Coronavirus disease and diabetes – Interplay of two pandemics

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ABSTRACT

“Coronavirus disease (COVID-19)” is induced by a novel enveloped virus having single-stranded RNA which was originated in Wuhan city of Hubei, province, China. The coronavirus has a protein envelope. On the outer surface, the virus has spike-like glycoprotein, which is responsible for the attachment and entrance inside host cells. It transmits rapidly affecting more than 160 countries globally, so, the World Health Organization (WHO) announced it as a pandemic. It is considered as a relative of severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 is caused by a beta coronavirus named SARS-CoV-2 that affects the lower respiratory tract and manifests as pneumonia in humans. It is an airborne disease as announced by WHO and the incubation period ranges from 2 to 14 days. The clinical spectrum of COVID-19 is heterogeneous, ranging from mild flu-like symptoms to acute respiratory distress syndrome, multiple organ failure and death. Till now, so specific treatment is invented so, prevention plays a significant role. The current situation is only limiting the spread of disease. Coronavirus infection leads to the activation of adaptive and innate immune responses, resulting in massive inflammation (to so-called cytokine storm), which in turn can lead to damage to various tissues, septic shock and multiple organ failure. According to WHO, older individuals and people having associated co-morbidities like diabetes, hypertension, cardiovascular disease, obesity, etc., are at higher risk of getting infected by the coronavirus. This review explains the renewed correlation between diabetes and COVID-19. It also highlights the potential mechanisms by which diabetes regulates the host immune response and host-viral interactions.

INTRODUCTION

“Coronavirus” induced atypical pneumonia was named as “Coronavirus disease of 2019, (COVID-19)” by the World Health Organisation on February 11th 2020. It was first identified in Wuhan, China. On March 11th the epidemic was upgraded to the pandemic by WHO. International virus classification commission named “COVID-19” as “Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)”. On January 30th 2020, the “Director-General” announced that the outbreak of 2019-nCoV constitutes a “Public Health Emergency of International Concern (PHEIC)”. According to WHO, the virus comes from a family of Coronaviruses (CoV) humans. “COVID-19” is a rapidly growing communicable disease affecting 160 countries moreover globally. Older age and persons having medical disorders as “high blood pressure, cardiovascular disease, lung disease, cancer or diabetes” are more
prone to complications than the general population. The number of confirmed cases are increasing rapidly. India has the second-largest population globally, and being a developing country, the death toll can exceed all the countries (Sohrabi et al., 2020). The number of diabetics in India was 31.7 million in the year 2002, and it is estimated that the number of diabetics in 2030 will be 79.4 million in India (Khatib et al., 2008). In hospitalized patients with COVID 19, DM is the most prevalence co-morbidity (Nakhleh and Shehadeh, 2020).

In this review, we discuss the conjectural role of angiotensin-converting enzyme II (ACE2) with type 2 DM and COVID 19.

**Structure of Corona Virus**

“Coronaviruses (CoV) are enveloped viruses with a single-stranded, positive-sense RNA genome (approximately 27–32 kb) known to cause respiratory infections in humans” (Kim et al., 2020). It has a crown-like appearance in electron micrographs. Four coronavirus genera have been identified, alpha(a), beta(β), gamma(g). Delta(d), with human coronaviruses (HCoVs), recognized in the alpha coronavirus and beta coronavirus genera (Li et al., 2020). The RNA genome is formed by a helically shaped capsid, i.e. Nucleotide protein (N) and surrounded by an envelope. There are three structural proteins associated with viral envelope- Membrane protein (M) and Envelop protein (E) are convoluted in virus assembly where Spike protein (S) helps in virus entry to the cell and gives a crown shape to the virus (Li et al., 2016) (Figure 1).

![Figure 1: Structure of Coronavirus](image)

**Mode of Transmission**

1. Respiratory droplets (droplet particles >5-10 μm in diameter)
2. Droplet nuclei (size <5μm in diameter)

3. Contact routes

When a healthy person comes in close contact (1 meter) with infected patients having respiratory symptoms (coughing or sneezing) is on high risk of getting infected through his/her mucosa (mouth or nose) or conjunctiva. Symptoms manifest in the form of cough, fever, and its severe form, it can even lead to Acute Respiratory Distress Syndrome (ARDS) (Kumar et al., 2019). Transmission can occur through objects which are around the patient. Therefore the transmission of coronavirus can occur through direct or indirect contact (World Health Organization, 2020).

**Clinical Feature Coronavirus Disease (COVID-19)**

The symptoms like fever, cough, shortness of breath will develop within 2-14 days following exposure and leads to severe complications like pneumonia, kidney failure, even death.

Recently genomic sequence of coronavirus was relatively similar to that of bat genome. Coronavirus infection in humans is mild in intensity whereas beta(β) coronavirus infection of either the “severe acute respiratory syndrome coronavirus (SARS-CoV)” or the “Middle East respiratory syndrome coronavirus (MERS-CoV)” emerged higher mortality rates.

**Suspected case**

Patients having acute respiratory syndrome-like “cough, shortness of breath” and a recent travel record (in a community transformation area of COVID-19)

OR

A person has been contacted to a COVID positive patient.

OR

Patients have acute respiratory syndrome with the absence of an alternative diagnosis.

**Probable case**

A suspected case for whom investigations could not be operated (any reason).

**Confirmed case**

An individual with positive COVID laboratory findings irrespective of clinical signs and symptoms World Health Organization (2020).

Several pathophysiologic information can be focused on the association between DM and COVID 19 condition. The first line of defence, i.e. innate immunity, is compromised in uncontrolled DM.
Thus my article aims to explain the correlation between COVID 19 and DM.

**Pathophysiology of SARS COV 2**

The lung contains sacks of alveoli where gaseous exchange takes place. Alveoli are made up of alveolar cells. SAR CoV-2 mainly invades alveolar epithelial cells resulting in epithelial symptoms. The virus target and binds to Angiotensin-Converting Enzyme II (ACE II) (receptor and surface proteins). By the process of endocytosis or direct fusion, the virus enters the host membrane. By entering the host cell virus encodes themselves and its RNA genomes invade into the cell cytoplasm. As the virus has single-strand RNA, it can directly produce protein and new genome in the cytoplasm by attaching to the host ribosome where it translates the viral RNA to make proteins that will make RNA polymerase. It will read the virus RNA to make a negative RNA strand. The negative again is read by RNA polymerase, and a positive RNA strand/strands are made. These positive RNA strands are read by endoplasmic reticulum to make structural component of the virus. These structural proteins are then transferred to the Golgi apparatus, in which a new virus is formed. These are then released from the host cell by exocytosis through secretory vesicles (Figure 2).

Replication of viruses occurs in alveolar cells that initiate the inflammatory response. These injured inflammatory cells release interferons, cytokines and intracellular components. Alveolar macrophages detect the cell injury and also response to cytokines that are released by damaged alveolar cells the alveolar macrophages then release some inflammatory infiltrate like “tumour-necrosis factor (TNF)-a, interleukin (IL) 1, IL 6, IL 8 and chemokines”. These inflammatory processes stimulate nerve endings which is responsible for the initiation of the cough reflex. Other inflammatory cells like neutrophils and monocytes reach the injured site, increasing the vascular permeability, thus causing interstitial oedema and subsequently pulmonary oedema in the lung alveoli. This leads to dyspnoea and hypoxemia (low oxygen level in blood), damaged endothelial cells release arachidonic acid metabolites (leukotrienes, prostaglandins). This causes bronchoconstriction leading to hypoxemia. Prostaglandins, TNF a, IL 1, IL 6 causes fever (a prominent feature of COVID-19). Due to hypoxia, tachypnoea, and tachycardia occur (Muniyappa and Gubbi, 2020).

“In the summary accumulation of fluid, the injured lung, ventilation-perfusion mismatch and hypoxemia is called ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS), which is the leading source of COVID-19.”

**Diabetes as a Risk Factor**

“Diabetes is a chronic inflammatory condition characterized by multiple metabolic and vascular abnormalities that can affect our response to pathogens”. At the beginning of 2000 diabetes has been expressed for the two prior coronaviruses (CoV) infections, SARS affecting beyond 8000 population, mainly in Asia and MERS in 2012 affecting 2000 above individuals, mainly in Saudi Arabia (Bloomgarden, 2020). Diabetes is a pandemic, non-communicable disease affecting more than half a billion people worldwide (Maddaloni and Buzzetti, 2020). Human pathogenic coronaviruses “SARS-CoV” and “SARS-CoV-2” attached to their target cells via “Angiotensin-Converting Enzyme 2 (ACE2)”, which is manifested by epithelial cells of the intestine, kidney, lung and blood vessels. The ACE2 expression is significantly increased in patients with diabetes type 1 or 2, who are on ACE inhibitors and angiotensin II type I receptor blockers (ARBs). This information suggests higher ACE2 expression with ACE inhibitors and ARB’s management (Fang et al., 2020). Thiazolidinediones and ibuprofen also increase ACE2 expression. In Diabetes Mellitus (DM), the ACE2 expression is reduced to predisposes to serious lung injury and ARDS with coronavirus disease. ACE2 receptors act as communication for SARS-CoV-2 to gain entry into the host pneumocytes by the process of endocytosis. ACE2- stimulating drugs helps SARS-CoV-2 to enter into a host cell and accordingly causes serious and more fatal disease. DM is exaggerated by pro-inflammatory cytokines response, mainly IL-1,6 and TNF-α, in the unavailability of proper immunostimulation; this can intensify complications like ARDS in COVID-19 patients.
Additionally, a recent study concluded that serious and hypercritical. COVID-19 confirmed a person has an increased risk of hypokalemia that occur from wasting renal potassium. Increased aldosterone secretion, reduced degradation of angiotensin-II, and successive higher urinary potassium loss can be illustrated by downregulation of ACE 2 receptor. Indeed initial standardization of serum potassium added as useful guidance to prevent COVID-19. Thus, the ACE2 receptor is not able to protect the lung from the novel coronavirus as the enzymes get destroyed by the virus (Pal and Bhansali, 2020). Dipeptidyl peptidase-4 (DPP-4) is identified as the primary receptor of MERS-CoV. In the case of diabetes, DPP-4 inhibitors are used worldwide, So the correlation between DPP-4 and SARS-CoV-2 should be investigated, which can provide a potential protective effect in drugs against COVID-19.

Proven Evidence
The first study published including 41 cases COVID infected people in Wuhan reported 32% was associated with other diseases including diabetes (20%), cardiovascular disease (15%) and hypertension (15%). Another study of 99 infected persons showed 52% of increased glycemic levels. A retrospective study including 138 COVID patients published on February 7th 2020 reported 64 (46.4%) had some underlying disease like diabetes 10% (14/138) and 22.2% (8/36) diabetic patients wherein intensive care unit (ICU). Among critically ill patients, diabetes has a mortality rate of 77.7% (7/9) (Wang et al., 2020). Diabetes prevalence of 10.3% was seen in a meta-analysis with 12 studies and 2,108 Chinese patients, which shows the equal prevalence of 10.9% as reported in 2013.

Complications
Diabetes ketoacidosis
Diabetic ketoacidosis (DKA) occurs when a diabetic person does not have sufficient insulin to deal with the glycemic level. The body needs energy by breaking down the fats, resulting in a buildup of ketones in the blood, which can easily cause serious health problems. So, DKA requires emergency medical attention.

Pneumonia
Inflammation of air sacs of lung referred to as pneumonia, people with diabetes having pneumonia are more significant risk of developing COVID-19. People with diabetes should undergo pneumococcal and annual influenza vaccinations.

Dehydration
COVID-19 patients having co-morbidity like diabetes can lose additional fluid because of fever, which can lead to dehydration, that requires intravenous fluids.

High blood sugar
The stress response is increased in the body, which increases glucose production. The body needs extra insulin at this time. So, patients with diabetes should routinely check their blood glucose level.

Methods of Prevention in Diabetic Patients with COVID
1. If a diabetic person develops any symptoms like fever, cough, dyspnoea, the health experts need to be reported.
2. The affected person should isolate themselves for 14 days.
3. Mild symptomatic cases should be treated at home only. Prevention should be done.
4. Blood glucose and urinary ketones should routinely be checked. Persistent vary in dosage and correction of bolus may be needed to sustain average glycemic level.
5. Anti-hyperglycemic agents should be avoided as that leads to volume depletion or hypoglycemia. Oral anti-diabetic drug doses may need to be reduced. The patients should follow frequent monitoring of blood glucose, sick day guidelines and drug adjustment.
6. Sodium-glucose cotransporter-2 inhibitors and metformin need to be stopped. Patients having severe disease require continuous monitoring of blood glucose level.
7. In the case of hospitalized patients, insulin is a preferred drug of choice (Gupta et al., 2020).

Clinical Management of Patients with COVID 19 and Diabetes
Till now no proven drug or vaccine is invented for COVID 19. Several studies are undergoing to evaluate the proper drug regimen for the treatment of coronavirus, including tocilizumab, remdesivir, ribavirin, lopinavir/ritonavir, interferon, arbidol, chloroquine phosphate, among others. However, the effectiveness of chloroquine in the treatment of COVID 19 is not clear, but in an in-vitro study, it was used for controlling SARS-CoV2 infection (Gao et al., 2020). A Chinese clinical trial including 100 patients showed that chloroquine is better in shortening the disease course inhibiting exacerbation of pneumonia, improving lung imaging findings and promoting a virus-negative
conversion. Some studies stated that hydroxychloroquine improves glycemic control in diabetic patients. As chloroquine/hydroxychloroquine affects glucose metabolism, caution should be taken in dose adjustment of the oral anti-diabetic drug to prevent a hypoglycaemic state in diabetic and COVID patients (Rekedal et al., 2010).

As per now, no data regarding the appropriate management of diabetic patients with SARS-CoV2 and COVID 19 are available. So continuous monitoring of blood glucose level and proper drug interaction can prevent in worsening of the symptoms. A multidisciplinary team approach, including infectologists, pulmonologists, nutritionists, endocrinologists, psychologists, and exercise rehabilitation specialists, may be necessary during the prolonged hospitalization periods and speedy recovery. Special care should be taken on diabetic related heart complicated patients as they are at higher risk for COVID 19 infection (Gerstein et al., 2002).

CONCLUSION

In India, the prevalence of diabetes is 7.3%. We are now at a critical stage of pandemic COVID-19. Diabetic patients for treatment of COVID-19 are at higher risk of complications and increased risk to hospitalization even death. Patients who have diabetes demand comprehensive care to lower the probability of mortality. Meanwhile, we must pay attention to the lifestyle and glucose management of patients with diabetes outside the hospital and provide them with precise medical services. Furthermore, we need to establish the genetic, molecular and immune mechanism that could explain the interplay between COVID and diabetes.

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Conflict of Interest

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