Type 2 diabetic Asian Indians and COVID-19: Lessons learnt so far from the ongoing pandemic

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has stalled the world due to global pandemic and also badly affected India with 9, 11, 871 confirmed cases and 24,309 deaths as of July 15, 2020 ranking India third topmost affected country in the world.[1,2] Early Indian data published by Indian Council of Medical Research (ICMR) has shown that around 63.3% of COVID-19 patients are between age group 50 and 60 years, with male preponderance and among the close contacts.[3] For medical fraternities, the concern is about the rate of spread, human to human transmission, clinical profiles, morbidity, and mortality with SARS-CoV-2. Old age, smoking, comorbidities like hypertension (HTN), diabetes mellitus (DM), ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), and stroke are few of the parameters predicting the course of disease and outcomes.[4,5] Current evidence suggests that DM is significantly associated with increased mortality risk of COVID-19 along with severe presentations like acute respiratory distress syndrome (ARDS), ICU requirement, invasive ventilator requirement, and longer duration of stay in the hospital.[6] Characterization of COVID-19 patients in India through initial publications shows 28.6% of the patients have comorbidities like HTN or DM.[7] It is still unclear whether patients with diabetes have a higher prevalence of COVID-19; however, patients with DM infected with COVID-19 have adverse outcomes making the management complicated. Certainly, DM is one of the important comorbidities in COVID-19 patients.

New Onset Diabetes in COVID-19

The presentation of diabetics with COVID-19 is severe compared to non-DM patients. Severe hyperglycemia and diabetic ketoacidosis in patients with previous history of diabetes are common observation. On admission, in few of the patients without any family history of diabetes with near normal HbA1c, new-onset hyperglycaemia has been noticed. This new-onset diabetes in COVID-19 patients also has been observed globally.[8] This so-called “COVID-19 related DM” is a matter of concern during management. Eventually, all of them are being managed by subcutaneous or intravenous insulin to achieve normoglycemia during hospitalization. However, “COVID-19 related DM” may achieve normoglycemia with insulin early compared to patient with preexisting DM, but associated steroid use may complicate the picture. There is a need to formulate registry of “COVID-19 related DM” from various COVID centers and hospitals of India. Further, whether these patients will become permanently diabetic in future or achieve remission needs to be explored.

Various biological mechanisms have been postulated for the associations and poor outcome of SARS-CoV-2 infection in DM. First, DM is associated with impaired immunity. Both long-term and short-term hyperglycemia alters chemotaxis, subsequent phagocytosis, and impaired complement fixation. Second, DM can lead to proinflammatory state with increased levels of cytokines including interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), which is associated with multi organ failure in patients with SARS-CoV-2. Third, the angiotensin-converting enzyme 2 (ACE2) receptor, the entry point for SARS-CoV-2 into human cells, is up-regulated in patients with DM facilitating the increased opportunity for virus to infect cells. Fourth, it is known that COVID-19 virus can infect endocrine pancreas cells via their expression of ACE2 receptors resulting in impaired insulin secretion making DM worse or new incidences of DM. Fifth, hyperglycemia increases glucose concentrations in airway secretions making lung cells prone to viral infection and replication.[9]

Association of Glycemic Control and Outcomes in Patients with COVID-19

In the first study in this pandemic, Zhu et al. show the association of glycemic control with mortality in COVID-19 patients. Among 7300 cases of COVID-19, overall Type 2 diabetes (T2D) is associated with higher mortality compared to nondiabetics. Further, well-controlled diabetics had less mortality compared to poorly controlled diabetics.[10] Patients with T2D presented with severe disease with raised markers of inflammation and elevated cytokines compared to nondiabetic individuals. Preexisting T2D patients required significantly more intensive integrated treatments like higher need of antibiotics, steroids, immunoglobulins, vasoactive drugs, noninvasive or mechanical ventilation to manage their symptoms of COVID-19 than
nondiabetic subjects. Also, patients with T2D had a greater occurrence of ARDS, acute heart injury, acute kidney injury, septic shock, and disseminated intravascular coagulation (DIC) and overall mortality than the nondiabetic group.\cite{10,11}

Recent evidence also supports the need of strict glycemic control. T2D with well-controlled blood glucose (BG) (mean: 115 mg/dL) required significantly less integrated treatments than those with poorly controlled BG (mean: 196 mg/dL). Poor glycemic control in patients with COVID-19 and preexisting T2D was associated with worse outcome, involving the increased need for medical interventions, multi-organ injuries, and higher mortalities. The levels of mean glycosylated hemoglobin (HbA1c) in these well-controlled and poorly controlled DM groups were 7.3% and 8.1%, respectively. The well-controlled cohort with glycemic variability between 70 mg/dL and 180 mg/dL is significantly associated with reduced medical interventions, major organ injuries, and all-cause mortality.\cite{10,11}

### Challenges for Diabetes Control in COVID-19 Pandemic

A typical Indian T2D phenotype is centrally obese with high insulin resistance, younger in onset, more prone to develop macro and micro vascular complications of DM. Various epidemiological surveys suggest that more than 50%–70% Indian diabetics have average HbA1c more than 8.5% which is way higher than desired glycemic control target of 7%. Thus, this poorly controlled DM makes Indian diabetics more prone for complications of diabetes including infections. Linear relation is noted with a number of complications of DM with duration of DM.\cite{12,14}

### Lessons Learnt from COVID-19 Pandemic till Date

The COVID-19 pandemic has put a major challenge on healthcare systems in India and possibly fear of worst may be yet to come. High-risk category COVID-19 as specified earlier contribute major cohort of morbidity and mortality in India. COVID-19 pandemic has been an eye-opener for Indian diabetic population. There is an urgent need for being aggressive for glycemic control in them. “COVID-19 related DM” may be another challenge for clinicians to manage. We have summarized the key suggestions for the management of diabetes during COVID-19 in Table 1.

In conclusion, COVID-19 pandemic has been a great challenge for developing country like India, in particular, for patients with chronic diseases like DM, HTN, IHD, and COPD. These noncommunicable morbidities form huge socioeconomic burden on the country, especially in such pandemic situations of SARS CoV-2. This pandemic has been a learning lesson for Indian diabetics to achieve a strict glycemic control and hence to prevent short/long term complications of DM including infections. Physicians need to be more vigilant in achieving the target glycemic control and enhance the efforts of patient’s awareness toward disease understanding, and management and prevention of complications during this pandemic.

| Table 1: Recommendations for management of diabetes during COVID-19 pandemic |
| Blood sugar monitoring is advised in patients with COVID-19, especially who are >30 years of age. |
| For COVID-19 patients presenting with hyperglycemia, early insulin initiation is preferable. |
| Basal insulin analogs are recommended as far as possible to minimize the risk of hypoglycemia. |
| Few antidiabetic agents can be stopped temporarily, e.g., metformin for increase in the risk of lactic acidosis, SGLT-2 inhibitors for risk of volume depletion and diabetic ketoacidosis, pioglitazone for risk of fluid retention and edema, injectable GLP-1 analogs for risk of nausea and vomiting. |
| Monitoring of blood glucose is essential for titration of insulin doses and prevention of hypoglycemia. |
| For indoor patients, the blood sugar should be maintained in the range of 70 mg/dL to 180 mg/dL. |
| Non-COVID-19 patients should be counselled and managed to achieve strict glycemic control with HbA1c target <7%. |
| For elderly diabetic patients who are not able to visit hospitals/clinics, use of telemedicine and video calls should be considered for diabetes consultations. |

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