



Post COVID-19 diabetes care—lessons and challenges

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The outbreak of COVID-19 all over the world this year has posed several new challenges to diabetes care and has also provided an opportunity for new lessons to be learnt in what seems to be transforming the way we treat diabetic patients.

Some of the issues and challenges that have emerged include the reported high incidence [1, 2] of COVID-19 infections among patients with diabetes mellitus (DM), the greater severity, and higher rates of progression resulting in a higher number of ICU admissions [3] and higher mortality reported in them [1, 2]. The increased predisposition of patients with diabetes to COVID-19 infections particularly severe infections with acute respiratory distress is believed to be related to a compromised innate immunity that accompanies uncontrolled DM and an exaggerated proinflammatory cytokine response involving IL-6 and TNF-alpha [4]. The situation would be worse if there are other comorbidities such as hypertension, chronic kidney disease, or coronary artery disease which often coexist with diabetes and are also associated with more aggressive COVID-19 infections. This calls for early and aggressive management of COVID-19 in diabetic patients to prevent adverse outcomes.

It is equally important to detect fresh cases of diabetes early and pick up hyperglycemic spikes in those known to be diabetic without delay—something which is very difficult at a time when the medical fraternity is struggling to manage the COVID-19 pandemic. A high degree of alertness with frequent self-monitoring of blood glucose levels is certainly advisable in known diabetic patients particularly insulin users to reduce the risk of being affected with COVID-19 infection and avoid any undesirable consequence should they get infected. As physicians involved in diabetes care, we need to advise our patients accordingly besides telling them to follow with

greater intensity all the general measures to prevent exposure to COVID-19 infection.

Just as it is important that we target and make every effort to achieve good glycemic control during these COVID times, it is equally important that we identify diabetes comorbidities and complications early and effectively manage them. It is well-known that several of these including hypertension, heart disease including heart failure, and chronic kidney disease are all associated with higher mortality in COVID-19 infections.

Challenges in diabetes management begin with difficulties in effective implementation of lifestyle measures particularly with respect to physical activity and exercise. These are surmountable and can be largely met by advising indoor exercise routines, yoga, and other innovative ways of enhancing physical activity. Fortunately, limited access to fast foods and other unhealthy dietary choices in restaurants should help, but one should still be advised to judiciously choose from available homemade and packaged dietary choices. Poor access to alcohol and limited opportunities for smoking during lockdown can also become a unique opportunity to seriously consider giving up these habits which can help prevent long-term complications of diabetes. Stress and the higher levels of anxiety and depression that can occur during periods of lockdown not only affect the mental health and sleep of the diabetic patient but also adversely affect glycemic control. Appropriate measures to relieve stress are also important to maintain glucose control.

Another important challenge in the management of diabetes mellitus has been regarding the appropriate use of various antidiabetic agents. This has been an area of concern as well as an area of intense speculation and debate. Advisories, not always supported by well-designed studies, are often confusing the treating physician. Overall, insulin appears to be a good option for glycemic control and is safe. It is advised that anti-hyperglycemic drugs that cause volume depletion or hypoglycemia are best avoided or used in small dosages. Metformin may show a higher propensity to lactic acidosis especially in those with volume depletion. SGLT2 inhibitors are contraindicated not only because they are associated with fluid loss but these groups of agents have also been found to be associated with a higher incidence of diabetic ketoacidosis

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and euglycemic ketoacidosis. Hence, SGLT2 inhibitors may need to be stopped in patients developing COVID-19 infections especially if these are moderate or severe [5, 6]. On the contrary, the DARE-19 trial is also ongoing to examine the role of dapagliflozin in preventing multiorgan failure in severe COVID-19 disease based on earlier reports of its beneficial effects in preventing heart and kidney failure.

DPP4 inhibitors are another class of antidiabetic agents which are believed to have a potential to reduce the incidence and severity of complications associated with COVID-19 infections particularly in diabetic patients. This is based on the belief and earlier observations in MERS-COV-infected diabetic patients that a DPP4-mediated immune dysregulation could result in higher rates of mortality and complications in diabetic patients. However, there is no direct evidence so far that the same is true of COVID-19 infections and also the beneficial effects of DPP4 inhibitors are yet to be proven in randomized controlled trials. Until then, this will remain a potential strategy only, particularly to prevent progression to the hyperinflammatory state in severe COVID infections [5, 6].

It has also been hypothesized that insulin resistance promotes inflammation and has been shown to be associated with increase in several inflammatory markers such as C-reactive protein, IL-6, and TNF-alpha and procoagulant markers such as fibrinogen and PAI-1. Pioglitazone, a potent insulin-sensitizing agent, would therefore be expected to significantly reduce insulin resistance-related inflammation and favorably affect the diabetic patient's response to COVID-19 infection [7]. While this appears to be a promising approach, we have to wait for clinical trials to provide necessary evidence for its use.

Hydroxychloroquine (HCQ) is an approved drug by DGCI for use in DM. Ever since the pandemic of COVID-19 unfolded, there has been a lot of interest in some of its properties which could be very useful in the treatment and prophylaxis of this novel infection. It is believed that HCQ lowers the acidity in endosomes and prevents the release of coronavirus from them into the cytoplasm [8]. While its activity against this virus has been shown in vitro, these have not clearly translated to significant clinical benefit in in vivo studies particularly in humans yet. A recent systematic search and narrative review with a special reference to India and other developing countries [8] has reported that 2 small human trials have found improvements in some parameters such as viral load. It has recommended that larger randomized clinical trials (RCTs) should be done urgently to confirm benefit especially in diabetic patients. Currently, HCQ given together with azithromycin is being evaluated for treatment of mild to moderate cases of COVID-19 to see if hospitalizations and deaths can be prevented. India is also testing HCQ for COVID-19 as one of four drugs being evaluated as part of the WHO Solidarity trial. As of now, we need to be cautious in recommending its use in the prevention or treatment of

COVID-19 and should wait for the results of these large trials. Since the drug is already approved for use in DM, we may consider its use for glycemic control more often in the current scenario in view of possible collateral benefits.

Statins and ACE inhibitors are 2 groups of drugs very commonly prescribed to diabetic patients, and it is necessary to critically evaluate the current evidence regarding the benefit or risk associated with their continued use. As for statins, there are several reasons to believe that they could benefit patients with COVID-19 coinfection. They could promote innate immune responses to CoV respiratory infections, lead to fewer severe viral pneumonias, and also help in preventing some of the cardiovascular complications of COVID-19. However, there is as yet no clinical evidence that these benefits actually accrue although there are compelling reasons to undertake appropriate clinical trials [9]. Since statins are cheap and are widely prescribed in patients with diabetes, a prudent approach may be to continue statins if already prescribed and consider starting statins without delay in those in whom a recommended indication presents itself.

The relationship of ACE and COVID-19 infections particularly pneumonias and ARDS is complex. While reduced ACE2 expression in DM is believed to predispose COVID patients to severe pneumonias and ARDS, it has also been postulated that ACE2 expression promotes entry of SARS CoV-2 virus into host pneumocytes [4, 5]. There is no clear evidence that would suggest withdrawing ACE inhibitors or ARBs in these patients, and hence, most international societies do not recommend stopping them.

The medical fraternity is eagerly awaiting the development of a successful vaccine against COVID-19, and there has been significant progress. Meanwhile, it should be emphasized that existing influenza and pneumococcal vaccines should be taken as recommended by diabetic patients.

Last but not the least, during these times of lockdown and even post lockdown, all diabetes physicians will have to deliver diabetes care more innovatively and increasingly use telemedicine and other novel approaches to be in touch with the diabetic patient while keeping face-to-face consultations to a minimum. This will ensure maximum benefit with minimum risk.

Let us prepare for all the new post COVID challenges in diabetes care even as we remain alert to newer lessons that are constantly emerging and will help us organize our practice.

References

1. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. *Diabetes Metab Syndr*. 2020;14:303–10.

2. Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr*. 2020;14:211–2.
3. Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *J Clin Virol*. 2020;127:104354.
4. Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. *Diabetes Res Clin Pract*. 2020;162:108132.
5. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020. [https://doi.org/10.1016/S2213-8587\(20\)30152-2](https://doi.org/10.1016/S2213-8587(20)30152-2).
6. Pal R, Bhadada SK. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? *Diabetes Res Clin Pract*. 2020;163:108146.
7. Carboni E, Carta AR, Carboni E. Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19? *Med Hypotheses*. 2020;140:109776. <https://doi.org/10.1016/j.mehy.2020.109776> Epub ahead of print.
8. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: a systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes Metab Syndr*. 2020;14(3):241–6.
9. Castiglione V, Chiriaco M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother*. 2020. <https://doi.org/10.1093/ehjcvp/pvaa042>.

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