

Etiopathogenesis of Covid: 19 Infection in Patients with Underlying Diabetes

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Abstract

Background: The pandemic due to coronavirus disease caused by SARS CoV-2 has caused significant morbidity and mortality across the globe. Underlying conditions such as hypertension, diabetes, cardiovascular diseases escalate the risk of various complications associated with covid-19 and leads to poorer prognosis. Therefore it is of prime importance to understand the cause of the severity of symptoms observed in patients with pre-existing type-2 Diabetes Mellitus. It is also imperative to decipher the chemical pathways involved in the causation of Diabetes which when intertwined with covid-19 leads to critical outcomes.

Objective: The increasing per capita income has meant that the burden of non-communicable diseases now falls at India's doorstep. So, we attempt to study diabetes in the backdrop of prevailing nCoV-2. According to World Health Organization (WHO), India had 69.2 million people living with diabetes in 2015. Thus it is crucial in a country like India with so many diabetic patients to explore the consequences of the pandemic on this cohort.

Methods and Materials: We systematically searched the PubMed and Google scholar database for the published articles on diabetes and Covid-19 till 11th July 2020.

Conclusion: The relationship between Diabetes and Covid-19 and the likely chemical pathways involved in the pathophysiology have been elucidated. Based on the evidence that is available it is not possible to draw any certain conclusions. Though the present data that we have warranted further research to expound upon the poor prognosis observed in

diabetic patients suffering from Covid-19.

Keywords: SARS CoV-2; chemical pathways; pathophysiology; Covid-19; type-2 Diabetes mellitus.

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously provisionally named 2019 novel coronavirus or 2019-nCoV) disease (COVID-19) in China at the end of 2019 has caused a large global outbreak and is a major public health issue. It has been hypothesized since the initial days of pandemic that people with underlying comorbidities had a poorer prognosis as compared to other individuals.

The International Diabetes Federation (IDF) estimates that worldwide, 415 million people have diabetes, 91% of whom have type 2 diabetes mellitus (T2DM). People with diabetes comprise 8.8% of the world's population, and IDF predicts that the number of cases of diabetes will rise to 642 million by 2040. According to Diabetes Atlas (2019) OF International Diabetes Federation that Over 77 million have now been diagnosed with diabetes in India. The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.¹¹

The aim of the article is to understand the etiopathogenesis of COVID-19 infection in patients already suffering from diabetes. Particularly in the Indian context since a large proportion of patients are suffering from diabetes it becomes important to study complications and pathogenesis of the infection in such patients.

Pathogenesis of Covid-19 infection:

Like the other coronaviruses, SARS-CoV-2

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is spherical and has spikes which are proteins extending from their surface. The spikes go and attach themselves to the cells present in the body. These viral cells then undergo a structural change and get fused with the cell membrane for replication. It has been found that the spikes in SARS-CoV-2 go and bind to angiotensin-converting enzyme 2 (ACE2) in the body.

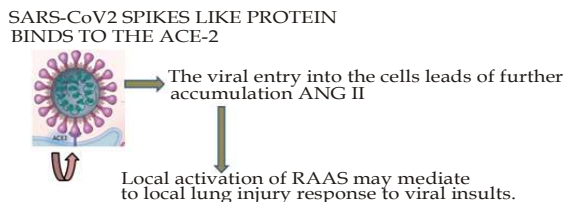


Fig. 1: Mechanism of SARS CoV-2

Angiotensin converting enzyme is expressed in various organs like heart, kidney, pancreas and epithelial cells of lungs. The binding of SARS-CoV2 and ACE2 results in exhaustion of ACE2 and further Ang (1-7). This disrupts the balance of the RAAS system which further causes exacerbation of acute severe pneumonia.

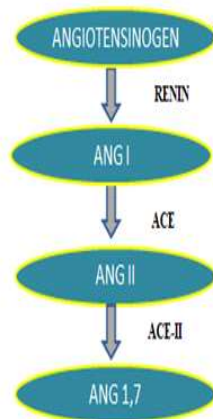


Fig.1.1: Renin Angiotensin Aldosterone System (RAAS) mechanism

Covid-19 and Diabetes

A relationship between diabetes and infection has long been clinically recognized. Increased glucose in the body along with insulin resistance leads to a build-up of glycosylation end products (AGEs) and other inflammatory cytokines causing tissue inflammation. It has been observed in a Chinese study which compared 39 SARS-CoV patients without previous diabetes, who did not receive steroid treatment, with 39 matched healthy siblings and showed that 20 of the 39 SARS-CoV patients developed diabetes during hospitalization. The pertinence of this study is related to the

findings that even patients who do not have pre-existing diabetes mellitus or insulin resistance are susceptible to developing diabetes during the course of covid-19 infection. Since immunostaining for ACE2 is strong in the pancreatic islets as compared to other exocrine tissues, it is suggested that SARS-CoV might have damaged islets and caused acute insulin dependent diabetes mellitus.¹⁴

In vitro studies have shown that pulmonary epithelial cells' exposure to high glucose concentrations significantly increases influenza virus infection and replication, indicating that hyperglycemia may enhance viral replication in vivo. Obesity causes inflammatory changes that is marked by conspicuous activation of inherent and adaptive immunity cells in adipose tissues. This leads to a chronic low grade systemic inflammation. Most of the patients suffering from Type 2 Diabetes mellitus are obese and this is an added risk factor for increased severity of covid-19 complications.¹³

Due to vascular and systemic changes an exacerbation of inflammatory changes and hypoxia is observed. The low levels of oxygen can stimulate monocyte macrophage complex to secrete a mass of tissue factors and initiate the exogenous coagulation pathway. This leads to a systemic state of hypercoagulation. Role of DPP4: Intake of food leads to the release of peptide hormones by the small intestine. These compounds, called incretins, have a glucagon-like function, i.e., that of increasing insulin secretion in response to food intake (activation of the entero-insular axis). The main incretins secreted after a meal are a glucagon-like peptide (GLP-1) and a glucose-dependent insulinotropic peptide (GIP). Both these incretins enhance post-prandial insulin secretion by pancreatic B-cells. Experimental studies have shown that its continuous infusion in diabetic subjects brings glycemia levels back to those comparable with non-diabetic controls, whereas single-dose subcutaneous administration is not effective. This is because the effects of GLP-1 are limited by its short half-life less than 2 minutes due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), a glycoprotein involved in several pleiotropic cell processes and capable of inactivating several hormones, including GLP-1 and GIP.

DPP4 enzyme is a type II transmembrane glycoprotein, expressed ubiquitously in many tissues, including the immune cells. Although its functions are not fully understood yet, DPP4 plays a major role in glucose and insulin metabolism.

DPP4 plays also an important role in immune regulation by activating T cells and upregulating

CD86 expression and NF- κ B pathway. It can be summarized that DPP4 increases inflammation in type 2 diabetes via both catalytic and non-catalytic mechanisms. Of note, the enzymatic activity of DPP4 causes the cleavage and may affect the function of several cytokines, chemokines, and growth factors.

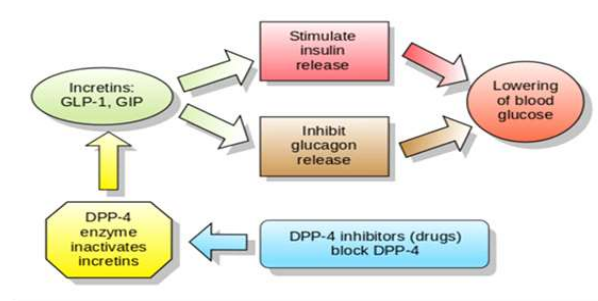


Fig. 1.2: GLP-1 and DPP-4 inhibitors

DPP4 inhibitors target the enzymatic activity of DPP4 and consequently block the breakdown of GLP-1. This increases insulin secretion and decreases blood glucose levels in patients with type 2 diabetes.

Anti-inflammatory and anti-adipogenic effects have been associated with the use of DPP4 inhibitors and GLP-1 receptor analogs.[14] Reduced macrophage infiltration directly via GLP-1 dependent signaling and reduced insulin resistance and inflammation by regulating M1/M2 macrophage polarization have been described with DPP4 inhibition and GLP-1 activation. DPP4 expression is higher in visceral adipose tissue and directly correlates with adipocyte inflammation and insulin resistance.

Dipeptidyl peptidase 4 (DPP4) was identified as a functional receptor for the spike protein of the MERS-CoV. [16] MERS-CoV also belongs to the beta coronavirus family[17]. It is unclear whether DPP4 inhibition or modulation should be the most appropriate strategy. However, DPP4 may represent a potential target for preventing and reducing the risk and the progression of the acute respiratory complications that type 2 Diabetes may add to the Covid-19 infection.

Specific complications in diabetic patients: The geriatric population and people with pre-existing medical conditions (such as diabetes, heart disease and asthma) appear to be more vulnerable to complications with COVID-19 virus. Diabetes in most of the patients often exists with hypertension, obesity which also increases the risk of cardiovascular diseases. Diabetic patients infected with the SARS-CoV-2 can be harder to treat due to fluctuations in blood glucose levels and due to complications arising out of diabetes.

Biochemical results demonstrate an atypical elevation of some indicative enzymes with SARS-CoV-2 pneumonia, including LDH, HBDH, ALT and GGT, which suggests injury of myocardium, kidney and liver. This result is consistent with the extensive distribution of SARS-Co-2 receptors ACE2 and can also partially explain why some patients died from multiple organ failure.¹⁸

The immune system is already compromised in such patients resulting in increased recovery time or sometimes death due to severe complications. The other probable reason for increased risk in diabetic patients is that higher glucose levels in the blood provide an ideal environment for the virus to thrive.

Given the previously reported impact of hydroxychloroquine on glucose metabolism, caution should be taken when the drug is administered to patients with diabetes and COVID-19. A dose adjustment of the oral antidiabetic drugs and/or insulin is necessary to prevent potential hypoglycemic events. Diabetes and its associated co-morbidities have a vicious relationship with hypoglycemia. Associated co-morbidities also increase the risk of hypoglycemia in patients with diabetes.¹⁸

Conclusion

Vascular and inflammatory changes in patients with pre-existing conditions lead to exacerbation of the covid-19 infection. The exact mechanism of disease progression is not very clear as of now. Yet it remains largely unknown how exactly the inflammatory and immune response occurs in these patients, as well as whether hyper- or hypoglycemia may alter the SARS-CoV-2 virulence, or the virus itself interferes with insulin secretion or glycemic control. Furthermore, the impact of usual diabetes drug treatment on COVID-19 outcomes, as well as therapeutic approaches for COVID-19 on glucose regulation remains unspecified. The available clinical data from the pandemic till date is insufficient to reach a final conclusion. However, there are a few inferences that can be assertively drawn from the limited understanding of Novel Coronavirus (2019-nCoV). The state of hypercoagulability and systemic inflammation associated with diabetes concatenate with the complication arising out of Covid-19 infection to give rise to an inflammatory storm. These two conditions combine to form a vicious circle which is detrimental to the prognosis of Covid-19. Although no therapy is currently established for SARS-CoV-2

patients, the field is moving rapidly with potential approaches being considered.

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