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MINI-REVIEW

Judicious use of sodium-glucose cotransporter 2 inhibitors in patients with diabetes on coronavirus-19 pandemic

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Abstract: Sodium glucose cotransporter-2 inhibitors (SGLT2i), a novel antidiabetic drug blocks the reabsorption of glucose in proximal tubules of kidney, are demonstrated to have cardiovascular and renal benefits for people with diabetes. The benefits are associated with the significant increase of intrarenal angiotensin-converting enzyme II (ACE2) expression and blood volume contraction. However, the increased ACE2 may be detrimental to patients infected with the coronavirus infection 2019 (COVID-19), which is found to invade cells via the entry receptor of ACE2. Besides, an SGLT2i-induced natriuretic effect may also increase the risk of acute kidney injury and affect the hemodynamic stability during systemic infection disease. In this article, we explain the mechanisms why the use of SGLT2i in people with diabetes may lead to worse outcomes and suggest clinician to judiciously use it during COVID-19 pandemic.

Keywords: Angiotensin-converting enzyme II; Coronavirus infection 2019 (COVID-19); Sodium glucose cotransporter-2 inhibitors,

Since the outbreak of pandemic novel coronavirus from Wuhan, Hubei province of China in the late 2019, the rapid spreading of the coronavirus disease 2019 (COVID-19) has continued affecting the global healthcare system and economy.[1] The most common manifestations of COVID-19 include fever, respiratory tract symptoms, gastrointestinal symptoms, and loss of taste and smell.[2] Aside from respiratory tract symptoms, COVID-19 may also invade heart and kidney, leading to acute cardiac dysfunction or acute kidney injury (AKI).[3] Although the reported mortality of COVID-19 was lower than the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, patients with comorbidities are more vulnerable to disease progression and have worse prognosis than healthy people.[4] Other than the initial reports from China, later reports from Italy showed that patients dying due to COVID-19 tended to be elderly (mean age of 79.5 years), had more underlying diseases such as diabetes mellitus (35.5%), ischemic heart diseases (30%), active cancer (20.3%), atrial fibrillation (24.5%), dementia (6.8%), and a history of stroke (9.6%).[5,6]

Similar to the SARS-CoV, the entry receptor of COVID-19 is angiotensin-converting enzyme II (ACE2), a zinc metalloprotease and a crucial regulator of the renin-angiotensin-aldosterone system (RAAS) that converts angiotensin I into angiotensin-(1–9) and angiotensin II into angiotensin-(1–7).[7] Angiotensin-(1–7) can bind to the G protein-coupled receptor Mas and counteracts the effects of angiotensin II. In contrast to the effect of ACE, the enhancement of ACE2 induces beneficial responses including vasodilatation, anti-inflammation, antiproliferation, and antifibrosis, which may be related to the improvement of cardiovascular and renal outcomes.[8] ACE2 is widely distributed in various human organs, including oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, kidney, brain, and blood vessels, and the distribution is highly associated with the clinical manifestations of COVID-19.[9] Therefore, there are controversies about whether or not the use of ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB) will enhance the ACE2 expression and promote virus replication. With regards to the clinical benefits of ACEI/ARB in patients with cardiovascular disease, several professional societies have made statements to provide guidance in the use of ACEI/ARB in COVID-19 patients.[10] Continuing to use ACEIs/ARBs in COVID-19 patients with clinical indications, such as heart failure, diabetes, and hypertension, is recommended, but the addition of new ACEIs/ARBs in other patients is not suggested.

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are demonstrated to have cardiovascular and renal benefits in addition to its antidiabetic effects.[11] The 2020 pharmacologic

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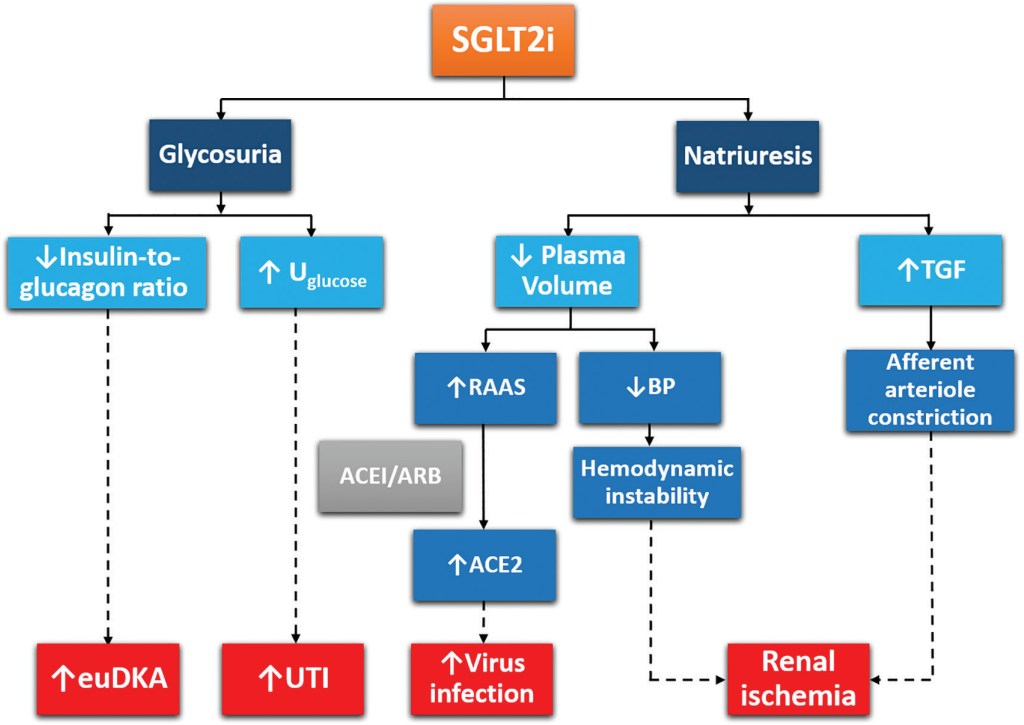

Fig. 1 SGLT2i may induce unfavorable outcome in patients with diabetes during COVID-19 pandemic. ACE2 = angiotensin-converting enzyme II, ACE1 = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BP = blood pressure; COVID-19 = coronavirus infection disease 2019; euDKA = euglycemic diabetic ketoacidosis; RAAS = renin-angiotensin-aldosterone system; SGLT2i = sodium glucose cotransporter-2 inhibitor; TGF = tubulo-glomerular feedback; $U_{glucose}$ = urine glucose; UTI = urinary tract infection;.

guidance to diabetes published by the American Diabetes Association has recommended using SGLT2i as the second-line treatment to metformin (first-line drug) for patients with high risk of or documented atherosclerotic cardiovascular disease, heart failure with reduced ejection fraction, or chronic kidney disease (estimated glomerular filtration rate of 30 to 60 ml/min/1.73 m2 or microalbuminuria).[12] Even in patients without the aforementioned comorbidities, SGLT2i is still the preferred choice owing to its advantages in minimizing hypoglycemia and promoting weight loss.[12] SGLT2i can block the reabsorption of filtrated sodium and glucose in the proximal tubules, and thus increase the sodium concentration in the distal tubules and induce afferent arteriole vasoconstriction via tubuloglomerular feedback. The mechanisms through which SGLT2i can induce the reduction in intraglomerular pressure are different from the effects of ACEI/ARB, which mainly come from the vasodilation of efferent arterioles. Besides, the natriuretic effect of SGLT2i can result in blood volume contraction that stimulates RAAS activity. Clinical experiments showed that the combined use of SGLT2i and ACEI/ARB significantly increases intrarenal ACE2 expression, which may be closely related to improving cardiac and renal function.[13] However, the increase of intrarenal ACE2 may no longer be beneficial in COVID-19 infection. Although the reported prevalence of AKI is only 0.5% to 7% among COVID-19 patients, both preexisting chronic kidney disease at admission and the development of AKI during hospitalization are found to be associated with in-hospital mortality.[14] The relatively high ACE2 expression on podocytes and proximal straight tubule cells may facilitate viral entry and replication, causing direct cytopathic injury associated with proteinuria and may induce occult renal damage. Even though only a few patients with COVID-19 met the clinical criteria of AKI, the direct cytopathic injury could still induce kidney damage and accelerate the progression of diabetic nephropathy. In addition, COVID-19 may induce cardiomyopathy and lead to unstable hemodynamics, causing renal ischemia. The natriuretic effect of SGLT2i induces blood volume contraction, interferes the hemodynamic stability, and may be detrimental during active disease. Another important concern is that use of SGLT2i for patients with diabetes with COVID-19 infection may increase the incidence of other complications, including urinary tract infection and diabetic ketoacidosis. To summarize the above inference, using SGLT2i may lead to a worse prognosis of patients with

Table

Clinical suggestions for using SGLT2i during COVID-19 pandemic

1. Patients with diabetes with documented COVID-19 infection
   a. Avoid the addition of SGLT2i for better glycemic control
   b. Discontinue previously prescribed SGLT2 during this period before complete recovery from COVID-19 infection because glycemic control can be usually achieved by titration of other antidiabetic agents (such as insulin)
2. Patients with diabetes without documented infection but under quarantine or isolation
   a. Avoid the addition of SGLT2i for better glycemic control
   b. Discontinue or decrease previously prescribed SGLT2i dosage because glycemic control can be usually achieved by up-titration of other oral antidiabetic agents or insulin
3. Patients with diabetes without documented infection and not under quarantine or isolation
   a. Avoid the addition of SGLT2i before COVID-19 vaccine is available unless the therapeutic benefit clearly outweighs the risk of cardiovascular mortality
   b. Do not increase previously prescribed SGLT2i dosage because glycemic control can be usually achieved by up-titration of other oral antidiabetic agents or insulin

COVID-19 = coronavirus infection disease 2019; SGLT2i = sodium glucose cotransporter-2 inhibitor.

diabetes under the COVID-19 pandemic.[15] The above hypothesis is illustrated in **Fig. 1**.

Because diabetic nephropathy is the major cause of end-stage renal disease, SGLT2i is generally recommended for patients with diabetes with nephropathy to delay the worsening of renal function by decreasing intraglomerular pressure and reducing microalbuminuria. However, clinicians should consider if SGLT2i use would promote virus replication by enhancing intrarenal ACE2 expression in COVID-19 patients, which may lead to deterioration of renal function and further impact the viral activity in the lungs and heart. Unlike ACEI/ARB, the clinical benefits of SGLT2i use to improve cardiac and renal outcomes may need more strong evidence to support its irreplaceability. Additional prospective trials are imperative to confirm the advantages and disadvantages of SGLT2i in COVID-19 patients, including combined use with ACEI/ARB. Due to the uncertainty of SGLT2i use in patients with COVID-19 infection, we have enumerated the following suggestions in **Table**.

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