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Commentary

SGLT2 inhibition during the COVID-19 epidemic: Friend or foe?

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Introduction

Type 2 diabetes mellitus (T2DM) is a risk factor for severe illness related to COVID-19 (Coronavirus Disease 2019), and is associated with at least a twofold increased mortality rate [1]. Several factors for a poor prognosis have been identified in the Coronavirus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and Diabetes Outcomes (CORONADO) observational study in France as well as other recent reports from the US and China [2]. However, the potential positive, negative or neutral influences of glucose-lowering agents on clinical outcomes during COVID-19 remain unclear. Sodium–glucose cotransporter type 2 inhibitors (SGLT2is) are now the preferred antidiabetic agents for patients with T2DM and at high or very high cardiovascular risk, including coronary artery disease, heart failure and renal impairment with albuminuria. However, these patients are more prone to develop severe complications when exposed to COVID-19 and have higher death rates due to cardiac or renal complications beyond pulmonary infection [2]. Therefore, it is of major clinical interest to ascertain whether SGLT2is can exert either favourable or deleterious effects on clinical outcomes during COVID-19 infection. For this reason, the present viewpoint is a brief discussion of the potential benefits and harms of SGLT2i treatment in patients with T2DM and COVID-19.

Potential benefits

SGLT2is exert anti-inflammatory effects on both systemic and tissue low-grade inflammation. Their underlying mechanisms are multiple, including a reduction in adipose tissue inflammation beyond that commonly observed with weight loss [3]. As an example, empagliflozin can increase fat utilization and browning of white adipose tissue, and attenuate obesity-induced inflammation and insulin resistance by activating M2 macrophages [4]. This effect is of potential interest because adipose tissue, including ectopic fat deposits, has been considered a contributor to the cytokine storm seen in patients with severe COVID-19 as well as being responsible for their poor prognoses, including death [2,5]. In addition, SGLT2is can produce other positive effects that could be beneficial in COVID-19 patients with hypoxaemia and interstitial lung oedema, including: increases in haematocrit; selective reduction of interstitial volume with minimal changes in blood volume; a shift in cellular energy metabolism and a reduction in hypoxia; diminution of oxidative stress; and cellular protection due to reductions in cytoplasmic Na^+ and Ca^{++} concentrations.

Dapagliflozin has been reported to reduce lactate levels through various mechanisms [6]. A lactate decrease reduces the activation of lactate/H^+ symporters, thereby diminishing H^+ ion pumping into cells. This means that the cytosolic pH might be maintained in the presence of dapagliflozin despite SARS-CoV-2 infection. This virus is responsible for creating a highly anaerobic environment by disrupting tissue oxygenation, whereas enhancing the production of lactate through anaerobic glycolysis amplifies oxidative stress and increases the release of proinflammatory cytokines. It has therefore been hypothesized that dapagliflozin might prevent the severe course of COVID-19 infection by preventing the lowering of cytosolic pH and reducing the viral load [6].

One concise anecdotal report described three non-diabetes patients who each received an SGLT2i when hospitalized for severe pneumonia due to COVID-19, and concluded there was a lack of efficacy of SGLT2is against the natural evolution of the infection [7]. The CORONADO study had no data on this issue because dapagliflozin has only recently been made available in France [2]. Thus, researchers are now waiting for the results of a large ongoing international randomized controlled trial [*Dapagliflozin* in Respiratory Failure in Patients with COVID-19 (DARE-19): ClinicalTrials.gov identifier: NCT04350593]. This is a multicentre parallel-group, double-blind, placebo-controlled study of hospitalized adult patients (900 patients with or without diabetes) with mild-to-moderate manifestations of COVID-19, but without the need for mechanical ventilation at the time of screening. All eligible patients had to have risk factors for developing serious complications of COVID-19 with a history of at least one of the following: hypertension; T2DM; atherosclerotic cardiovascular disease; heart failure and/or chronic kidney disease stages 3/4. The study is evaluating the efficacy of dapagliflozin 10 mg vs. a placebo given once daily for 30 days in addition to the background local therapeutic standard of care. The primary efficacy endpoint is the time to the first occurrence of either all-cause death or morbid

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disease complications (respiratory, cardiovascular, kidney) during the 30-day follow-up.

Potential concerns

One adverse event commonly reported with SGLT2is in both randomized controlled trials and observational studies is a twofold higher risk of diabetic ketoacidosis (DKA) compared with placebo or other active glucose-lowering agents [8]. Moreover, the risk is higher in older patients with T2DM of long duration and lower insulin secretion capacity. Although this adverse event is extremely rare in the general population with T2DM, it may represent an important concern during the COVID-19 outbreak. Indeed, SARS-CoV-2 infection can also cause DKA, as was observed in China [9], the UK [10] and France [2]. Patients with COVID-19 and DKA generally also had severe hyperglycaemia requiring very high doses of insulin, and such metabolic disturbances may result from severe insulin resistance combined with decreased insulin secretion due to beta-cell dysfunction and perhaps even destruction by SARS-CoV-2 [10]. In contrast, the use of SGLT2is is more commonly associated with euglycaemic DKA, as hyperglycaemia is damped down by the concomitant increase in glucosuria [8]. However, whether SGLT2is can increase the likelihood of COVID-19-related DKA, especially among patients with severe insulin deficiency, remains unknown yet plausible.

Conclusion

SGLT2is exert a variety of effects that could favourably influence outcomes in COVID-19 patients, although this idea has yet to be demonstrated in the well-designed randomized controlled trial that is currently underway. Nevertheless, concerns over the possibly increased risk of DKA should not be ignored. In patients with asymptomatic or mild COVID-19, SGLT2i treatment should be continued to maintain the best possible glucose control and perhaps also to take advantage of its various other positive effects beyond glucose control. However, in patients with more severe COVID-19 who require hospitalization, caution is recommended, as is also the advice to withhold SGLT2is because of a possible increased risk of DKA and to shift to insulin therapy with appropriate intensification on the basis of glucose monitoring.

Disclosure of interest

No conflicts of interest are directly relevant to the content of this manuscript.

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