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Review Article

COVID 19 and Diabetes: Possible Effects of Pharmacological Agents during the Course of Infection in Diabetes?

Amit Kumar Das*

Diabetologist, Shree Hospital and Maternity, Muzaffarpur, Bihar, India

***Corresponding Author:** Amit Kumar Das, Diabetologist, Shree Hospital and Maternity, Muzaffarpur, Bihar, India.

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Abstract

In patients infected with COVID-19 most frequently reported comorbidities is diabetes. Severe complications including multi-organ failure and Adult Respiratory Distress Syndrome are at high risk for patients with uncontrolled diabetes. The ongoing global COVID-19 pandemic forces both the patients of diabetes and the health care providers to face several challenges for diagnosis and management of acute complications of diabetes. This short review is focused on the link between COVID-19 and diabetes and on some open questions emerging and also discussed effects of commonly used drugs in patients with diabetes on the course of COVID-19 infection.

Keywords: *Diabetes; SARS-Cov-2; COVID-19; ACE2; Diabetes Therapy*

COVID-19 and diabetes: The burden

Around the world infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which lead to Coronavirus disease 2019 (COVID-19), has abruptly reached pandemic proportions. At the time of these article is written the number of confirmed cases of COVID-19 worldwide has reaches to more than a million and has dramatically increasing day by day [1]. Acute respiratory distress syndrome (ARDS), severe pneumonia and multi-organ failure may develop as mild to moderate clinical features in majority of COVID-19 patients which leading to high death rate [2]. In COVID-19 prevalence and prognosis marked sex differences have emerged notably [3]. Except under the age of 50 years males is reported to be significantly higher in age-specific risk of disease than in females. Even among all age ranges males are having at least two fold higher in age-specific risks of death and hospitalization than in females [4]. It has already established that patients who have comorbidity like diabetes, dyslipidemia, hypertension and cardiovascular disease (CVD) are having higher chance of getting infected as well as more prone to experience severe form of the COVID 19 [5]. As per Onder G., *et al*. in the 60 - 69-year age group the fatality rate by age groups displays very similar patterns and rising consistently Amon all the countries despite overall mortality considerably varies globally [6]. It has already well established that the comorbidity triggers SARS-CoV-2 and further increases mortality and a greater number of comorbidities also correlated with poorer clinical outcomes [7].

Clinical manifestations of COVID-19 according to the latest reports are heterogeneous in nature [8]. From various studies it has been concluded that at least one comorbidity were reported 20 - 51% of patients who were admitted in hospitals with COVID 19 and most common comorbidities were diabetes (10 - 20%), hypertension (10 - 15%) and other cardiovascular and cerebrovascular diseases (7 -

40%)[9-11]. Even Onder G., *et al.* has confirms that presence of diabetes as comorbidity can be as high as 35.5% [6]. As per International Diabetes Federation (IDF), in 2019 around 4.2 million deaths attributed to diabetes and its complications [12] 65% of diabetic patients are over 65 years old [13]. Severity of COVID-19 and diabetes have significant correlation which also confirmed by a meta-analysis of nine studies from China (n = 1936) (OR, 2.67, 95% CI; 1.91 - 3.74; p < 0.01) [14]. Even by another study report from Chinese Centre for Disease Control on 44,672 patients of COVID-19 had confirmed that case fatality rate was 7.3% in patients with diabetes as opposed to 2.3% in those without diabetes [15]. COVID-19 and diabetes are two pandemics with extremely different connotations currently have dramatic impact on economic health resources and global mortality.

This short review is focused on the link between COVID-19 and diabetes and on some open questions emerging and also discussed effects of commonly used drugs in patients with diabetes on the course of COVID-19 infection.

Is there a link between diabetes and severity OF SARS-CoV-2 infection: What lies beneath

Type 2 diabetes mellitus (T2DM) specially among elderly (> 60 years of age) lower respiratory tract infections are very common in nature [16]. Susceptibility to SARS-CoV-2 infection significantly increase during uncontrolled diabetes with worse COVID-19 progression and outcomes has been observed in this high risked patients [17]. Impaired immune response and increased levels of pro-inflammatory markers are suspected to be crucially involved in diabetic patients with COVID-19. Cytokine storm namely TNF-α, IL-6, IL-8, IL-2 receptor is trigger by surge in pro-inflammatory markers such as C-reactive protein, ferritin, leukocyte, pro-calcitonin and circulating cytokines in diabetic patients with severe COVID-19 compared to patients without diabetes [18]. It has been long hypothesised by few highly rated article that presence of poorly controlled glycaemia and possibly due to impaired lymphocyte, monocyte/macrophage and neutrophil function, an altered immune response developed in diabetic patients [19,20]. Coagulation abnormalities in the course of the SARS-CoV-2 infection might be more prone to develop in patients with diabetes compared to patients without diabetes as severe forms of COVID-19 were also present with concentrations of D-dimer and fibrinogen which also known to be significantly associated with worse prognosis [18,21].

Innate and adaptive immune response due to the poor glycaemic control during diabetes further increase the chance of potential secondary bacterial infection in the lungs [22,23]. Strong association between type 2 diabetes, abnormal secretion of adipokines and cytokines like interferon and TNF-$\boldsymbol{\alpha}$ and as well as obesity may further impair immunity and predispose to severe infection [24]. Virulence of SARS CoV-2 has been postulated to increase due to the raise in plasminogen levels in patients with diabetes [25]. Furin involved in the entry of coronaviruses into the host cell which basically is a type-1 membrane bound protease, is increased because of uncontrolled diabetes and mainly responsible for rapid increase in viral replication during this co-morbid condition [26].

In pathogenesis of COVID-19 role of angiotensin converting enzyme 2 (ACE2) receptor is intriguing. By binding to ACE2 receptor SARS CoV-2 enters in to the host cell and this involves in production of several protein and enzymes [27]. Down regulation of ACE2 in diabetes are evidences by several research and may predispose to more severe lung injury [28]. Compared to survivors, non-survivors also had high prevalence of overweight and obesity (88% versus 19%).

CVD, Diabetes and ACE2 modulation: Unanswered questions on hypertension and lipid lowering drugs

In patients with T2D compare to non-diabetic patients the risk of developing CVD is 2- to fivefold higher mainly due to diabetes-related coronary atherosclerosis [29]. Nearly 12% of patients who has clinical features of COVID-19 may impacted with cardiovascular damage [30]. Destabilization of coronary plaques and he direct viral damage re suspected to play a consistent role for this complication. In diabetic patients with COVID-19 the poorer outcomes observed may therefore contribute by myocardial injury [31].

Following the identification of ACE2 as the receptor for SARS CoV-2 there has been a lot of interest in ACE inhibitors and ARBs. Cellular levels of ACE2 increased by ACE inhibitors and ARBs mainly by inhibiting the conversion of angiotensin 1 to angiotensin 2. Viral binding

and entry into cell could theoretically increase by increase in ACE2 expression. Cytosolic pH which could reduce as a result of increased activity of ACE2 mainly because of increased angiotensin 1 - 7 and reduced angiotensin 2 as a result of ACE inhibition, which could result in more favourable environment for viral endocytosis [32]. limited availability of the serine protease TMPRSS2 which is required for viral binding is the main reason that despite Increased ACE2, it might not result in increased viral entry [33]. Vasodilatory and antifibrotic effects of angiotensin 1 - 7 and increased ACE2 have been shown to be protective against lung injury in animals [34]. Ebola virus infection mortality was reported to reduce by treatment with ARBs [35]. In patients with COVID-19 use of ACE inhibitors and ARBs not satisfactorily demonstrated by any controlled studies, thus there is no conclusive clinical studies. European Society of Hypertension, European Society of Cardiology Council on Hypertension and American Heart Association because of lack of evidence for either benefit or harm advise continuing with ACE inhibitors and ARBs in case a patient develops COVID-19 [36].

High rate of lipid alterations in blood serum also associated with type 2 diabetes mellitus (T2DM) and where statin is the first line treatment option. It has been observed that ACE2 protein expression in the heart and in the kidney were increased by atorvastatin rabbits with atherosclerosis [37].

Obesity was already reported to be a risk factor of poor prognosis in patients with COVID-19 which also a major risk factor for incident T2DM. Compare to non-critical patients of COVID 19, critically ill patients with COVID-19 has higher body mass index (BMI) (25.5 kg/m2 versus 22.0 kg/m^2) [38].

Impact of glucose lowering drugs on COVID-19 infection: clinical evidence for correct selection

On the severity of COVID-19 the precise effect of glucose lowering drugs is not known. There are some theoretical considerations which can co-relate the effect of various class of glucose lowering drugs in COVID 19. Though gastrointestinal tolerability in sick patients is of concern but still in lower respiratory tract infections and pulmonary tuberculosis metformin has shown modest benefits [39]. If there is vomiting or poor oral intake metformin may also need to be stopped. ACE2 levels have been shown to increase in diabetes patients by thiazolidinediones [40]. However, the risk of congestive heart failure and increase in fluid retention caused by thiazolidinediones make these agents unfavourable for treatment during COVID 19 infection. In experimental animals models there is evidenced of increase ACE2 and increase surfactant by glucagon-like peptide-1 agonists [41]. Sulfonylureas are effective but preclude their use because of risk of hypoglycaemia but can be considered whenever blood glucose monitoring is possible.

It had documents in early studies that for Middle East respiratory syndrome DPP4 is the prime receptor which is responsible for coronavirus entry into cell [42]. DPP4 is the functional receptor for MERS-CoV Unlike SARS-CoV and SARS-CoV-2, which binds to ACE2 to entry into lung cells [43]. Even in some studies it has documented that use of DPP4i may be harmful as potentially interfere with immune response but clinical data from DPP4 inhibitors has shown that this is generally not the case [44]. Recent study confirms that in the lung, precisely in alveolar type 2 cells DPP4 shares patterns of expression with ACE2 which is the main target of Sars-CoV-2 [45]. DPP4i did not significantly impact on mortality and clinical outcomes, according to data from Chen., *et al.* in moderate-severe COVID-19 infected patients with uncontrolled diabetes [46].

SGLT-2 inhibitors especially if used along with ACE inhibitors could also activate ACE2 indirectly [47]. SGLT-2 inhibitors hypothetically reduce viral entry by reducing in oxygen demand of tissues by raising cytosolic pH [48]. When SGLT-2 inhibitors used in sick patients with COVID-19 need to be observed the possibility of euglycaemic ketoacidosis as well as caution about dehydration.

By attenuating the effect of a disintegrin and metalloprotease (ADAM-17), insulin has also been shown to increase ACE2 expression in host cell [49]. In hospitalized patients with COVID-19 to control serum glucose insulin remains the agent of choice. Single dose of basal insulin and periodic self-monitoring of glucose is definitely can be considered as most trusted strategy to control blood sugar for diabetes patients infected with COVID 19 especially those requiring intensive care.

Consequences of COVID-19 on diabetes

After recovery from mild, asymptomatic or severe COVID-19 infection concerns are also rising regarding the risk of incident diabetes. In genetically susceptible patients certain viral diseases can trigger autoimmune type 1 diabetes or from mass collapse of β cells even produce fulminant. A Chinese study has suggested that that infection with SARS-CoV also causing hyperglycemia over the course of infection which also uses ACE2 as entry receptor, could damage the islets of Langerhans [50]. Another Chinese study reported, 17% of patients with COVID-19 had pancreatic injury assessed by elevations of plasma amylase and lipase levels among whom moderately elevated plasma glucose was present in 67% of patients [51]. Regarding COVID-19 and risk of new-onset diabetes the question remains.

In patients infected with COVID-19 should diabetes be screened?

In clinical practice a large number of patient presented whose elevated blood glucose level remains untreated for long duration of time. Even few cases diabetes detected only at the time of occurrence of chronic complications. It has already been established that on the prognosis of COVID-19 uncontrolled and untreated diabetes has high impact. Therefor author highly support the fact that all patients whether they are asymptomatic or symptomatic or even admitted at hospital should be systematically screen for unrecognised or pre-diabetes by using HbA1c.

Future challenges

Diabetes patients with uncontrolled hyperglycemia are especially vulnerable to increased morbidity and mortality of COVID-19. Holistic diabetes care involves protecting these patients as healthcare systems transform into the "new normal." Once the function of the healthcare facilities starts for diabetes follow-up, anticipatory care involves assessing patients for end-organ damage, checking vaccination status such as for influenza and pneumococcal vaccinations, and also evaluating for psychiatric illnesses like anxiety and depressive symptoms of these patients in order to get appropriate psychiatric and psychological if necessary. Adherence to precautionary measures against COVID-19 infection such as regular handwashing, cough hygiene, and social distancing [52] must be reinforced to the patients even after lockdown measures are revoked. Clinics must also be reorganized to incorporate safety measures and equipment to avoid the spread of infection. As we usher in a "new normal" for persons with diabetes, greater collaboration between the diabetes specialists-endocrinologists- and primary care physicians is encouraged so that not only preventive care is continued at the grassroot levels, but screening for diabetes and its complications continue with timely referral to specialists. The anticipated future then, after this crisis, is one of strong partnerships between doctors, patients, and institutions which are pivotal in improving the quality of diabetes care amidst formidable challenges in this global pandemic.

Conclusion

So, the global pandemic of COVD-19 and restricted operation and movement of peoples and goods can affect human lives in many ways. Global pandemic of COVD-19 and restricted operation and movement of peoples and goods can lead to acute life-threatening complications of diabetes and its diagnosis and management. The course of COVID-19 infection considerably influences by the presence of diabetes being a risk factor for poor outcomes. Till date knowledge of interfere with SARS-Cov-2 access in lung cells or in other tissues by the various drugs that are tried are completely lacking. The COVID-19 pandemic has acutely stimulated the expansion of the use of telemedicine and digital medicine. The need for social distancing to minimise viral spread has necessitated the rapid uptake of tele health modalities to deliver health care.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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