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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Letter to the Editor

SGLT-2 inhibitors for COVID-19 — A miracle waiting to happen or just another beat around the bush?

To the Editor

In the absence of an effective drug or vaccine against novel severe acute respiratory syndrome corona virus (SARS-Cov-2) till date, "repurposing approach" of old pharmaceuticals has been applied to combat against 2019-coronavirus disease (COVID-19). Hydroxychloroquine, anti-retrovirals, type-1 angiotesin receptor blockers, statin, vitamin D, melatonin etc are being tried with questionable benefits [1]. While there are intensive debates regarding safety of different classes of antidiabetics at the advent of COVID-19 [2,3], multiple ongoing studies are evaluating the adjuvant role of various antidiaetics like dipeptidyl peptidase-4 (DPP-4) inhibitors [4,5], pioglitazone [6], glucagon-like peptide-1 (GLP-1) agonists [7] in reducing the severity of COVID-19. Dapagliflozin, an inhibitor of sodium-glucose transporter-2 (SGLT-2) has been recent addition to the trend [8].

Higher lactate dehydrogenase (LDH) and lactic acidosis have been found to statistically significantly associated with COVID-19 ($p = 0.0001$) [9]. Cure and Cure [10] have hypothesized that dapagliflozin might be beneficial in this context as it decreases lactatemia through different mechanisms (Table 1). With hyperlactatemia the Lactate-H^+ symporter gets activated to carry lactate and H^+ into the cell leading to decreased intracellular pH. At the same time, Na^+-H^+ exchanger (NHE), an antiporter which works to throws out H^+ in lieu of Na^+, also gets activated leading to cellular swelling. This, in turn, reverses the Na^+/Ca^{2+} exchange system to protrude Na^+ resulting in intracellular Ca^{2+}. The resulting cellular swelling and excitotoxicity lead to apoptosis [11]. SGLT-2 inhibitors inhibit this very NHE, thus protects from cellular lysis [10,12]. SGLT-2 inhibitors, irrespective of glycemic status decreases pro-inflammatory cytokines including those directly involved in "cytokine storm" of COVID-19 [13]. Moreover, SGLT-2 inhibitors promote the activation of alternative renin-angiotesin-aldosterone pathway through greater expression of angiotesin converting enzyme type-2 (ACE2) [14], a pathway that is grossly perturbed by SARS-CoV2 [15].

SGLT-2 inhibitors possess organ-protective effects beyond its glycemic benefits [16]. As large-scale analysis has revealed that patients with cardiometabolic and renal impairments are particularly vulnerable for worst COVID-19 outcome [17], SGLT-2 inhibitors might afford additional vital organ protection in the settings of COVID-19. With these hopes "Dapagliflozin in Respiratory Failure in Patients with COVID-19" (DARE-19, clinical trial number NCT04350593) [8], a phase-3 multi-national double-blind placebo-controlled randomized trial has been started. The study population includes hospitalized patients ≥18 years of age with mild-moderate COVID-19 infection having at least one of the following: type-2 diabetes, hypertension, diabetes, atherosclerotic cardiovascular disease, heart failure, stage 3-4 chronic kidney disease. Patients with severe disease, type-1 diabetes, history of diabetic ketoacidosis (DKA) within last 6 months or on treatment with any SGLT-2 inhibitors were excluded. Patients will be treated with either dapagliflozin 10 mg once daily or placebo on top of standard of care. The primary efficacy endpoint of the study is time to first occurrence of all-cause death or comorbid disease complications through the follow-up period of 1month.

Although the proposed mechanistic benefits of SGLT-2 inhibitors in COVID-19 settings seem to be lucrative, the decision to take-up this trial is not beyond criticism. Expert panel has recommended against the use of SGLT-2 inhibitors among COVID-19 patients due to risk of dehydration and euglycemic DKA [18]. Although association between SGLT-2 inhibitors and peripheral arterial disease (PAD) is still unclear [19], there are instances of severe PAD complicating the course of COVID-19 [20]. In this view the DARE-19 trial seems to be an extremely risky proposition. Moreover, therapeutic armamentarium targeted against the associated metabolic perturbations must be instituted judiciously but extrapolation of the same drugs to combat against SARS-CoV2 will probably be proved to be a futile approach with every possibility of missing the actual target, the virion. This ultimately results in beating the bush for treatment of comorbidities at the cost of losing the track to treat a viral infection.

Table 1
Rationality of using dapagliflozin in COVID-19.

A. Reduced serum lactate level
1. Reduces oxygen consumption in tissues and channelizes glucose towards the aerobic pathway, thus diminishing lactate production
2. Reduces lactate release from adipose tissue
3. Increased renal excretion of lactate
B. Inhibition of NHE
C. Organ protective effective (heart, vasculature, kidney)
D. Activation of alternative RAAS pathway by activating ACE2
E. Decreased proinflammatory cytokines
F. Glycemic control

Conflict of interest

Nil.

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