Clinical considerations in patients with diabetes during times of COVID19: An update on lifestyle factors and antihyperglycemic drugs with focus on India

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A B S T R A C T

Background: Diabetes is recognized as an important comorbidity in patients with COVID-19 and a large amount of literature has become available regarding this. The aim of this article is to review the literature regarding various aspects of association between diabetes and COVID-19 and to highlight clinically relevant points with focus on India.
Methods: We searched Pubmed and Google Scholar databases for articles regarding diabetes and COVID-19 published between March 19, 2020 and August 30, 2020.
Results: Diabetes and poor glycemic control are associated with increased severity and mortality in patients with COVID-19. Several clinical scenarios about hyperglycemia and COVID-19 are identified and each of these needs specific management strategies.
Conclusion: It is prudent to maintain good glycemic control in patients with diabetes in order to minimize the complications of COVID-19. There is a need for well conducted studies to asses the role of individual antihyperglycemic therapies in COVID-19 and also the behavior of new onset diabetes diagnosed either after COVID-19 infection or during this time.

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After the first reported case of COVID-19 in China in December 2019, the pandemic has rapidly spread worldwide. The association of diabetes and COVID-19 was identified initially and clinical considerations about the same were published by us in a highly cited article, one of the first on this subject, in March 2020 [1]. Present article is an update of the previous article since much information has become available about the relationship between diabetes and COVID-19 since then, with focus on India.

We searched Pubmed and Google Scholar for articles regarding diabetes and COVID-19 published between March 19, 2020 and August 30, 2020. In this article, we present pertinent points relating to clinical aspects and new evidence which has emerged during this period.

1. Diabetes and COVID-19: predisposition and severity

a *Risk of COVID-19 in patients with diabetes:* Diabetes is one of the commonest comorbidities in patients with COVID-19 and was present in about 10% of 7162 patients with COVID-19 who had comorbidities in data reported by CDC USA [2]. Studies from different parts of world have shown varying prevalence of diabetes in patients with COVID-19. Prospective observational data from UK has shown uncomplicated diabetes in 19% of 16,749 COVID-19 cases. The largest study in primary care setting revealed diabetes to be present in 9.8% of 121,263 patients with COVID-19[3] in Spain. The question of increased risk of acquiring infection with SARS CoV2 is still unsettled as many studies have shown a similar prevalence of diabetes in general population and in patients with COVID-19.

b *Effect of diabetes on disease course and severity:* Most studies have shown that presence of diabetes is associated with increased severity of COVID-19[4].

c *Effect of glycemic control on disease course and severity:* There is evidence that good glycemic control could reduce the severity of

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COVID-19.Well controlled diabetes was associated with significantly lower mortality compared to individuals with poorly controlled diabetes (adjusted HR, 0.14; 95% CI, 0.03–0.60; p = 0.008)[5] in a recent study.

d *Effect of COVID-19 on pre-existing diabetes:* Worsening of glycemic control is seen in patients with diabetes who develop COVID-19, and often patients present with ketoacidosis and hyperosmolar state [6]. Several factors like cytokine storm, use of corticosteroids and limited access to diabetes expert, could be responsible for this.

e *New onset diabetes in patients with COVID-19:* COVID-19, like any severe infection could unmask preexisting diabetes. In addition, two factors namely cytokine induced beta cell injury and direct injury to beta cells by virus, could lead to new onset diabetes. Presence of angiotensin converting enzyme-2 (ACE-2) receptors on beta cells could predispose to the latter. Therefore it is imperative that all patients with COVID-19, particularly hospitalized patients be screened for COVID-19[7].

f *Effect of glycemia at admission in non-diabetic individuals and mortality:* Patients without preexisting diabetes who have high fasting blood glucose at the time of hospitalization with COVID-19 were seen to have a higher risk of mortality (HR 2.30 [95% CI 1.49, 3.55]) than those who have normoglycemia [8]. This is particularly important for India and other developing countries where there are a large number of people having undiagnosed diabetes [9]. Further, during this time, tendency for rapid conversion of prediabetes to diabetes, as seen in Asian Indians, could lead to many individuals presenting with hyperglycemia [10].

Indian Data of Diabetes and COVID19: India has witnessed a surge in cases of COVID-19 in recent times, however total mortality and mortality per million population has remained low [11]. Information about diabetes in COVID-19 in Indian patients is sparse at present. In a study in 522 patients hospitalized with COVID-19 till April 20, 2020 in Jaipur, Western India, diabetes was present in 5.5% of patients [12]. Another study in patients from Rajasthan reported a prevalence of diabetes to be 4.7% in 234 patients with COVID-19 [13]. Clearly, further studies are needed to ascertain this limited data.

2. Effect of nationwide lockdown during COVID19 pandemic

The imposition of lockdown and restrictive measures in many regions to contain the pandemic has posed challenges in access to healthcare, supply of medicines and insulin [14]. Moreover, dietary irregularities, reduced exercise, and mental stress have led to weight gain as seen in a questionnaire-based study by in 150 patients with type 2 diabetes as shown by us [15]. In a study in 143 patients with diabetes in Central India, 39% patients reported worsening of hyperglycemia [16]. A small study on 52 patients with type 1 diabetes in north India showed a statistically significant increase in average blood glucose and HbA1c during lockdown [17]. This is in contrast to the findings of improved glycemic control and reduced glycemic variability in studies in type 1 diabetes done in Spain, Italy and United Kingdom [18–20].

Restrictions during lockdown could also be an important contributing factor in development of diabetes in predisposed individuals. In a study in 100 people without diabetes, weight gain was reported by 40% respondents and this led to about 7% increase in number of people with high ADA diabetes risk score [21]. This is especially important for South Asians who have a higher risk of conversion from prediabetes to diabetes PMID: 30287102. Not only does this finding have an implication for future burden of diabetes and its complications, it could also lead to increased morbidity because of COVID-19.

3. Antihyperglycemic drugs and diabetes in COVID-9

As the understanding of infection with SARS CoV2 has evolved, two factors have come to be recognized as important determinants of pathophysiology of disease. These are the role of ACE2 receptors and the recognition of cytokine storm. ACE2 receptors are important for viral entry into cell and ACE/ACE2 ratio is a determinant of lung pathology [22]. Cytokine storm is recognized as an important event leading to lung injury, acute respiratory distress syndrome and severe disease course. Consequently, an attempt is being made to understand the role of various anti-diabetic agents in patients with COVID-19 based on their effects on ACE2 expression and inflammatory response. Most of the evidence is from experimental studies in cell lines and animals with limited clinical evidence in COVID-19. One notable exception is metformin which has been studied in retrospective analyses in patients hospitalized with COVID-19. Table 1 shows the studies examining the effect of metformin on mortality due to COVID-19. The largest study showed that metformin use for at least 90 days in the preceding 12 months was significantly associated with reduced mortality in hospitalized patients with COVID-19; however this benefit was observed in women only. This could be attributed to the preferentially greater anti-inflammatory effect (preferential effect on interleukin-6) of metformin in women [37].

Considerations about the use of other anti-diabetic agents remain the same as in any acute infection [23]. Most oral antihyperglycemic drugs can be used in patients with mild disease. Insulin remains the mainstay of treatment of hospitalized patients with COVID-19. Concerns about the need to minimize exposure of healthcare workers has led to exploring alternative options of insulin delivery like basal insulin, intermittent bolus insulin and use of CGMS and insulin pump [24].

4. Effect of drugs used for treatment of COVID-19 on glycemic parameters

Hydroxychloroquine has been used to treat COVID-19 and retrospective studies have shown improved viral clearance and reduction in severity [25]. However, randomized controlled trials have failed to show benefit with a possibility of increased QTc interval and arrhythmias especially when HCQS was used along with azithromycin [26]. There is need for caution about hypoglycemia when used in patients with diabetes who are on other antidiabetic drugs.

Corticosteroids have shown improvement in mortality in ventilated patents with COVID-19[27]. However, good glycemic control is prudent while using steroids. Also indiscriminate use in mild disease is detrimental and is strongly discouraged.

5. Role of remote consultation and telemedicine

Telemedicine has proved to be useful in providing consultation and education to patients in times of restricted social mobility and continues to be utilized in view of the need to minimize direct contact of patients with hospital/healthcare facility [28,29]. However, there are challenges and limitations of telemedicine especially in developing countries. These include poor internet connectivity, poor digital literacy, hearing problems, among others [30].

6. Preventive measures in patients with diabetes

Apart from the usual preventive measures like social distancing and use of masks, good glycemic control needs to be emphasized in order to minimize severity of COVID-19. There is no chemoprophylaxis recommended in patients with diabetes. Benefit of

Table 1
Retrospective cohort studies of effect of metformin on mortality in hospitalized patients with COVID-19.

Author	Country	Number of patients with T2DM and COVID-19/patients on metformin	Odds ratio for mortality (95% CI)	P value (metformin *vs.* non-metformin groups)	Remarks
Crouse et al. [35]	USA	220/76	0.33 (0.13, 0.84)	0.0210	Association between metformin and reduced mortality significant even after excluding patients with chronic kidney disease and heart failure
Cariou et al. [36]	France	1317/745	0.80 (0.45, 1.43)	0.4532	No association between metformin and mortality
Bramante et al. [37]	USA	6035/2316	Women: 0.790 (0.637, 0.978); Overall: 0.808 (0.651, 1.003)	Women 0.013; Overall: NS	Association between metformin and reduced mortality significant only in women
Luo et al. [38]	China	283/104	0.23 (0.07, 0.77)	0.02	Effect of metformin on reduction in mortality observed even though glycemic control was similar in both groups

Table 2
Hyperglycemia scenarios during COVID19, mortality risk, and principles of management.

S No	Hyperglycemia scenarios	Situation in India	Mortality	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	- 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	-Likely possibility in known patients with diabetes -Also, in individuals not known to be having diabetes[a]	High	Hospital (inpatients)	- 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[a]
3	Hyperglycemia in pregnancy with COVID19	[a]	[a]	Home, hospital (inpatients)	- Use capillary blood glucose for screening (oral glucose tolerance test avoided)[a] - SMBG and CGMS for monitoring	-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	- Hospital (in-patients), Intensive care (if ketoacidosis or marked hyperglycemia) - Outpatients	- Insulin (for marked hyperglycemia and ketoacidosis) - Oral drugs	- In-hospital diabetes expert and/or COVID19 care team[b] - Teleconsultation in case of outpatients care

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[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.

nutritional supplements like vitamin C, zinc, selenium, vitamin A and vitamin D etc. has been seen *in vitro*, however clinical evidence is not sufficient to recommend their supplementation [31]. Vitamin D deficiency has been shown to be correlated to mortality in COVID19, however benefit of intervention has not been demonstrated [32]. It is reasonable to advise a healthy balanced diet with increased servings of protein, fruits, vegetables and nuts [33].

7. Which categories of patients of hyperglycemia need consideration?

In light of the evidence about role of diabetes and hyperglycemia in determining the severity of COVID-19, and the effect of the disease and lockdown on the glycemic status of people with and without diabetes, it is becoming increasingly important to recognize the different scenarios where diabetes and COVID-19 interact.

A recent article by a consortium of diabetes experts in India has identified five categories of patients with hyperglycemia who need consideration in today's times of COVID-19 pandemic [34]. Each of these need appropriate management as given in Table 2.

Mortality due to COVID-19 is high even in those individuals not known to have diabetes. With a large pool of undiagnosed people with diabetes in India, it is reasonable to recommend a blood glucose check in Asian Indians above 30 years who have COVID-19.

8. Conclusion

As a common comorbidity in patients with COVID-19, the enormity of literature on this subject is not surprising. However, there is a lack of well conducted studies examining the risk of COVID-19 in patients with diabetes, role of glycemic control and the effect of various antihyperglycemic agents. Also there is a need to

study the behavior of new onset diabetes occurring after COVID-19 infection and as a result of lifestyle changes due to restrictions on mobility. Till the time more evidence is generated, it is reasonable to aim for good glycemic control in patients with diabetes and to take all precautions to avoid infection with SARS CoV2.

Conflict of interest

The authors declare no conflict of interest.

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