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Strict glycemetic control is needed in times of COVID19 epidemic in India: A *Call for action* for all physicians



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During the current COVID-19 pandemic, there is sufficient data to suggest that diabetes is an important comorbid disease which can increase severity and mortality related to COVID-19. Key pathological factors that contribute to increased mortality in patients with diabetes are; defects in T-cell immunity, baseline high levels of cytokines and presence of co-morbidities [1,2]. Those with comorbidities (obesity, coronary heart disease, hypertension, chronic kidney disease chronic obstructive pulmonary disease, immuno-suppressed conditions etc.) and elderly are particularly at high risk [1,3]. It is possible that Indians with diabetes may have lower mortality than seen in western countries because of younger age of contracting COVID19 but this issues remains unproven [4,5]. With this background, in the following sections we discuss the role of patients' glycemetic status before they have COVID-19 infection, at the time of admission, and during the hospital stay, *vis-à-vis* morbidity and mortality, and briefly outline key management issues (Table 1).

Previous studies have shown that a high proportion of patients with diabetes in India have poor glycemetic control [6–8], and that many already have diabetes-related complications [8–10]. Uncontrolled hyperglycemia could be exacerbated by disordered lifestyle during lockdown and consequent weight gain. Such patients with uncontrolled hyperglycemia will obviously have high blood glucose levels during admission and also during hospitalization when they contract COVID19. This is the first scenario which is quite well known.

The second scenario is when a patient not known to have diabetes develops COVID-19 infection and high blood glucose and even ketoacidosis is detected at admission to the hospital [11]. High blood glucose levels at the time of hospitalization may be due to undetected diabetes or as a result of recent weight gain during complete and partial lockdown [12]. Weight gain during lockdown may be due to multiple factors; disordered diet, poor exercise, and widespread mental stress, as previously shown [12,13]. In India, unwarranted use of dexamethasone in mild COVID19 infection and

other seasonal flu, increases the risk of hyperglycemia. High fasting blood glucose (FBG) at the time of hospitalization in people not known to have diabetes puts them at higher risk (HR 2.30 [95% CI 1.49,3.55]) for mortality than those who have normoglycemia. The odds ratio for 28-day in-hospital complications in those with $\text{FBG} \geq 7.0$ mmol/l (126 mg/dL) and 6.1–6.9 mmol/l (110–125 mg/dL) vs < 6.1 mmol/l was 3.99 (95% CI 2.71, 5.88) or 2.61 (95% CI 1.64, 4.41), respectively [14].

The third scenario is hyperglycemia in pregnancy. Pregnancy in diabetes and gestational diabetes, should be intensively controlled with the help of self-monitoring of blood glucose (SMBG) and continuous glucose monitoring system (CGMS). Screening of women with capillary glucose should be done to avoid visiting laboratory [15]. Consultations for antenatal checks, nutritionist, and diabetes educators must be done as appropriate with the use of teleconsultation.

The fourth scenario is in-hospital hyperglycemia that needs to be controlled well. However there are a number of factors which pose challenges; triggers for hyperglycemia [surge of cytokines (“cytokine storm”), frequent use of corticosteroids, etc.], ketoacidosis and hyperosmolar states, inability to monitor blood glucose levels frequently because of reduced contact between healthcare worker and patients, and non-inclusion of diabetes expert in the critical care team in many hospitals. Data suggesting markedly lower risk of all-cause mortality in the hospitalised patients with well-controlled blood glucose (adjusted HR, 0.14; 95% CI, 0.03–0.60; $p = 0.008$) compared to those from the poorly controlled blood glucose group [16] should encourage us to go all out for aggressive glycemetic control.

The fifth scenario is new onset of diabetes which is now being reported during COVID19 infection [17]. Besides unmasking of previous hyperglycemic state, beta cell injury is a likely possibility in such cases. In this context, it is important to know that angiotensin converting enzyme-2 (ACE2) receptors, through which SARS-CoV-2 attaches to the cells, are present on the cells of endocrine pancreas, at even greater density than in the Type 1 and Type 2 alveoli in lungs [18]. It is, therefore, possible (but not proven) that beta cell destruction may occur due to COVID19 attack on pancreatic beta cells, similar to alveolar injury in lungs. Indeed, 17% of patients with severe COVID19 have been shown to have pancreatic

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Table 1
Hyperglycemia scenarios during COVID19, mortality and principles of management.

Hyperglycemia scenarios	Situation in India	Mortality ^a	Place of Care	Management/solutions	Means/Healthcare provider
1. Pre-existing poor glycemic control without covid19, or mild covid19	Uncontrolled glycemia in about 60–70% patients	High when infected with COVID19	Home, outpatients	<ul style="list-style-type: none"> - Reconnect with patients, - emphasize importance of good glycemic control; - Empower change in therapy in simple manner 	Tele consultation
2. Hyperglycemia at admission (both patients with and without diabetes) with COVID19	<ul style="list-style-type: none"> - Likely possibility in known patients with diabetes - Also, in individuals not known to be having diabetes^a 	High	Hospital (in-patients)	<ul style="list-style-type: none"> - HbA1c to rule out previous diabetes. - Escalate therapy if required as soon as COVID-19 is diagnosed. - Escalate metformin if no abdominal distress or other contraindications. 	In-hospital diabetes expert and/or COVID19 care team ^b
3. Hyperglycemia in pregnancy with COVID19	^a	^a	Home, hospital (in-patients)	<ul style="list-style-type: none"> - Use capillary blood glucose for screening (oral glucose tolerance test avoided)^a - SMBG and CGMS for monitoring 	<ul style="list-style-type: none"> - Teleconsultation. - In-hospital management^b if needed
4. Hyperglycemia during hospital stay with COVID19	Not well researched but likely	High	Hospital (in-patients), intensive care unit	Aggressive management with insulin	In-hospital diabetes expert and/or COVID19 care team ^b
5. New-onset diabetes	^a	High	<ul style="list-style-type: none"> - Hospital (in-patients), Intensive care (if ketoacidosis or marked hyperglycemia) - Outpatients/home 	<ul style="list-style-type: none"> - Insulin (for marked hyperglycemia and ketoacidosis) - Oral drugs^a 	<ul style="list-style-type: none"> - In-hospital diabetes expert and/or COVID19 care team^b - Teleconsultation in case of outpatients care

SMBG, Self-monitoring of blood glucose; CGMS, Continuous glucose monitoring system.

^a Not well researched in India.

^b In absence of diabetes expert, simplified management regimen (insulin initiation and continuation algorithm and fluid and electrolyte treatment) should be followed by COVID19 care team. Teleconsultation between COVID19 care team/critical care team and diabetes expert should be encouraged.

injury in one study [19]. It is possible that injury to beta cells, already under attack from cytokines (cytokine-induced apoptosis) [20], could cause acute insulinopenia, and ketoacidosis [11]. Previously, acute-onset diabetes has been shown with SARS-CoV infection and beta cell injury has been implicated in its pathogenesis [18]. Viral 'sepsis' could induce resistance to action of insulin, posing additional challenges to management (e.g. high insulin requirement).

There are a number of other factors which may affect glycemic control in patients with diabetes in India. Patients were not able to contact their physicians during lockdown, or do not visit them due to fear that hospitals are hotspots of COVID19. Telemedicine is not acceptable to many patients (especially the elderly) who are not technologically abled [21,22]. Economic problems exacerbated by lockdown and COVID19 [23] may lead to non-compliance to medications and insulin. Non-availability of insulin and glucose strips during the period of lockdown was shown to worsen the glycemic control in patients with type 1 diabetes [24].

We can make efforts to efficiently manage each of these scenarios of uncontrolled glycaemia. All of us must strongly advice and advocate for good glycaemic control in all patients specifically those with COVID19 aiming for low morbidity and mortality [25]. Glycemia must be controlled at all times; when not hospitalised, during pregnancy, during quarantine, at the time of admission, and during hospital stay. Practice of SMBG should be emphasized. Patients with risk for foot lesions/infections should be counselled for proper foot care and self-examination of feet, and treated as much as possible using tele consults [26].

All patients diagnosed with COVID19, even if not known to have diabetes, must get screening blood glucose measurement done [27]. Blood glucose monitoring in hospital should be done frequently, by patient or healthcare provider, keeping safety in mind. When available, CGMS with real time remote monitoring is a good option. Metformin should be continued (until it cannot be

tolerated, or patient is unable to take it) since it may decrease mortality in COVID19 [28]. Insulin must be used to control surge of blood glucose which may also occur due to steroid therapy and/or sepsis. Hypoglycemia, which may occur due to nausea, vomiting, aversion to food, mismatched IV fluids or use of hydroxychloroquine, should be looked for and corrected. Aggressive fluid and electrolyte therapy for marked hyperglycemia and ketoacidosis must be balanced against possible cardiac and renal compromise. Ideally, diabetes expert must be part of the caregiver team in hospital. However, often a diabetologist/endocrinologist is not available to provide care in hospitalised patients, hence, development of an easy-to-use guidance algorithm for drug and insulin would be useful [29]. A critical and often neglected point is the advice given to the patient at discharge from hospital. The 'return to normalcy' in severe COVID19 can take a long time and the residual effects of the infection are only now being understood. The job of a physician does not end with the discharge of the patient. Proper education and guidance of these patients-for good monitoring and glycemic control at home is imperative.

To enable good metabolic and blood pressure control, we must proactively connect with the patients (phone calls, messages) and emphasize (through tele consults, messages, face-to-face consults) that importance of glucose control is more relevant now than ever before [30]. Messages regarding correct diet, exercise (any exercise, indoor exercises), adequate sleep, and adherence to therapy must be re-iterated. Patients must be advised unequivocally that weight gain must be avoided, and blood pressure should be maintained as close to normal as possible. Elderly must be carefully counselled so that hypoglycemia does not occur. Individuals without diabetes should be advised to lose weight if obese, follow correct lifestyle and get blood glucose tested. Uninterrupted insulin supply must be ensured for patients with type 1 diabetes.

We believe that the available information on COVID19 and diabetes necessitates a *call for action* for all medical community in

general and experts in diabetes in particular, to ensure implementation of previously recommended and evidence-based interventions for the patients, even more aggressively than hitherto been the case.

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None.

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