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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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 coronavirus 2 (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 angiotensin 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 antidiabetics 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 hyper-lactatemia 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 throw out H+ in lieu of Na+, also gets activated leading to cellular swelling. This, in turn, reverses the Na+/Ca2+ exchange system to protract Na+ resulting in intracellular Ca2+. 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-angiotensin-aldosterone pathway through greater expression of angiotensin 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 1 month.

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.

Conflict of interest

Nil.

Funding

Nil.

References

[1] M. Phadke, S. Saunik, COVID-19 treatment by repurposing drugs until the vaccine is in sight, Drug Dev. Res. (March) (2020), http://dx.doi.org/10.1002/ddr.21666, Epub ahead of print. PMID: 32277357; PMCID: PMC7228332.
[2] R. Pal, S.K. Bhadada, Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? Diabetes Res. Clin. Pract. 163 (April) (2020), 108146, http://dx.doi.org/10.1016/j.diabres.2020.108146.

[3] A. Cerioli, A.P. Stoian, M. Rizzo, COVID-19 and diabetes management: what should be considered? Diabetes Res. Clin. Pract. 163 (April) (2020), 108151, http://dx.doi.org/10.1016/j.diabres.2020.108151.

[4] G. Jacobelli, COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res. Clin. Pract. 162 (March) (2020), 108125, http://dx.doi.org/10.1016/j.diabres.2020.108125.

[5] ClinicalTrials.gov, Effects of DPP4 Inhibition on COVID-19, 2020 https://clinicaltrials.gov/ct2/show/NCT04341935.

[6] E. Carboni, A.R. Carta, E. Carboni, Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19? Med. Hypotheses 140 (April) (2020), 109776, http://dx.doi.org/10.1016/j.mehy.2020.109776.

[7] S.R. Bornstein, R. Dalan, D. Hopkins, G. Mingrone, B.O. Boehm, Endocrine and metabolic link to coronavirus infection, Nat. Rev. Endocrinol. 16 (6) (2020) 297–298, http://dx.doi.org/10.1038/s41574-020-0353-9 (April).

[8] ClinicalTrials.gov, Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19), 2020, Available from: https://www.clinicaltrials.gov/ct2/show/NCT04350593 (Last accessed 1 May 2020).

[9] R. Mardani, A. Ahmadi Vasmejani, F. Zali, A. Gholami, S.D. Mousavi Nasab, H. Kaghazian, et al., Laboratory parameters in detection of COVID-19 patients with positive RT-PCR; a diagnostic accuracy study, Arch. Acad. Emerg. Med. 8 (2020) e43.

[10] E. Cure, M.C. Cure, Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis, Diabetes Metab. Syndr. 14 (2020) 405–406.

[11] Y. Matsumoto, S. Yamamoto, Y. Suzuki, T. Tsuibo, S. Terakawa, N. Ohashi, et al., Na+/H+ exchanger inhibitor, SM-20220, is protective against excitotoxicity in cultured cortical neurons, Stroke 35 (2004) 185–190.

[12] L. Uthman, A. Baartscheer, B. Bleijlevens, C.A. Schumacher, J.W.T. Fiolet, A. Koeman, et al., Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na+/H+ exchanger, lowering of cytosolic Na+ and vasodilation, Diabetologia 61 (2018) 722–726.

[13] F. Bonnet, A.J. Scheen, Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease, Diabetes Metab. 44 (2018) 457–464.

[14] D. Kawanami, K. Matoba, Y. Takeda, Y. Nagai, T. Akamine, T. Yokota, et al., SGLT2 inhibitors as a therapeutic option for diabetic nephropathy, Int. J. Mol. Sci. 18 (2017) 1083.

[15] H. Cheng, Y. Wang, G.Q. Wang, Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19, J. Med. Virol. (March) (2020), http://dx.doi.org/10.1002/jmv.25785, Epub ahead of print. PMID: 32221983.

[16] M.G. Minze, K.J. Will, B.T. Terrell, R.L. Black, B.K. Irons, Benefits of SGLT2 inhibitors beyond glycemic control - a focus on metabolic, cardiovascular and renal outcomes, Curr. Diabetes Rev. 14 (2018) 509–517.

[17] W.J. Guan, W.H. Liang, Y. Zhao, H.R. Liang, Z.S. Chen, Y.M. Li, et al., Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis, Eur. Respir. J. (March) (2020), 2000547, http://dx.doi.org/10.1183/13993003.00547-2020.

[18] S.R. Bornstein, F. Rubino, K. Khunti, G. Mingrone, D. Hopkins, A.L. Birkenfeld, B. Boehm, S. Amiel, R.I. Holt, J.S. Skyler, J.H. DeVries, E. Renard, R.H. Eckel, P. Zimmet, K.C. Alberti, J. Vidal, B. Gelenzele, J.C. Chai, L. Ji, B. Ludwig, Practical recommendations for the management of diabetes in patients with COVID-19, Lancet Diabetes Endocrinol. 8 (6) (2020) 546–550 (April), doi:10.1016/S2213-8587(20)30152-2 Epub 2020 Apr 23. PMID: 32334646; PMCID: PMC7180013.

[19] S. Chatterjee, D. Bandypadhyay, R.K. Ghosh, U. Majumdar, A. Aneja, C.J. Lave, et al., SGLT-2 inhibitors and peripheral artery disease: a statistical hoax or reality? Curr. Probl. Cardiol. 44 (2019) 207–222.

[20] B. Zhou, J. She, Y. Wang, M. Xa, Venous thrombosis and arteriosclerosis obliterans of lower extremities in a very severe patient with 2019 novel coronavirus disease: a case report, J. Thromb. Thrombolysis (April) (2020) 1–4, http://dx.doi.org/10.1007/s11239-020-02084-w.

Subhankar Chatterjee*
Department of General Medicine, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India

*Corresponding author at: Siddhivinayak Apartment, Litchi Bagan, Bariatu, Ranchi, Jharkhand, India.
E-mail address: chatterjeaspiresubhankan.92@gmail.com

13 May 2020
Available online 28 May 2020