Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SGLT-2 inhibitors as cardioprotective agents in COVID-19

To the Editor,

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus is a global pandemic impacting nearly 10 million people worldwide. Since the initial detection in December 2019, this novel coronavirus has posed major challenges to the human race. The disease has a varied spectrum of presentation with respiratory system being most commonly affected followed by the cardiovascular (CV) system in later stages of the disease.[1] Multiple risk factors accounting for an adverse outcome include older age, male sex and presence of comorbidities such as diabetes, hypertension, chronic kidney disease and obesity.[1,2] Acute respiratory failure and fulminant myocarditis have been reported as the most common causes of death.[1] A lack of a specific therapy for COVID-19 has ushered in a global race for development of new drugs and vaccines. Emergence of the novel coronavirus also led to repurposing of several drugs such as anti-malarial drugs chloroquine and hydroxychloroquine, anti-HIV drugs viz. lopinavir/ritonavir. However, the safety and efficacy of these drugs have not been completely established in the current scenario.

Pathogenesis and current treatment options

Transmission of SARS-CoV-2 to humans occurs through respiratory droplets with median incubation period being 5.1 days. The SARS-CoV-2 infection is caused following binding of the viral spike protein to human angiotensin-converting enzyme-2 (ACE-2) receptors expressed on Type II pneumocytes in the lungs. Viral entry occurs by endocytosis and then utilising the host cell machinery, synthesis of viral structural protein and genome occurs followed by release of mature virions by exocytosis. Viral replication leads to a dysregulated immune response with a release of several pro-inflammatory cytokines such as IL-1, IL-2, IL-6 culminating in a cytokine storm resulting in acute respiratory distress, myocarditis, thromboembolic complications, multiorgan failure and death.[1] In addition, this inflammatory milieu leads to an increased production of free radicals and hence increased levels of oxidative stress. Use of anti-inflammatory and immunomodulatory agents such as corticosteroids, IL-6 inhibitors (tocilizumab, sarilumab) have shown to be promising therapies for COVID-19 infection. A significant chunk of patients have serious cardiovascular complications such as myocardial infarction, myocarditis, heart failure and arrhythmias with a recent study showing marked cardiac damage and ongoing cardiac inflammation even in patients recovered from COVID-19 infection.[3] This calls for a need for cardio-protective strategies as one of the therapeutic approaches especially in critically ill patients.

SGLT2 inhibitors: a new ray of hope

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i), a novel class of antidiabetics, acts on the SGLT transporters located in the proximal convoluted tubule of the nephron and promotes excretion of glucose leading to a decrease in plasma glucose levels. While originally intended as a promising anti- diabetic drug, recent studies have highlighted its role in reduction of cardiovascular mortality and hospitalization for heart failure even in absence of diabetes.[4] SGLT2i have been reported to prevent the release of various proinflammatory cytokines such as IL-6.[5] Dapagliflozin is known to cause a reduction in lactate levels by decreasing its release from epicardial adipose tissue and causing a lowering in oxygen consumption in tissues and promoting glucose utilisation in the aerobic pathway.[6] Decreased lactate levels reduces the activation of lactate/H^+ symporter and thus maintaining an adequate cytosolic pH. This leads to a decreased entry of SARS-CoV-2 into cells due to an increase in the cytosolic pH. In addition, SGLT2i leads to an increase in the ACE-2 level which leads to greater production of the angiotensin 1–7 which is a potent vasodilator, anti-oxidant and anti-fibrotic which helps in the prevention of acute respiratory distress syndrome (ARDS) and alleviating cytokine storm.[7] Increased ACE-2 levels were initially thought to increase viral entry however recent evidence stands contrary to the same as there is a limited availability of a serine protease transmembrane protease serine 2 (TMPRSS2) which is required for binding to ACE2 receptors.[6,7]

SGLT2i have previously been shown to have potent cardio- and reno-protective effects in patients with type 2 diabetes, heart failure and/or chronic kidney disease[4] and this class of drugs may afford protection to these vital organs in the setting of COVID-19 infection. SGLT2i inhibits the activity of the Na^+/H^+exchanger isoform (NHE1) which leads to decreased cardiac remodelling and heart failure progression.[8] Inhibition of NHE-1 leads to increased mitochondrial Ca^{2+} levels resulting in an increased ATP production in the cardiac tissues. SGLT2i such as empagliflozin has also been shown to ameliorate myocardial oxidative stress as well as decrease in cardiac fibrosis. This may have a putative role in COVID-19 patients with myocarditis and adverse cardiac remodelling.[8] In addition, SGLT2i cause an increase in glucagon levels which has a positive inotropic and chronotropic effect hence leading to cardiovascular protection. These drugs also cause a switch in the myocardial fuel utilization from glucose towards ketone bodies and free fatty acids leading to better cardiac energetics.[8] In critically ill COVID-19 patients, there is an increased activation of neurohumoral mediators such as renin-angiotensin system (RAS) along with oxidative stress and inflammation which is detrimental to the functioning of the cardiovascular and renal systems. SGLT2i leads to intrarenal RAS suppression along with

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lowering of renal and cardiac sympathetic nervous system activity thus offering adequate cardiorenal protection.[9] SGLT2i also downregulates expression of inflammatory genes and reduces oxidative stress leading to the amelioration of cardiorenal dysfunction. In addition, SGLT2 inhibitors have also been shown to reduce myocardial sensitivity to ischaemia-reperfusion injury thus further enhancing the cardio-protective benefits.[10] The renal protective action of these drugs are mediated by the restoration of tubuloglomerular feedback leading to vasoconstriction of afferent arterioles and a decrease in albuminuria. In addition, SGLTi with its anti-inflammatory effects does have an impact on tubular functions especially in critically ill-patients and thus decreases the chances of acute kidney injury.[9]

Challenges in use of SGLT-2i in COVID-19

Use of SGLT-2i in diabetic patients with COVID-19 infection was initially met with resistance and speculation owing to the concerns of volume depletion, blood pressure reduction, risk of euglycemic diabetic ketoacidosis (DKA) during acute illness. An increased risk of euglycemic DKA occurs due to a reduced appetite leading to decreased carbohydrate consumption along with dehydration due to high fever or vomiting/diarrhoea and the osmotic diuretic effect of COVID-19 infection.[11] In addition, drug interactions are major concerns while prescribing SGLT2i. In view of these complications, health agencies had warned about safety concerns for SLGT2i and the risk of DKA in patients with both diabetes and COVID-19 infection. In this setting, they have recommended to avoid SGLT2 inhibitors in all patients with risk factors for developing symptoms or serious complications of COVID-19.[11] The potential role of SGLT-2i is being explored in the form of Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19, NCT04350593) trial[12] which is a phase III multinational RCT. This trial includes patients with mild-moderate COVID-19 infection and at least one of the following: type 2 diabetes, hypertension, atherosclerotic cardiovascular disease, heart failure and stage 3–4 chronic kidney disease who shall be randomised to receive either dapagliflozin 10 mg once daily or placebo along with standard of care. The primary endpoints include the time to first occurrence of all-cause death or comorbid disease complications during follow-up of one month.[12] The current evidence for the use of SGLT-2i in COVID-19 infection is very limited with a series from Italy reporting lack of benefit amongst three non-diabetic patients who were administered empagliflozin 10 mg for 5–7 days as an "off-label" adjunctive therapy. However, in this series it was the length of hospital stay and improvement in computerised tomography (CT) chest findings as the primary end-point and not cardio-renal protective effects.[13]

In absence of data on long term cardiovascular consequences of COVID-19 infection and recent evidence of significant cardiac involvement and ongoing cardiac inflammation even in recovered patients, there is a need for cardioprotective strategies and SGLT-2i are a promising aspect in this regard. SGLT-2i can be a potent adjunctive therapy in COVID-19 patients with myocardial injury or acute myocarditis as an effective cardioprotective agent. Their anti-inflammatory and neurohormonal actions further strengthen their role as cardioprotective agents in COVID-19 infection 19 which has been seen to have deleterious effects on cardiac functions. In the current scenario, risk-benefit analysis must be done while initiating these agents in newly diagnosed critically ill diabetic COVID-19 patients keeping in mind the risk of DKA in these patients. SGLT-2i does appear as a promising adjunctive therapy in COVID-19 patients owing to its strong cardio- and reno-protective effects however, further studies are needed to confirm these hypotheses.

Author contributions

KG and SK contributed to the conception of the work. KG and SK drafted the initial manuscript and edited the final manuscript. Both the authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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