created a huge burden in the health care facilities. COVID 19 disease is caused by emerging mutants of Severe acute respiratory syndrome corona virus 2(SARS CoV-2). The virus is highly contagious and infects through the respiratory route. It invades the respiratory tract mainly the lungs causing pneumonia. Patient usually presents with fever, nonproductive cough, breathlessness, myalgia and fatigue. Severe cases can rapidly progress to acute respiratory distress syndrome and multi organ failure, death may occur due to complication. Furthermore early identification and diagnosis of high risk cases like hypertension and diabetes and prevention of the serious complication in them help in decreasing the burden on the intensive healthcare facilities. As we know the doctor to patient ratio in a developing country like India is very low, thus it becomes very important for the doctor to know the impending risk in his/her patients. So we have made an effort to understand the pathophysiology involved, the treatment protocols followed in patient of type 2 diabetes mellitus with COVID 19 infection. Regular monitoring of the blood sugar levels during the hospital stay becomes important to detect the red flags of complication. Assessment of the severity of the disease and prognosis in type 2 diabetes mellitus patient and non-diabetics has been contrasted. This might help provide better intensive care management for all the patients at early stage and decrease the morbidity and mortality in the COVID 19 patients. We have tried to unfold the relationship between two hyper inflammatory diseases that is type 2 diabetes mellitus which is chronic inflammatory condition and SARS CoV 2 which causes acute inflammation. It should be noted that both the diseases have tendency to cause multi organ dysfunction and failure.

**Key words:** COVID19, SARS CoV-2, Type 2 diabetes mellitus, Cytokine storm, Microangiopathy, Multiorgan failure, Acute respiratory distress syndrome

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### INTRODUCTION

Background- SARS CoV-2 is a virus in family of coronaviruses. Due to mutation in SARS CoV-2 there are newly emerging spectrum of COVID 19 diseases. The virus is highly contagious and infects through respiratory route. It invades the respiratory tract mainly lungs causing coronavirus pneumonia. In severe cases, disease can rapidly progress to ARDS (acute

respiratory distress syndrome), septic shock, MODS (multi-organ dysfunction syndrome). Death may occur due to the complications. In India, the first wave of the disease came in April 2020 affecting all age groups but causing more mortality in elderly. Then, a second wave came in march-2021 affected more commonly the adults. The individuals with significant comorbidity like hypertension, diabetes mellitus, cancer, bronchial asthma, cardiovascular diseases and kidney ailments are at constantly increased risk of developing more severe infection, more suffering and higher risk of mortality. Type 2 diabetes mellitus is found to be the second most common co- morbidity in COVID 19 illness [1]. Although diabetes mellitus type-2 is a significant co-morbidity in novel corona virus infection but the exact impact of blood glucose levels in the outcome of patient post infection remains unclear. According to various studies, the patients with well controlled

diabetes mellitus had early recovery and better outcome and on the other hand ones with the poorly controlled blood sugar levels had less recovery rates and more mortality [2]. The purpose of this study is to gather the evidences regarding the prognostic value of blood sugar levels with the prognosis of the patient. Thus, evidences are needed to comprehend the prognosis of type 2 DM patients infected with COVID 19 and understand the pathogenesis involved in the same. On a whole the study will help us to manage the patients more effectively and efficiently. It has been observed that the patients with diabetes are more susceptible to all kind of infections as compared to non-diabetics. The higher susceptibility for infection has been observed in last decades in other corona virus epidemics like SARS CoV-2 in 2000's and MERS in 2017 [3]. Hyperglycemia has a negative impact on control of inflammation and viremia. For patients with COVID 19 and pre-existing diabetes, clinicians have been facing challenges to improve their outcome. There has been uncertainty regarding the level of blood glucose to be maintained and its risks and benefits in the overall treatment.

The pathophysiological mechanism responsible for the impact of type 2 DM on COVID 19 illness progression is yet to be understood. Diabetic patient's incapability to generate an adequate immune response predispose them for severe infection. This is suggested by a degree of lymphopenia observed in diabetics with COVID illness. Increased renin angiotensin and angiotensin convertase enzyme is observed in diabetes mellitus and corona virus utilizes this angiotensin convertase enzyme to bind and infect the cell thus there is increased risk of severe infection in diabetes [4].

### Objective

To understand the pathophysiological mechanisms involved in the disease severity in type 2 diabetes mellitus patients.

To gather the evidences regarding the prognostic value of blood sugar levels with the prognosis of the patient.

### METHODOLOGY

We reviewed articles from PubMed, and Google scholar. Almost 150 articles appeared related to our topic. We included article which focused on COVID in a already diagnosed diabetes patient and its impact. Preference was given to recently published articles. Articles chosen are relevant and focus on second wave of COVID 19. We use guidelines issued from ICMR and WHO on their website for management of cases. Data used are announced by health ministry of India.

### Review

#### Pathophysiology of COVID in type 2DM

Diabetes is hyper-inflammatory condition and seems that it may increase susceptibility for COVID-19 independently of other underlying diseases. There are several possible mechanisms: (a) inflammation,

(b) hyper-coagulable state, and (c) activation of renin-angiotensin-aldosterone system (RAAS) and dysregulation of sympathetic nervous system.

T2DM patient with uncontrolled hyperglycemia are independent risk factor for increased severity and mortality [5]. The pathophysiological mechanism which might be the cause of increased severity is as follows

Infection with COVID 19 leads to release of various inflammatory mediators, cytokines, lipopolysaccharides and toxic metabolites. Viral infection also increases the reactive oxygen species in the circulation. Also interferons modulate the natural killer cell activity which have a pivotal role in further increasing the vascular permeability and other pro-inflammatory substances. Viral binds to ACE receptor and increases the angiotensin thus activating RAAS. ROS, inflammatory mediators and RAAS together cause insulin resistance and hyperglycemia. Inflammatory cytokines cause lung fibrosis and lead to acute lung injury and ARDS (acute respiratory distress syndrome). These mediators and ROS tend to alter the vascular permeability by causing endothelial damage. Endothelial damage and platelet aggregation at the site of injury predispose the individual to thrombotic and embolic events which can be fatal. Viral infection raises the coagulation proteins like fibrinogen and D-dimer which increases the blood viscosity and further predispose to thromboembolic events, DIC(disseminated intravascular coagulation) and mortality [6,7].

In DM, hyperglycemia causes increased blood glucose levels in monocytes which lead to production of mitochondrial reactive oxygen species and activation of hypoxia inducible factor 1 alpha. It also promotes COVID 19 viral replication within the monocytes [8]. Various studies have shown that the T2DM patients infected with COVID 19 had increasing needs for regular insulin administration and higher risk of developing diabetic ketoacidosis as compared to those not infected with COVID 19 virus [9].

Hyperglycemia alters the immune function as we know type 2 DM patients are immunocompromised, it also predisposes to development of a dysregulated immune response against the COVID 19 virus which leads to more micro and macro vascular complications. ACE2 is expressed on surface of various human cells like endothelium, intestinal cells, kidney cells, myocardium, and pancreatic islets cells. COVID 19 virus causes direct and prolonged damage to beta islet cell of pancreas leading to hyperglycemia.

Viral binds to ACE and alters the conversion of angiotensin I to angiotensin II and elevated angiotensin I levels in the circulation. Angiotensin I enhances vasodilation and inhibits the action of angiotensin II. Angiotensin I causes vasodilation and inhibits the angiotensin II mediated vasoconstriction. It also stimulates release of bradykinin. Thus it may leads to fall in blood pressure, vascular dysfunction and cardiovascular remodeling.

COVID 19 inflammation causes ACE-2 enzyme down regulation which has a protective role against acute lung injury. ACE-2 acts a negative regulator of rennin angiotensin system prevents acute injury to lung. ACE convert angiotensin I to angiotensin II which induces lung edema and promotes lung injury.

The ACE 2 receptors on the host cells interact with the spike glycoprotein on the virus, facilitating viral entry into the host cells [4]. Hyperglycemia increases the glucose intracellular and thus increases the metabolic rates within the cells, this can lead to tissue hypoxia and accumulation of by products which may cause interstitial lung damage which can lead to ARDS (acute respiratory distress syndrome). Hyperglycemia leads to dysregulation of glucose metabolism leading to endothelial injury and glucotoxicity. This further increases the glucose at the lung gaseous exchange surface and alters the exchange of gases and lead to further hypoxia. DM is a pro inflammatory condition which increases the endothelial damage furthermore and increase levels of ROS. This damages all the vital organs causing inflammation and can lead to multiorgan dysfunction. Endothelial damage increases risk of thrombosis at that site. Inflammatory mediators, cytokines and chemokine's further exacerbate inflammation at endothelium and leads to accumulation and aggregation of inflammatory cells, although this immune reaction is unbalanced and is dysregulated. Further ROS (reactive oxygen species) cause further damage at the site of endothelial injury. The thrombus might dislodge and lead to embolic complications. ARDS, MODS, pulmonary embolism, DVT (deep vein thrombosis) and DIC increased the risk of major cardiovascular complications and mortality in individuals. We know diabetes is associated with macro and micro vascular angiopathy. COVID 19 viral infection increases the risk of more such complications due to inflammatory state throughout the body.

Patients with type 2 DM have a continuous low grade inflammation through various pathways. These pathways get highly active in co-existing COVID 19 infection leading to inflammatory state. DM patients have defective innate and adaptive immunity. This leads to delay in T1 mediated immune response and development of a later hyper inflammatory response with is obviously a dysregulated one. Diabetes is associated with increased proinflammatory cytokines which lead to formation of the advanced glycation end products. AGE products could be implicated in further increasing the cytokine storm.

Diabetes mellitus patients have higher affinity for the viral binding on cells, entry of virus into the cells, reduce viral clearance and altered T cell function. They also have a higher susceptibility to hyper inflammation and cytokine storm. Altered immune responses include defective phagocytosis by the neutrophils, macrophages and monocytes. There is also altered inflammatory cell chemo taxis at the site of injury.

#### **Statistical analysis of type 2 diabetes mellitus patients infected with covid-19**

Diabetes is the 5th leading cause of death throughout the

world. People with the diabetes are one of the high risk groups for COVID 19 disease [10]. Patient with diabetes are at high risk of infection. With proper glycemic control the risk of infection can be reduced significantly.

According to a retrospective study which was done in Iran from March to September 2020 done on 16391 patient of which 1365 were diabetic and 15026 were non diabetic. As compared to the non-diabetic patients the diabetic patient were older and the risk of comorbidities and complication were higher as compared to non-diabetic ones. Symptoms were also more prevalent and more severe in diabetic patients. The history of contact with definitive case of COVID 19 was higher in non-diabetic subjects. Diabetic patients had a higher mortality (14.4%) as compared to non-diabetic subjects (3.3%). Among the non survivors, they were found to be significantly older and chronic diseases were higher [11].

#### **Major complication of type 2 DM infected with Covid 19- long Covid**

Long COVID is defined as the persistence of symptoms beyond 3 months after infection due to the multi-organ damage caused by acute infection and occurs in about 10% of patients with COVID-19.

One of the sequelae of COVID 19 includes new onset of diabetes mellitus and acute complication of diabetes like diabetic ketoacidosis. The symptoms of the post COVID syndrome can be due to organ dysfunction, drugs or hospitalization. Post COVID syndrome is not a single clinical entity rather a group of symptoms the pathophysiology of which is not completely understood. The symptoms may be due to persistently dysregulated inflammatory and immune responses or some autoimmune mechanism due to molecular mimicry between the host and the viral proteins. Further nutrient deficiencies due to prolong hospitalization may be a cause which is more prevalent among the Indians.

The pandemic has resulted in poor control of diabetes, early progression of pre diabetes to diabetes, increase in the number of new onset diabetes. The cause for the same may be due to prolonged corticosteroid treatment long duration of the poor glycemic control lead to microvascular injury and thus organ damage which is exacerbated in covid19 infected patient. In poorly control diabetes mellitus, lung fibrosis is a common complication which leads to persistent symptoms in them. Also post COVID 19 infection like rhino-cerebral mucormycosis are much more prevalent in diabetes [12]. High dose of corticosteroid therapy which is commonly used in India for treatment of moderate to severe covid19 patient leads to severe hyperglycemia, electrolyte imbalances and myopathies. Patient with the long standing diabetes mellitus may have autonomic neuropathy and disfunction which may lead to postural hypotension and tachycardia. Prolonged hospitalization, protein deficiencies and limited mobilization in Indian with already lower muscle masses may lead further to sarcopenia. This leads to post COVID fatigue syndrome. Covid19 causes capillary dysfunction that is endothelial

inflammation and damage, micro thrombi, micro emboli which are further exacerbated in diabetes can lead to brain fogging and memory problems.

Rehabilitation of the patient recovering from COVID 19 require multidisciplinary approach to prevent and treat post COVID syndrome. Strict glycemic control and control of other comorbidities would alleviate the development of post COVID syndrome and help to manage it effectively.

### Prognosis of Covid in type 2 DM patients

The occurrence, severity and mortality in COVID 19 infection is much more in diabetic patients as compared to non-diabetics. The acute complications of DM are much higher in COVID infected patients as compared to non-infected individuals. Diabetic ketoacidosis and Hyperglycemic hyperosmolar syndrome are the 2 acute complications of diabetes. Close monitoring of blood glucose, ketone bodies, and serum electrolytes is required for early diagnosis and management of complications. Iv fluids should be administered judiciously taking into account the markers of perfusion to prevent volume overload and pulmonary edema like complications.

According to a retrospective study done on 174 patients which included both diabetic and non-diabetic subjects, enzymes like lactate dehydrogenase, gamma glutaryl transferase, and alanine transaminase were abnormally high suggesting vital organ injury like myocardium and liver more in diabetic patients as compared to non-diabetics. On the other hand Hemoglobin, albumin, prealbumin, and total proteins were found to be lower in the diabetes which shows the diabetic patient were more malnourished. The cytokine storm produced by the viral proliferation leading to inadvertent neutrophilia and hyper coagulated state is responsible for the persistent inflammation and multi organ dysfunction. Interleukin 6 and serum ferritin, erythrocyte sedimentation rate, C-reactive protein were found to be much higher in the diabetic patients as compared to the non-diabetic patient. Interleukin 6 is very good bio marker for the severity of disease and the outcome of the patient as it is expressed for a longer duration in the circulation as compared to other cytokines. High levels of serum ferritin indicate exorbitant monocyte, macrophage system activation leading to an inflammatory storm. High resolution computed tomography scan are being used to assess the disease severity and CT score are calculated which are graded as mild moderate and severe with score 0-8, 9-15, and 16-25 respectively. Diabetics were found to have a severe disease and a higher CT score as compared to non-diabetics [13].

### CONCLUSION

COVID 19 is giving rise to tremendous challenges in the entire world and efforts have been devoted in understanding the pathophysiology of COVID 19 in patient already diagnosed with diabetes mellitus. From the above following discussion we have understood that

covid19 infection in a diabetic patient poses as serious health hazard. Therefore in view of pandemic, more stress should be given on eating nutritious and low glycemic index food along with some amount of physical activity daily in a patient diagnosed with diabetes mellitus. The patient should regularly monitor the blood glucose level. If the patient experiences any sort of COVID 19 related symptoms or if there is unanticipated hike in blood sugar levels should consult a health care provider. As there are evolving treatment strategies being developed every day but the definitive treatment is yet to be developed, prevention is the best policy to be applied by following strict COVID guidelines such as social distancing, wearing a proper mask, having healthy lifestyle and approach the health care provider if there is COVID related illness. Diabetes produces a prolonged inflammatory state in the body. The diabetic patients required higher and repeated insulin doses to maintain the glycemic controls and other oral hypoglycemic like sodium glucose co transporter dynamics and metabolism is altered due to viral binding on SGLT receptors. So, insulin is preferred over oral hypoglycemic.

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