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A Review on the Association of COVID 19 and Diabetes

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ABSTRACT

The COVID-19 disease caused by the coronavirus has emerged as one of the most important pandemics of the century posing a significant threat to humans. The current data available reports that diabetic patients have higher risk for contracting the infection by SARS-CoV-2 in comparison to the general population. Diabetes is a predisposing factor that often aggravates the development of severe as well as the critical forms of the disease COVID-19 characterized by the need for, intensive hospitalization, mechanical ventilation, and increased mortality rates. The correlation of diabetes with the development of severe as well as critical forms of COVID-19 along with its prognostic impact is still under investigation. The people with existing conditions of diabetes should be considered as a susceptible group for the aggravated forms of COVID-19 disease and the strategies for safeguarding the health of the patients debilitated by diabetes in this ongoing pandemic is a requirement of the hour. This review provides a bird's eye view of the available literature reporting the association of COVID-19 in diabetic people and its prevention.

INTRODUCTION:

The emergence of the novel "Coronavirus disease 2019" (COVID-19) as a pandemic has posed significant challenges to both the patients, as well as frontline healthcare, who works in the maintenance of health as well as in the prevention of the risks that are related to several pre-existing conditions of chronic nature. It all started in December 2019 when a novel beta coronavirus leading to acute respiratory syndrome was identified at Wuhan in China. The gene sequencing of the samples of the lower respiratory tract in the infected patients made the characterization of this new virus possible and has lead to its identification to be referred to as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease was named the COVID-19 by the World Health Organization (WHO) in February 2020 and declared as a pandemic on March 12, 2020 (1,2). COVID-19 is caused by the etiological agent named SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) that has infected around 160 countries globally. The transmission of the virus is mainly by the respiratory droplets that are released by the infected people(3) and it has an incubation time of 6–8 days on average which is followed by about 1–2 weeks of associated symptoms. A wide variety of clinical manifestations have been reported comprising throat pain, cough, lack of appetite, fever, loss of taste and smell, myalgia, and respiratory tract associated problems like pneumonia and failure in respiratory functions in severe cases. In worst cases, causes death (4). A significant proportion of asymptomatic or mild cases being infected have been observed(5–7).

Following the threat created by the ongoing pandemic, the knowledge on COVID-19 is on a progressive increase. Diabetes has been reported to be prevalent in COVID-19 patients. The characteristic contribution of diabetes to the patients in the development of severe and critical forms of COVID-19 along with the prognostic impact on the course of COVID-19 is still under research. The People harboring a pre-existing condition of diabetes are considered to be at significant proximity to the disease when compared to the people with infections that resulted due to perturbations in their innate immunity. While the humoral immunity remains unaffected relatively, the people harboring diabetes have been reported to possess impaired phagocytosis, neutrophil chemotaxis, cell-mediated immunity, and bactericidal activity. As the overall death is associated with cardiovascular is on the declining side, among diabetic people, pneumonia is increasingly causing death. Whether diabetic people are highly susceptible to COVID-19 is yet to be research but perceptions exist that the risk can be higher for both infection and progress of severity(8).This review discusses the researches in patients with diabetes and its impact on contracting COVID-19.

PATHOGENESIS OF SARS-COV-2

The Coronaviruses are considered to be single-stranded, positive-sense RNA containing viruses, possessing a 28 to 32 kb sized genome that is enclosed by capsid that is constituted by the nucleocapsid protein (N). The helical structure is enveloped and is found in association with three structural proteins comprising of the envelope protein (E) and membrane protein (M) involved virion assembly and spike protein (S) mediating access into the host cells(9,10). The S protein is said to be further characterized by the presence of a receptor-binding domain (RBD) S1 subunit facilitating the binding of the host angiotensin converting enzyme 2 (ACE2) receptor for SARS-CoV and SARS-CoV-2, and an S2 required for fusion of the membrane (11–13). The RBD of MERS-CoV is said to attach to the susceptible cells through the enzyme dipeptidyl peptidase 4 (DPP4) rather than the ACE2 (14). A study has demonstrated the presence of specified structural alterations recently on the RBD that is specific for the SARS-CoV-2 has resulted in the enhancement of the affinity of ACE2 receptor binding (15). The Host cell factors are further involved in the mediation of the viral entry by the employment of two serine proteases namely the Transmembrane protease, serine 2 (TMPRSS2) as well as the furin which is involved in the activation of the S protein for the fusion of the membrane through the cleavages as well as in the assistance in the viral processing, respectively (16). Once the infection with SARS-CoV-2 starts a complicated yet an orchestrated response of the innate as well as the adaptive immune system begins which clinically correlates to the 3 proposed phases characterized by viremia, a short acute phase followed by a phase of recovery (17). The innate immune response is constituted by the identification of a virus -associated molecular pattern by the employed pattern recognition receptors like the Toll-like receptors which lead to the expression of a type I interferon and factors of inflammation that activate the defense mechanism of the macrophages and the natural killer cells for clearing the pathogen. The Dendritic cells are involved in the bridging of the innate as well as the adaptive immune response by the activation of the B-lymphocytes and T –lymphocytes (9). The adaptive immune system is considered to be crucial in the controlling of the persistence of infection and is characterized by the production of the monoclonal antibodies with a neutralizing effect on the glycoproteins of the viral envelope by the CD4+ T cells and in the destruction of the virus-infected cells due to the toxic nature of the CD8+ T cells (9). In the case of acute phase infection, the SARS-CoV is capable of invading the CD4+ and CD8+ cells leading to their apoptosis as well as lymphocytopenia,

which is considered to be a marker that is often associated with the severity of the disease (11,16).

ASSOCIATION OF COVID 19 AND DIABETES

Diabetes and infections

Both types of diabetes have been reported to increase the susceptibility of an individual to the infections and its aggravations (17). The presence of dysfunction of the Neutrophils, reductions in the T cell responses, and disordered nature of the humoral immunity are considered to contribute to the disease (18), and bacterial as well as the viral respiratory tract infections are said to be common particularly (19). Diabetes is associated with an increase in morbidity as well as mortality due to pneumonia, and hyperglycaemia upon admission for the cases of pneumonia (>11 mmol/l) (20). In the earlier cases of the SARS epidemic that occurred in 2002/2003, diabetes was considered to be an independent predictive factor for the risk of death (21) and a similar association of diabetes with the Middle East respiratory syndrome-coronavirus (MERS-CoV) that caused the epidemic outbreak in 2012 (22).

Diabetes as a risk factor

Diabetes is a risk factor that can potentially end up making the patient require hospitalization and also increase the risk of mortality in COVID-19 infection. The presence of Diabetes and other debilitating complications can often result in the increase of the risk of morbidity as well as mortality that occurs during acute infections due to the suppression of the innate as well as the humoral immunity. The glycated hemoglobin (HbA1c) >9 % have often been assumed to lead to increased risk of about 60 % for the requirement for hospitalization and other pneumonia-related complication in case of bacterial based infection (23). Past viral pandemics have said be witnesses for the association of diabetes to an increased level of morbidity and mortality. Diabetes was earlier linked to the complications and death in the Severe Acute Respiratory Syndrome (SARS-CoV-1) outbreak that occurred during 2002-2003 (21). Similarly, diabetes was found to triple the hospitalization rate and has also quadrupled the need for intensive care unit (ICU) enrollment during the outbreak of Influenza A (H1N1) infection that occurred in the year 2009 (24). Diabetes was found to be prevalent in about 50% of the population in the 2012 outbreak of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (25) in comparison to the overall population. The death rate was found to be 35 % risk in diabetic patients with MERS (26,27).

Diabetes and COVID-19

Diabetic people need a timely integrated intervention strategy for the prevention of disease. Enhancement in self-management, healthcare services as well as public health measures needs to be implemented (Fig. No.1). Diabetes mellitus is considered a leading agent responsible for poor prognosis in COVID-19 patients (Fig. No. 2) (28). The evaluator investigations carried on the pneumonia cases by unknown origin revealed initially in Wuhan and patients with exposure to the Huanan seafood market before Jan 1, 2020, that around 20 % of them had diabetes (29). Similarly, among the 1099 COVID-19 patients subjected to study by the research carried out by Guan et al. revealed that about 7.4 % of the sample were diabetic and this percentage increased to 16.2 % with the patients with severe disease (5); the further investigation revealed that about 35.8 % of patients in the need of ICU enrollment, ventilation, and the death cases were diabetic. Data from studies done in Italy revealed that above two-thirds of the COVID-19 patients who died suffered from diabetes (30). In summary, diabetes is a frequent risk factor in COVID-19 patients. In COVID-19 patients, the prevalence of diabetes was found to be two times higher in the ICU/severe cases when compared to the non-ICU/severe cases. The diagnosis of diabetes mellitus in a particular cohort of patients diagnosed with COVID-19 infection was revealed to evidence a sub-group of patients at a 2.26-fold higher risk of morbidity and mortality (31). Additionally, the patients who were obese, as well as glucose intolerant, were found to be particularly susceptible to the COVID-19 disease (32). Unfortunately, no availability of data on anti-diabetic medicines and homeostasis of glucose in COVID-19 patients has been reported. The altered glucose homeostasis in severe cases of SARS pneumonia has been reported to be the main factor leading to poor prognosis as well as death. The COVID-19 induced diabetes by the augmentation of insulin resistance by a direct or indirect action (21); supporting this view, the previously established studies have reported that ACE2 can serve as a therapeutic target for the amelioration of microcirculation in the islet (33), and the ACE2 is also expressed by the pancreatic beta cells (34).

Figure No. 1: COVID-19 prevents infection in people with diabetes (35)**.**

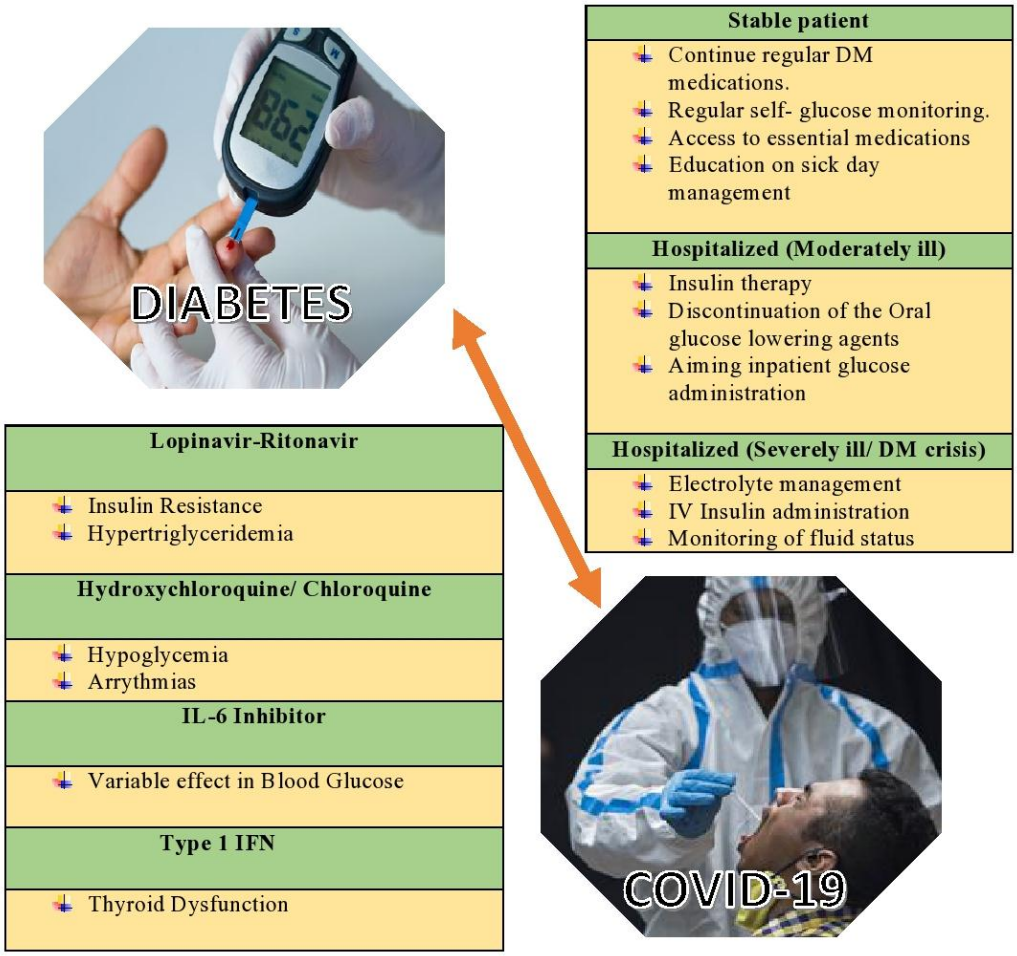

Figure No. 2: Inter-relationship between COVID-19 and Diabetes(28)

Diabetes in COVID-19 Patients:

The Emergence of researches and reports obtained have suggested that the COVID-19 was found to be common in the patients debilitated by diabetes, hypertension as well as cardiovascular disease (CVD), despite the prevalence rate found were varied in different researches as well as in the global data. In the case of pooled data obtained from the 10 Chinese studies (n=2209) depending on the analysis of health status in the patients with COVID-19, Singh et al., in their study in 2020 reported a peaked prevalence of diabetes, hypertension as well as cardiovascular disease in about 21 %, 11 %, and 7 % patients, respectively. Similarly, the meta-analysis of 8 trials was found to 46,248 COVID-19 patients (36), Yang et al., 2020 has reported the prevalence of hypertension, diabetes, and CVD in 8%, 17%, and 5% respectively, in the patients with COVID-19 (37). Similarly, the Epidemiology Working Group of the Chinese Center for Disease Control and Prevention has investigated about 20,982 patients with COVID-19 who exhibited hypertension, diabetes, and CVD that were associated with nearly 13%, 5%, and 4% of patients respectively (38). On the contrary, an Italian study done by Onder et al. reported diabetes in nearly 36% of the cases, while CVD in nearly 43% of the 355 patients who were admitted with COVID-19 (39). Similarly, in a small study enrolling 24 patients in the United States, Bhatraju et al. (2020) diabetes was reported to be associated with 58.0% patients who had COVID-19 (40). Another study from the COVID 19 surveillance group of Italy (n=481) revealed that about 34% of patients with COVID- 19 were diabetes, a reported prevalence of 11% from the data of 7,162 COVID-19 patients were recorded by the response team from the Centers for Disease Control and Prevention (CDC), USA (41).

The severity of COVID-19 in patients with diabetes

To date, about eight meta-analyses have been carried out for assessing the severity of COVID-19 in patients debilitated by hypertension, diabetes, etc. While 5 of this analysis that calculated either a relative risk (RR) or an odds ratio (OR) with significant 2- to 3-fold increase (Chen et al.,2020 OR 2.67; 95% CI, 1.91–3.74; Wang et al.,2017 OR 2.47; 95% CI, 1.67–3.66) (42,43) in severity; 2 meta-analysis have only revealed a non-significant trend (Li et al., RR 2.21; 95% CI 0.88– 5.57; Yang et al., OR 2.07; 95% CI, 0.89-4.82) (37,44). In one meta-analysis that was based on the pooled data from a conducted 6 studies, Hu et al. 2020 significantly reported a higher percentage of critical cases (44.5%; 95% CI, 27.0–61.9%) in diabetic patients with COVID-19. However, interpretation required certain caution. First,

there was a lack of uniformity in the definition of severity across the studies included for meta-analyses and varied in the study (45). The severity in COVID- 19 disease has been defined by the World Health Organization, if they follow a pattern comprised of: Blood oxygen saturation ≤93%, Respiratory frequency ≤30/minute, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within a period of 24–48 h; while the criteria defined by Centre for Chronic Disease Control (CCDC) involves hypoxia, dyspnea, >50% lung involvement within 24–48 h (38). Second, many mentioned earlier studies with overlapped data have been included in the meta-analyses. Third, all the meta-analyses had calculated the risk or odds ratios of severity, on comparison of the diabetic patients requiring mechanical ventilation or intensive care unit (ICU) admission with the patient with diabetes without need for hospitalization. Thus, it was found that none of these meta-analyses were able to calculate the risk of severity between the patients with and without diabetes cohorts. Therefore, the conclusion obtained from these meta-analyses was able to suggest that the patients having severe COVID-19 were more likely to have diabetes. Fourth, the comorbidities like diabetes were likely to increase the severity such as CVD, obesity, hypertension, chronic kidney disease (CKD).

ACE2, SARS-CoV-2, and diabetes

The receptor binding domain of the SARS-CoV-2 virus employs the host ACE2 (angiotensin converting enzyme 2) to fuse the viral as well as the host cell membranes (46). The ACE2 is considered to be a type 1 integral glycoprotein highly expressed in the case of the endothelium, kidney, lungs, and heart (47). The ACE2 is involved in the conversion of angiotensin I and II to angiotensin-(1–9) and angiotensin-(1– 7), respectively. They have anti-inflammatory as well as cardioprotective influential properties. Based on the animal studies, the expression of ACE2 is in low levels in normal conditions in the lung tissues (48) but is upregulated when there is an injury to the lung (49). Certain animal studies (50) and pilot studies performed on humans (51) have suggested the potential therapeutic role of the ACE2 against acute inflammatory lung injury. Furthermore, it has been found that the SARS downregulates the expression of ACE2 in the infected cells and has been assumed to perpetuate the inflammatory injury (52). In 2003, the patients with SARS possessed higher rates of hyperglycaemia upon admission than the non-SARS pneumonia patients which was irrespective of their status of pre-morbid glycaemia, disease severity, or the utilization of glucocorticoid. Subsequently, the SARS-CoV virus was found to exhibit binding to the ACE2 in the case of pancreatic islet cells, damaging them and leading to acute hyperglycaemia with

a possible contribution to an increased mortality rate, even among the non-diabetic people (21). A similar mechanism may be responsible for the operation in the SARS-CoV-2 infection which contributes to hyperglycaemia due to excessive complications as well as increased mortality rate.

TREATMENT OF DIABETES DURING COVID 19 INFECTION:

Improper control on the glycaemic level is considered to be a risk factor for the threat caused by serious infections and other adverse results (53). The major issue is that the infections caused by improper control of the glycaemic levels and the treatment for the condition of hyperglycaemia are considered to be difficult during the disease owing to improper food intake, fever, and administration of drugs like glucocorticoids in the patients possessing respiratory issues. The maintenance of optimal glycaemic control requires the frequent monitoring of blood glucose and the continuous alterations in the antidiabetic treatment after the measurement of the existing glucose levels. The drug Dipeptidyl peptidase 4 (DPP-4) inhibitors and Linagliptin can be employed in patients with an impaired kidney function without posing the risk of hypoglycaemia. Sulphonylureas may be responsible for inducing hypoglycaemia in patients with a low-calorie food intake. In many type 2 diabetes infected patients insulin treatment is generally preferred and has to be initiated but is considered too complicated due to limited time for the instruction and insulin titration. Patients who were previously treated with basal insulin require fast-acting bolus insulin for the correction of hyperglycaemia. The Hospitals possess both experiences as well as algorithms for the treatment of patients throughout the intercurrent disease, but the time consumed in the achieving of a labile glycaemic control is considered to be a major problem in the situations where the time is considered less. In the case of patients with type 1 insulin doses must be titrated by employing the frequent monitoring of glucose and ketone bodies for preventing hypoglycaemia in patients that have decreased food intake and the addition of fast-acting insulin is required for avoiding severe hyperglycaemia and ketoacidosis.

Prophylaxis for preventing COVID-19 in diabetic people:

General prophylactic measures are considered to be mandatory for the patients and other people involved in the frontline for the prevention of contracting the COVID-19. There are specific concerns about some of these agents for people with diabetes (Table No. 1).

Table 1: Diabetes patients using proposed therapeutic agents for COVID-19 [38]

Therapeutic agent	People with diabetes
Chloroquine/ hydroxychloroquine	✓ Hypoglycaemia: must be used with precautions when administered along insulin and insulin secretagogues. ✓ Leads to the prolonging of QT interval: must be carefully administered to people with other comorbidities.
Lopinavir/ritonavir	✓ Can lead to deterioration of glycaemic control resulting in Hyperglycaemia ✓ Interaction with statins has the potential to increase the risk of acquiring hepatic and muscle toxicity
Glucocorticoids	✓ Hyperglycaemia ✓ Increases susceptibility to the secondary bacterial infection due to lowered immunity
Remdesivir	✓ Hepatotoxicity is a complication when used in combinations with statins and in pre-existing fatty liver disease

No efficient drug has been approved so far for the pre-or post-exposure chemoprophylaxis and hence evidences from randomised clinical trials are required at this hour of pandemic. The Chloroquine was experimented to demonstrate antiviral activity against five out of seven well known human coronaviruses including the COVID-19 causing virus (54) and was found to be a leading candidate for the prophylactic application (55). Various ongoing trials in China encouraged preliminary findings (56). Several trials have been in development such as the PHYDRATrial (NCT04318015) and COPCOV study (NCT04303507). Diabetic patients have also been enrolled in these studies. A cluster-randomized controlled trial has been designed for the evaluation of the efficiency of lopinavir/ritonavir in the postexposure prophylaxis (NCT04321174) (55). Table No. 2 shows the possible benefits of anti-diabetic agents in patients with diabetes and COVID-19.

Table 2: Benefits of anti-diabetic drugs in diabetes patients with COVID-19[61-65]

Anti-diabetic drugs	Benefits in experimental studies	Proposed benefits in COVID-19 patients
Metformin	Protective immunity in pneumonia cases	confers cardiovascular benefits
Pioglitazone	Leads to reduction of markers like proinflammatory cytokines, leads in reducing lung injury	Reduces proinflammatory cytokines thereby decreasing cytokine storm induced damage
DPP-4 inhibitors	Antibodies to DPP4 exhibited inhibition of MERS-CoV in in vitro studies. No effect of DPP- 4 inhibitors.	Confers Anti-inflammatory activity. Confers benefit if SARS-Cov-2 employs DPP4 as entry receptor, if mutated.
SGLT-2 inhibitors	Confers favorable effect on the reduction in the oxidative stress, autophagy as well as the inflammation	Confers cardio-renal outcomes of value protective.
Insulin	Reduces inflammatory markers	Anti-inflammatory and positive anabolic effects render insulin as a preferred candidate for any infections

Vaccines

With the publishing of the genome sequence of SARS-CoV-2, various candidates for vaccines are in the developmental process. The advanced candidates have been transferred for clinical trials and numerous other vaccines are at the pre-clinical stage. Most of the candidate vaccines were designed to induce the production of antibodies against the viral S protein or RBD. Multiple platforms have been subjected to development. The mRNA-based vaccines involve mRNA encoding a protein antigen. The DNA vaccines that encode for the S

protein of the SARS-CoV and MERS-CoV have elicited T cells and antibody responses, as well as the protective immunity in the mouse model and human studies (57,58). An inactivated vaccine candidate has displayed good cross-neutralization to different strains of COVID-19 and has received approval for human trials. A candidate vaccine called Ad5-nCoV encoding S protein of SARS-CoV-2 has been demonstrated safe for administration to humans and for proceeding to a Phase II clinical trial in the regions of China. A DNA vaccine candidate called INO-4800 targetting the S protein of SARS-CoV-2 is developing (59). A viral vector vaccine named ChA-dOx1 nCoV-19 composed of a nonreplicating adenovirus vector of chimpanzee and genetic sequence for the synthesis of S protein has been designed (60).

CONCLUSION

COVID-19 has been found to have rapid spreading capacity since its identification in Wuhan and has exhibited a wide spectrum of severity in the infection cases. The early isolation, diagnosis, and management of the disease can contribute collectively to the establishment of control over the disease and the disease impact. Diabetes and other complicated conditions were found to be significant predictors of the risk and level of morbidity and mortality in COVID-19. Taking together all the aspects, diabetic patients are considered to be a high-risk group to be treated and require special intervention strategies for reducing the serious forms of COVID19 marked by an increased requirement for hospitalization. Patients characterized by existing conditions of diabetes must follow the general prophylactic measures without any relaxations for avoiding infection with COVID-19. The findings from multiple studies call for an enhanced focus on future prevention strategies and immunization programs in the diabetic patient in addition to the conventional social distancing and self-isolation practices.

Declaration of competing interest

The authors have declared no conflict of interest.

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