MINI REVIEW

Diabetes and COVID19: a bidirectional relationship

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The advent and rapid spread of the coronavirus disease-2019 (COVID19) pandemic across the world has focused attention on the relationship of commonly occurring comorbidities such as diabetes on the course and outcomes of this infection. While diabetes does not seem to be associated with an increased risk of COVID19 infection per se, it has been clearly demonstrated that the presence of hyperglycemia of any degree predisposes to worse outcomes, such as more severe respiratory involvement, ICU admissions, need for mechanical ventilation and mortality. Further, COVID19 infection has been associated with the development of new-onset hyperglycemia and diabetes, and worsening of glycemic control in pre-existing diabetes, due to direct pancreatic damage by the virus, body’s stress response to infection (including cytokine storm) and use of diabetogenic drugs such as corticosteroids in the treatment of severe COVID19. In addition, public health measures taken to flatten the pandemic curve (such as lockdowns) can also adversely impact persons with diabetes by limiting their access to clinical care, healthy diet, and opportunities to exercise. Most antidiabetic medications can continue to be used in patients with mild COVID19 but switching over to insulin is preferred in severe disease.

INTRODUCTION

Coronavirus disease 2019 (COVID19), caused by the novel severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) is the most significant pandemic to have affected humanity in the last 100 years. As of March 2021, more than 120 million documented infections have occurred worldwide, with more than 2.6 million deaths. As the COVID19 pandemic spreads, it appears likely that a significant proportion of the world’s population will be infected at some time or the other. Therefore, the interaction of COVID19 with other commonly occurring medical conditions needs to be studied so as to anticipate and thereby better manage the effects that they may have on one another.

Diabetes is one such comorbidity that affects more than 430 million people worldwide as of 2019 [1] and has the potential to unfavorably modify the natural history of COVID19. Conversely, COVID19 itself has been postulated to cause diabetes and to worsen glycemic control in pre-existing diabetes. Over the past year, a number of narrative, as well as systematic reviews analysing the link between diabetes and COVID19 infection, have been published [2–6], and their conclusions are summarized in Boxes 1 and 2. In this article, we attempt to build upon these earlier studies and critically analyse the bidirectional link between these two conditions, providing insights into the clinical implications of the relationship wherever applicable.

EFFECTS OF HYPERGlyCEmIA ON COVID19

Diabetes and risk of COVID

Individuals with diabetes do not seem to be at higher risk of being infected with SARS-CoV2, compared to the general population [2–4]. This is not entirely unexpected, as SARS-CoV2 generally affects the upper respiratory tract to begin with, and diabetes is in general not associated with a demonstrable increase in risk of upper respiratory tract infections (URTI) [5]. It is also possible that individuals with diabetes tend to follow non-pharmacological measures, such as mask wearing and social distancing more stringently than the general population, since they appreciate their higher risk of adverse outcomes of infection; this could have driven down infections in this population and masked a true increase in biological susceptibility.

Hyperglycemia and risk of adverse outcomes with COVID. In contrast to individuals without diabetes, COVID-19 infection in those with diabetes is associated with an increased risk of adverse outcomes such as more severe disease, pneumonia, ICU admissions, need for assisted ventilation and mortality. It is, however, not clear how much of this excess risk can be attributed to hyperglycemia, as people with diabetes (especially type 2 diabetes) have a higher frequency of other risk factors for severe COVID19 (such as advanced age, obesity, and cardiovascular disease) compared to those without diabetes.

A. Pre-existing diabetes and risk of adverse outcomes. It has been shown that among individuals with known diabetes, poor glycemic control preceding COVID19 infection (as measured by glycated hemoglobin levels) independently predicts adverse outcomes [6]. This reinforces the need for patients with all types of diabetes to maintain tight glycemic control during the pandemic period, a recommendation that might prove challenging to implement, given the difficulties in accessing chronic
B. Effect of mild degrees of hyperglycemia ("pre-diabetes") on COVID outcomes. There have been several studies looking at the effect of hyperglycemia (not necessarily in the range diagnostic of diabetes) on adverse COVID outcomes. Even slightly raised blood glucose levels (in individuals not hitherto known to have diabetes) have been shown to be associated with poor outcomes in COVID19. Wang et al. [11] studied 605 patients from two hospitals in Wuhan, China and found that those with fasting blood glucose (FBG) of 6.1 to 6.9 mmol/l (mg/dL here) at admission had a nearly threefold increased odds of 28-day in-hospital complications, (FBG) of 6.1 to 6.9 mmol/l at admission had a nearly threefold increased odds of 28-day in-hospital complications, compared to those with FBG below 6.1 mmol/l. From Guangdong (China), Zhang et al. [12] showed that FBG at admission accurately predicted 30-day adverse outcomes (acute respiratory distress syndrome, multiple organ dysfunction, ICU admissions, septic shock, or death), irrespective of the presence or absence of pre-existing diabetes. Indeed, it has recently been suggested that blood glucose levels should be considered as a "vital sign" while evaluating hospitalized patients with COVID19 infection [13].

C. Effect of new-onset hyperglycemia on COVID outcomes. In a study from Wuhan, it was found that the risk of ICU admission was highest for patients with new-onset diabetes, followed by individuals with known diabetes and was lowest in those with new-onset hyperglycemia without diabetes [14]. However, Bode et al. [15] have shown that hyperglycemia without diabetes is associated with worse outcome in COVID19 compared to pre-existing diabetes. The poor outcomes associated with new-onset diabetes may reflect the fact that these hitherto undiagnosed and untreated patients would have more profound hyperglycemia and uncorrected metabolic risk factors compared to those with previously diagnosed diabetes [16]. The bulk of currently available evidence seems to suggest that new-onset hyperglycemia (irrespective of whether or not it meets the criteria for a diagnosis of diabetes) is associated with worse outcomes in COVID19 [17, 18].

Antidiabetic drug therapy in COVID19 infection. There have been no formal clinical trials comparing various antidiabetic agents in the context of COVID19 infection, so most of the available recommendations are based on expert opinion [19, 20]. In general, there is no contraindication for the use of any of the available antidiabetic agents in the setting of mild to moderate COVID19 infection, and the patient can continue with his/her usual drug regimen, provided glycemic control is appropriate [21]. In severe COVID19 infection, it is always advisable to switch the patient to insulin therapy [21].
with Coxsackie B virus, mumps virus, cytomegalovirus, rubella virus, and enteroviruses being the most commonly implicated agents. This theory holds that limited virus-mediated damage to beta cells releases hitherto sequestered antigens that lead to activation of autoreactive T-lymphocytes, culminating in an autoimmune response that ultimately destroys the remainder of the beta-cell mass, leading to insulin-dependent type 1 diabetes [30]. This process usually takes weeks to months and cannot explain the immediate onset of diabetes during the acute phase of COVID19 infection but may underlie disease development in some patients who develop diabetes in the weeks to months following recovery from infection. Research regarding this type of diabetes remains inadequate.

Diabetogenic effects of host responses to COVID19 infection. Host responses to COVID19 infection in the form of disorganized and exuberant immune response, can also lead to perturbations in glycemic status. As with any other acute infection, severe COVID19 is associated with non-specific activation of the immune system, with outpouring of counter-regulatory hormones and pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) alpha, both of which are known to induce insulin resistance and hyperglycemia [31]. Sudden reduction in insulin sensitivity can precipitate diabetes in individuals with borderline beta-cell function and may even manifest as hyperglycemic crises in those with previously undiagnosed (and untreated) diabetes.

**Hyperglycemia during COVID19 pandemic in individuals without COVID19 infection**

In this context, it should not be forgotten that the COVID19 pandemic and the consequent policy responses such as lockdowns, have had profound effects on the lives of individuals with pre-existing diabetes. Analysis of a large French database showed that COVID-19-induced lockdowns were associated with far-reaching changes in dietary habits and physical activity levels, and these changes occurred in both favorable and unfavorable directions [33]. In many parts of the world, individuals with diabetes have faced difficulties in achieving requisite amounts of physical activity and accessing healthy foods during the pandemic [34]. Many of these patients would have put off their regular physician visits for fear of contracting the virus from the hospital or physician’s office. Deterioration in glycemic control is therefore not an unexpected consequence of the COVID19 pandemic, and predictions have been published as to the magnitude of this deterioration [35]. However, it is heartening to note that a few studies have actually shown improvement of glycemic control during the COVID19 pandemic [36, 37]. This may be due to increased awareness of the deleterious effects of diabetes particularly with reference to COVID, as well as patients having had more time to manage their diabetes in the “new normal” of working from home. There could, however, be a selection bias in these studies as only well-motivated patients would have ventured to seek clinic-based care during the lockdown.

Ghosh et al. [38] analyzed 282 patients with new-onset diabetes diagnosed during the COVID pandemic and compared them with 273 individuals newly diagnosed with diabetes immediately prior to the pandemic. They found that individuals with new-onset diabetes during the COVID pandemic had higher fasting and postprandial glucose levels and glycated hemoglobin compared to those diagnosed before the pandemic, even though the two groups did not differ significantly in any other respect including exposure to COVID (as measured by SARS-CoV2 antibody levels). Interestingly, based on data from multiple studies, Misra et al. [25] have stated that individuals without COVID19 infection who were diagnosed with either type 1 or type 2 diabetes during the pandemic, tended to present with more severe hyperglycemia than was the case prior to the pandemic (with a higher frequency of DKA in those presenting with type 1 diabetes). The worse metabolic profile of new-onset diabetes during the COVID pandemic is probably a reflection of increased stress, reduced physical activity and access to healthy foods and delayed diagnosis due to reluctance to visit
physicians and hospitals during the pandemic and subsequent lockdown. It is likely that exacerbation in income inequalities following the lockdown will further worsen health outcomes, especially in countries like India where most healthcare is paid for “out-of-pocket” by the patient [39].

CONCLUSIONS

The bidirectional relationship between COVID19 and hyperglycemia-diabetes presents a major challenge to healthcare systems as the pandemic spreads across the globe. It is essential that individuals with pre-existing diabetes get their blood glucose levels under control at the earliest so as to minimize adverse outcomes of COVID19, should they contract the infection. At the same time, physicians involved in the care of patients with COVID19 should be aware of the diabetogenic potential of this virus and look for new-onset hyperglycemia and diabetes in their patients, especially those treated with corticosteroids.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas 9th Edition 2019. Available at https://www.diabetesatlas.org/en// [Accessed on 24th February 2021].

2. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020;8:782–92.

3. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109:531–8.

4. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol. Invest. 2020;43:867–9.

5. Unnikrishnan R, Misra A. Infections and diabetes: risks and mitigation with reference to India. Diabetes Metab. Syndr. 2020;14:1889–94.

6. Williamson G, Guidinger C, Kelly NR. Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. J Chem Inf Model. 2019;59:3:1689–99.

7. Ghosh A, Arora B, Gupta R, Anoop S, Misra A. Effects of nationwide lockdown during COVID-19 epidemic on lifestyle and other medical issues of patients with type 2 diabetes in north India. Diabetes Metab. Syndr. 2020;14:917–20.

8. Targher G, Mantovani A, Wang XB, Yan HD, Sun QF, Pan KH, et al. Patients with diabetes are at higher risk for severe illness from COVID-19. Diabetes Metab. 2020;46:335–7.

9. Baron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol. 2020;8:813–22.

10. Feldman EL, Savellieff MG, Hayek SS, Pennhurst S, Kretzler M, Pop-Busui R. COVID-19 and diabetes: a collision and collision of two diseases. Diabetes. 2020;69:2945–69.

11. Wang S, Ma P, Zhang Z, Song S, Wang Z, Ma Y, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia. 2020;63:2102–11.

12. Zhang B, Liu S, Zhang L, Dong Y, Zhang S. Admission fasting blood glucose predicts 30-day poor outcome in patients hospitalized for COVID-19 pneumonia. Diabetes Obes. Metab. 2020;22:1955–7.

13. Kesavaev J, Misra A, Saboo B, Aravind SR, Hussain A, Czupryniak L, et al. Blood glucose levels should be considered as a new vital sign indicative of progress during hospitalization. Diabetes Metab. Syndr. 2021;15:221–7.

14. Zhang Y, Li H, Zhang J, Cao Y, Zhao X, Yu N, et al. The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: A single-centre, retrospective, observational study in Wuhan. Diabetes Obes. Metab. 2020;22:1443–54.

15. Bode B, Garrett V, Messier J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci. Technol. 2020;14:831–21.

16. Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes. Metab. 2020;22:1897–906.

17. Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract. 2020;167:108382.

18. Stefan N, Birkenfeld AL, Schulze MB, Ludvig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat. Rev. Endocrinol. 2020;16:341–2.
