JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
JDI UPDATES

One year into the clash of pandemics of diabetes and COVID-19: Lessons learnt and future perspectives

The coronavirus disease 2019 (COVID-19) pandemic has infected more than 176 million people worldwide and caused more than 3.8 million deaths[1]. Diabetes mellitus is another pandemic affecting approximately 463 million people globally. Although diabetes does not increase the risk of contracting COVID-19, it has emerged as one of the most important comorbidities affecting the prognosis of COVID-19 patients[2]. Both type 1 and type 2 diabetes are associated with increased COVID-19 mortality[3]. Furthermore, their prognosis is further worsened by the presence of microvascular and macrovascular diabetic complications[4]. In fact, the relationship between COVID-19 and diabetes is bidirectional, further complicating the issue (Figure 1).

The COVID-19 pandemic has significantly disrupted diabetes-related acute care, exemplified by a territory-wide study in Hong Kong in the early months of the pandemic. There was an abrupt 25% drop in hospitalization rates for both severe hyperglycemia or hypoglycemia since the first confirmed local case of COVID-19[5]. People with diabetes might avoid attending hospital to minimize the risk of contracting COVID-19, and to avoid burdening the already hard-hit healthcare system. Hence, being caught in the perfect storm of diabetes and COVID-19 pandemics, practical guidance has been devised for people with diabetes and healthcare professionals to support them during this challenging time[6].

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Received 20 July 2021; revised 2 August 2021; accepted 5 August 2021

The rapid spread of the COVID-19 pandemic has also forced governments to implement containment or lockdown, inducing significant lifestyle changes that adversely affect bodyweight and glycemic control. Studies in Japan showed that patients with diabetes adopted a more sedentary lifestyle since the declaration of a state of emergency in April 2020[7]. Notably, glycemic and bodyweight control inversely correlated with physical activities, and positively correlated with changes in meals and snacking[8]. The association between bodyweight reduction and improvement in glycemic control reiterated the importance of maintaining a healthy lifestyle during the COVID-19 pandemic[7].

Glycemic control bears an important prognostic implication in COVID-19. A recent study in China showed that patients with pre-admission glycated hemoglobin ≥6.5% were more likely to develop respiratory complications from COVID-19 than those with glycated hemoglobin <6.5%[9]. Therefore, does better glycemic control improve COVID-19-related outcomes in people with diabetes? Data from several retrospective studies from China were reviewed and discussed by Naruse[10], reaffirming the importance of good glycemic control in COVID-19 patients with diabetes. The largest retrospective longitudinal multicenter study of 7,337 Chinese patients with COVID-19 showed that patients with pre-existing diabetes were more likely to require medical interventions and had higher mortality (adjusted hazard ratio 1.49) than those without. Importantly, compared with patients with worse glycemic control (defined by the highest blood glucose >10.0 mmol/L), those with better glycemic control (defined by their blood glucose of 3.9–10.0 mmol/L) had much lower mortality, as well as lower inflammatory and tissue injury markers[10].

The commonly used medications among people with diabetes, metformin and renin–angiotensin–aldosterone system (RAAS) inhibitors, have been extensively evaluated for their benefits and safety in COVID-19 patients. Experimental studies have shown the anti-inflammatory and anti-viral actions of metformin beyond its glucose-lowering effect [11]. Lui *et al.*[12] critically appraised recent clinical studies on the use of metformin in COVID-19 patients with diabetes and the association with mortality. Available evidence so far suggested that metformin might be associated with reduced mortality, and the risks and benefits of using metformin had been determined in a multicenter retrospective analysis of 1,213 COVID-19 patients with pre-existing type 2 diabetes in China. Lactic acidosis was not observed in metformin-treated patients with mild COVID-19, and the risk of acidosis was only increased in those individuals with more severe COVID-19, impaired renal function and receiving a high dose of metformin. Hence, in mild cases of COVID-19, it is not necessary to discontinue metformin, whereas in more severe cases, metformin should be used cautiously with close monitoring for potential adverse effects.

Concern has been raised on the use of RAAS inhibitors (RAASi) in COVID-19 patients, because the expression of angiotensin-converting enzyme 2, the entry receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), might be increased by RAASi. It is therefore crucial to clarify whether RAASi can worsen COVID-19 outcomes. The controversy was deliberated by Amano[13], and it was concluded that RAASi should not be stopped merely for concerns of worse

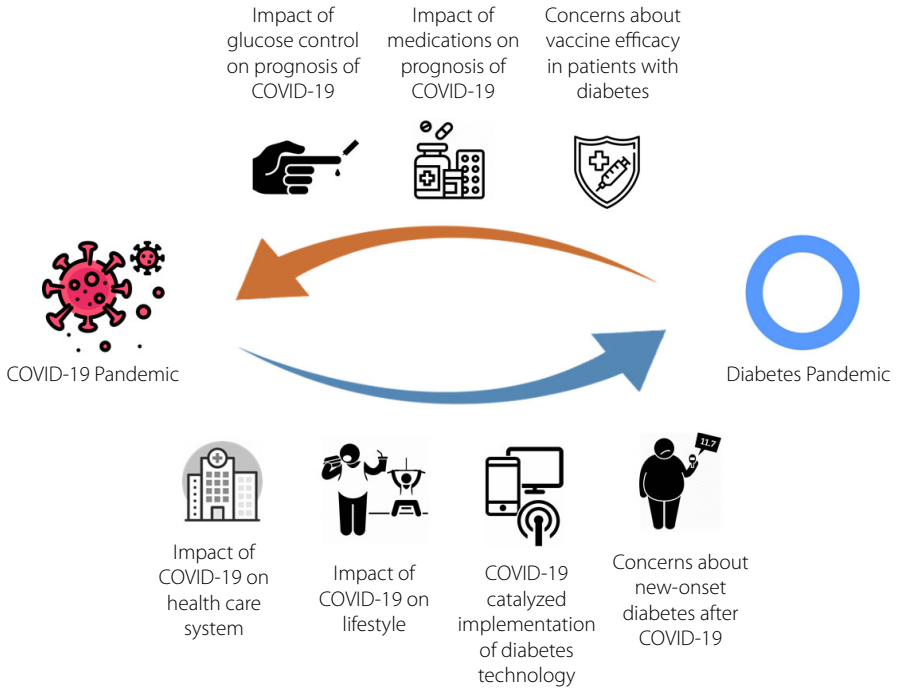

Figure 1 | The bidirectional relationship between diabetes and coronavirus disease 2019 (COVID-19). The impact of the diabetes pandemic on the COVID-19 pandemic includes: the association of glucose control and medication use with the prognosis of COVID-19; and the potential concerns about COVID-19 vaccine efficacy in patients with diabetes. The impact of the COVID-19 pandemic on the diabetes pandemic includes: the health care system, such as diabetes-related acute care; the lifestyle of patients with diabetes; catalyzing the implementation of diabetes technology; and the potential concerns about new-onset diabetes after COVID-19.

COVID-19 outcomes. This was based on evidence including the findings from a large case-population study in Spain showing that RAASi exposure, both pre-admission and during hospitalization, was not associated with any signal of increased risk of requiring hospitalization, intensive care unit admission and mortality in COVID-19 patients.

The COVID-19 pandemic has catalyzed the incorporation of diabetes technology into daily diabetes care. During the pandemic, telemonitoring has allowed safe fasting during Ramadan, without severe hypoglycemia or diabetic ketoacidosis, in people with type 1 diabetes receiving insulin pump therapy[14]. Furthermore, with the help of continuous glucose monitoring, reassuring data showed that adolescents and children with type 1 diabetes did not have deterioration in glycemic control and had even fewer hypoglycemic events during the pandemic[15]. Regarding in-patient management of COVID-19 patients with diabetes, a prospective study in China showed the potential beneficial effects on COVID-19-related outcomes using continuous glucose monitoring compared with point-of-care testing of capillary glucose[16]. Using telemedicine to follow up patients with diabetes during the COVID-19 pandemic appeared to perform as well as clinic visits in terms of improvements in glycemic control[17].

Hopefully, timely vaccination can bring an end to this fight against the COVID-19 pandemic. The kinetics and durability of the neutralizing antibody response to SARS-CoV-2 were not affected by the presence of diabetes[18], supporting the rationale that vaccination would also effectively protect individuals with diabetes. Data are scant focusing on patients with diabetes in the clinical trials of vaccines, and there are some preliminary data showing similar vaccine efficacy in this subgroup[19]. Given their propensity to develop more adverse COVID-19-related outcomes, vaccination should be prioritized for people with diabetes. Last, but not least, the long-term sequelae of COVID-19 must not be overlooked. With reports of new-onset hyperglycemia and diabetic ketoacidosis among COVID-19-infected individuals, it remains to be elucidated whether COVID-19 can induce new-onset diabetes, which might be answered with the global registry of the CoviDIAB Project[20].

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed Consent: N/A.
Approval date of Registry and the Registration No. of the study/trial: N/A.
Animal Studies: N/A.

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Doi: 10.1111/jdi.13644