Can sodium-glucose co-transporter-2 (SGLT-2) inhibitor reduce the risk of adverse complications due to COVID-19? – Targeting hyperinflammation

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Introduction

The novel coronavirus outbreak, initially termed 2019-novel coronavirus (2019-nCoV), and later renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and later COVID-19, was designated as a pandemic by the World Health Organization (WHO) on 11 March 2020. Clinical observations indicate that the novel COVID-19 infection symptoms can present with a spectrum of infection from asymptomatic to severe upper respiratory tract pneumonia, which presents with a fever and dry cough to multiorgan failure. The high rate of human-human transmission associated with COVID-19 presents significant public health and clinical treatment and management challenges.

The risk factors associated with COVID-19, assessed via observational data, show that both the severity and mortality risk increase with age. Older patients (mean age 63 years old; range 53–71) are more likely to experience the composite endpoint of ICU admission, mechanical ventilation, or death when compared with younger patients (mean age 46 years old, range 35–57), and underlying presence of comorbidities. Comorbidities associated with cardiovascular disease (CVD) are particularly notable was shown to be associated with c.3-fold increased odds of severe COVID-19 infection and an 11-fold increase in all-cause mortality. In addition, a large nationwide analysis in the UK has shown that both type 1 (3.51; 95% CI 3.16–3.90) and type 2 diabetes (2.03; 1.97–2.09, as well as obesity, chronic kidney disease, or hypertension) were independently associated with a significantly increased odds of in-hospital death with COVID-19.

Systemic inflammation although forms part of the hosts’ innate and adaptive immune response to control and resolve the COVID-19 infection, plays an important role in the adverse outcomes associated with COVID infections via the production of proinflammatory cytokines and the activation of CD4 and CD8+ T cells, the immune system is mobilized to promote inflammation and clean the infected cells, control in vivo viral replication, and limit the spread of the virus. However, excessive production of proinflammatory cytokines has been associated with the overall severity of patients’ disease and progresses. Excessive production of proinflammatory cytokines is termed a "cytokine storm" and, in COVID-19, has been associated with clinical endpoints of acute respiratory distress syndrome and multiorgan dysfunction. The cytokine storm observed in some COVID-19 patients may contribute to and influence the observed CV outcomes. Specifically, systemic inflammation can promote hypotension, left ventricular dysfunction, tachycardia, and destabilization of vascular plaques. In addition, systemic inflammation also stimulates human macrophages with oxidized LDLs (oxLDLs), leading to an increased IL-6 release, which is atherogenic.

As such, preventing excessive production of proinflammatory cytokines and/or protecting vital organs, mainly those central
to the cardiovascular system, appears to be crucial in reduc-
ing COVID-19 severity, morbidity, and mortality.

The potential role of sodium-glucose co-
transporter-2 inhibitors

The pandemic of COVID-19 likely represents the greatest medical, psychological, and socio-economic threat to soci-
eties in the 21st century. Understanding the pathophysiology and clinical implications of COVID-19 and developing novel preventive and therapeutic treatment strategies are para-
mount. Due to the novelty of COVID-19, approved treatment is scarce; however, numerous clinical trials have been launched to repurpose or reposition existing drugs as cura-
tive treatments or for the reduction of associated symptoms.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitor is a glu-
cose-lowering therapy that reduces glucose reabsorption and increases urinary glucose excretion at the renal proximal convoluted tubule. SGLT-2 inhibitors such as Dapagliflozin, Empagliflozin and Canagliflozin show potent cardiovascular protective effects in patients with type 2 diabetes, heart failure and/or chronic kidney disease as well as efficacy in reducing HbA1c, weight and blood pressure – three param-
ters linked with adverse outcomes with COVID-19. Given the relation between these conditions and COVID-19 mortal-
ity and morbidity, repurposing SGLT-2 inhibitors could be efficacious in protecting vital organ systems in patients with COVID-19. Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19), a collaborative multi-centre study, 1250 adults hospitalized with COVID-19 and have a risk for developing at least one of COVID-19 complications, such as type 2 diabetes, hypertension, heart failure, chronic kidney disease and/or Atherosclerotic CVD. Patients randomly treated with dapagliflozin 10 mg (n = 625; mean age, 61 years; 42% women; 50% with type 2 diabetes) or matching placebo (n = 625; mean age, 62 years; 44% women; 52% with type 2 diabetes) for 30 days. For the primary endpoint, which was organ failure or death, out of 156 events in the trial, 70 of those events occurred in the dapagliflozin group and 86 in the placebo group. Since the number of events was relatively small, this did not reach statistical significance. Despite this, the findings are interesting and provide some reassurance regarding the safety profile of dapagliflozin.

Dapagliflozin and Empagliflozin are approved to treat chronic heart failure with reduced ejection fraction; however, their cardio-protective mechanisms have yet to be estab-
lished. SGLT-2 inhibitors also inhibit the Na+/H+ exchanger isoform (NHE-1). Inhibition of these proteins reduces cardiac remodelling and limits heart failure from deteriorating. By inhibiting NHE-1, the calcium level in the mitochondria of cardiac tissue increases, which facilitates greater ATP synthesis. Empagliflozin is also credited to reduce cardiac fibrosis and myocardial oxidative stress. The combined purported anti-inflammatory and cardiac effects of SGLT-2i suggest that these drugs could be beneficial treatments for COVID-19 patients with myocarditis and adverse cardiac remodelling.

Therefore, the objective of this review was to comprehen-
sively summarise reports from in vitro, in vivo and clinical studies regarding the putative anti-inflammatory mechanisms associated with the cardioprotective effect of SGLT-2 inhibitors. The outcomes may indicate mechanisms that support the use of SGLT-2 inhibitors in managing and treating severe complications in COVID-19 due to cardiovascular risk factors and hyperinflammation.

Hyperinflammation/cytokines storm in COVID-19

Cytokine storm (CS) and its associated syndrome is observed as an uncontrolled secretion of high levels of multiple inflammatory compounds, resulting in a body-wide inflam-
mation, which may lead to organ failure. As seen in both severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), both of which are caused by coronaviruses and both of which may result in pneumo-
nia, the rapid viral replication and associated high level of infiltration of the body tissues by inflammatory cells and resulting cytokine storm, cause acute damage to the lungs and acute respiratory distress syndrome (ARDS), which ultimately leads to mortality. Emerging data show that a propor-
tion of severely affected patients by COVID-19 exhibit a similar pattern of proinflammatory chemokines as observed in both SARS and MERS. Researchers have assessed the blood serum levels of a range of cytokines in COVID-19 infected patients. Using a pool of 13 ICU and 28 non-ICU hospitalized patients, they assayed the patients’ serum for the presence of multiple different cytokines and found that all of the following exhibited increased levels:

- Interleukins: 1B, 1RA, 7, 8, 9 and 10;
- Growth factors and colony-stimulating factors: fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating fac-
tor (GM-CSF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF);
- Others: interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflamma-
tory protein 1 alpha (MIP1A), gamma interferon (IFNγ), tumour necrosis factor (TNFα).

Of these chemokines, ICU patients who exhibited the most severe symptoms, IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα were increased compared to less severely ill patients. Notably, the team did not show any difference in IL-6 levels between the critically ill ICU and other hospitalized patients. Critically, however, the same group of researchers, assessing the data from a retrospective cohort study conducted over a number of locations, detected a statistically significant higher level of IL-6 in patients who did not survive COVID-19 infection compared with a group of survivors. Other researchers have subsequently corrobo-
rated the increased IL-6 levels found in critically ill patients infected with COVID-19. In another study, ICU patients with the highest serum levels of cytokines, such as IL-6, TNFα, IL-1β, IL-8, IL2R, correlated with the presence of ARDS, hypercoagulation and disseminated intravascular coagulation (DIC), which combined to showcase thrombosis,
thrombocytopenia and gangrene of the fingers and toes. They proposed that the cytokine storm conditions not only increase the damage seen in the lungs but also contribute to other complications which result in mortality.

While patients suffering from severe COVID-19 infection have low numbers of circulating lymphocytes, these lymphocytes are activated. Assessing the numbers of some subtypes of lymphocytes, one study showed that patients who suffered from more severe infection generally had a lower number of the specific cell types when compared with less critically ill patients. In detail, severely ill patients showed a decrease in CD8+ T-cells of 61.9% and NK cells of 47.62%, while in less ill patients, these cell numbers were reduced by 28.43% and 34.31%, respectively. Again, this study confirmed the finding that severely ill patients have higher IL-6 levels in circulation than those suffering from a milder illness. Furthermore, the number of cell subtypes and cell markers was increased in the most seriously ill patients. Specifically, HLA-DR was increased on both CD4+ and CD8+ T lymphocytes, while CD8+ cells also expressed high levels of the cytotoxic components, perforin, granolysin and others, and CD4+CCR4+CCR6+Th17 cells were proportionally over-represented.

Identifying the correlation between the trio of severity grades assigned to COVID-19 illness and the clinical findings and outcomes and therapeutic responsiveness of patients, Siddiqi and Mehra designed a 3-stage classification system. They show that only a small sub-set of COVID-19 patients move through the earlier stages of the illness into the third, highest severity level, stage and exhibit excessive inflammation via the extra-pulmonary systemic hyperinflammation syndrome, wherein the makers associated with systemic inflammation are excessively high. These findings support the proposal that the method and timing of blockading the CS and introducing anti-inflammatory treatment are pivotal to aid in reducing COVID-19-associated mortality.

**Cytokines storm and comorbidities in COVID-19**

The mechanisms associated with the pathophysiology of COVID-19 infection remain to be elucidated; however, there appears to be a general consensus that the majority of severe cases and those which lead to patient death occur in the elderly or patients with existing health conditions, specifically CVD, diabetes, lung and kidney conditions, high blood pressure and cancer.

A large (1500+ patient) meta-analysis showed that the cardiovascular and metabolic conditions with the highest association with COVID-19 disease severity were hypertension, cardio-cerebrovascular disease, and diabetes, present in 17.1% (95% CI 9.9–24.4%), 16.4% (95% CI 6.6–26.1%), and 9.7% (95% CI 6.9–12.5%), respectively. Patients presenting with either diabetes or hypertension were twice as likely as others to develop an illness that necessitated ICU admission, while patients with the cardio-cerebrovascular disease were three times more likely than others to need ICU admission. In a sub-group comprising 355 Italian patients who suffered from fatalities following COVID-19 infection, many had multiple comorbidities, with a mean of 2.7 comorbidities found. Many instances link damage to organs, including the heart, liver and kidneys, occurs in addition to pneumonia observed in response to COVID-19 illness. These findings support the proposal that treatment of the existing comorbidities must be considered in COVID-19 cases, particularly in the elderly, who may suffer from multiple, advanced conditions.

Several groups have established a link between the inflammatory response involving inflammatory cytokines, including the well-known TNFα, and damage to the heart tissues. To corroborate the correlation between a substantial inflammatory response and myocardial damage, one group, Guo et al., identified an increase in C-reactive protein, a marker of inflammation, with increased troponin T (TnT) levels. These patients who had pre-existing CVD all showed poor outcomes from COVID-19 infection.

**Sodium-glucose co-transporter-2 inhibitor and possible anti-inflammatory effect – preclinical evidence**

In experimental models, SGLT-2 inhibitors have been shown to exert a direct effect on the expression of inflammatory mediators, reduce oxidative stress, and modulate renin-angiotensin system (RAS) activity, immune response, and obesity-induced inflammation indirectly in kidneys (Figure 1). While both the cardiovascular- and renal-protective effects of SGLT-2 inhibitors have been extensively documented in large-scale clinical trials, studies to determine the anti-inflammatory pathways of SGLT-2 inhibition in renal tissue are only now defining the pathological mechanisms.

In diabetic animal models, empagliflozin has been shown to directly inhibit the expression of proinflammatory mediators such as TNF-α, monocyte chemotactrant protein-1 (MCP-1) and transforming growth factor-beta (TGF-β), as well as downregulating the renal expression of both interleukin-6 (IL-6) and nuclear factor κB (NF-κB). Similarly, in animal models with diabetes, dapagliflozin has been found to attenuate IL-6 and TNF-α expression levels in cardiac tissues, as well as downregulate the renal expression of MCP-1, TGF-β and intercellular adhesion molecule-1 (ICAM-1). In-vitro studies in our laboratory have shown that the proinflammatory cytokines TNF-α and INF-Y significantly increased expression of IL-6 in Human Cardiac Microvascular Endothelial cells (HCMEC), which was significantly inhibited by a clinically relevant concentration of Canagliflozin, Dapagliflozin and Empagliflozin in cardiac tissues.

In a subsequent study, the stimulatory effects of TNF-α and INF-Y on IL-6 expressions in Human Umbilical vein endothelial cells (HUVEC) were significantly inhibited by canagliflozin 1 μM, 10 μM, and 100 μM (p < .0009, p < .0001, and p < .0001, respectively, compared to inflammatory stimulus alone). However, no significant inhibitory effects of dapagliflozin and empagliflozin on IL-6 expression were observed.
Another indirect pathway proposed to be involved in reno-cardiovascular protection by SGLT-2 inhibitors is RAS activation; In this pathway, angiotensin II is the critical effector that induces a number of inflammatory mediators as well as adhesion and growth factors in diabetic kidneys. However, the evidence to support the association of SGLT-2 inhibitors with the intrarenal RAS activation in patients with type 2 diabetes is both limited and inconsistent. While one research team found that dapagliflozin inhibited RAS activation in an animal model of diabetic nephropathy, another team, in a separate study, found that persistent treatment with the SGLT-2 inhibitor TA-1887 did not result in systemic or RAS activation in CKD animal model.

The association of chronic inflammation with obesity and metabolic disorders is well documented. Empagliflozin was shown to mediate fat browning by promoting energy expenditure. It attenuates obesity-related inflammation, decreases plasma IL-6, MCP-1 and TNFα levels while elevating adiponectin, IL-33 and fibroblast growth factor (FGF) 21 levels in obese mice. In addition, canagliflozin attenuated the increased expression levels of proinflammatory markers in neural tissues and reduced inflammatory cytokine levels in obesity-induced animal models.

There is also evidence to suggest that patients with diabetes show disrupted intra-renal response to hyperglycemia which results in renal hyperfiltration due to impaired renal blood flow. Therefore, since SGLT-2 inhibitors significantly reduce the inflammatory response and improve the glycaemic profile, they thereby reduce renal hyperfiltration, and these oral antidiabetic drugs may exert a positive impact on renal hemodynamics. Another potential mechanism involving improved hemodynamics is the findings that SGLT-2 inhibitors increase sodium delivery to activate the tubule-glomerular feedback loop, leading to reduced intraglomerular pressure.

Emerging evidence suggests that SGLT-2 inhibitors may indirectly contribute to the immune response by reducing oxidative stress and glucose levels. Previous findings have indicated an association between hyperglycemia-induced increased proinflammatory cytokines and impaired immune function. Furthermore, a recent line of evidence from ex vivo studies demonstrated that the SGLT-2 inhibitor empagliflozin reduces IL-1β levels, which is associated with T-cell differentiation and innate immunity. Furthermore, this inhibitor suppresses activation of the inflammasome pyrin domain-containing 3 (NLRP3) in human-derived macrophage cell cultures, which in turn mediates IL-1β expression via caspase-1 activation. During acute infection, NLRP3-deficient mice exhibit a limited inflammatory immune response as they do not produce IL-1β, which highlights the critical role of NLRP3 inflammasome in the immune and inflammatory responses. Further animal studies are needed to understand the reno-cardiovascular protective role of SGLT-2 inhibitors in immune and inflammatory responses.

Recently, SGLT inhibitors have been reported to reduce oxidative stress in renal and cardiac tissues of diabetic animal models. In a diabetic rat model, Empagliflozin has been shown to lower the production of reactive oxygen species in aortic vessels by reducing expression of both where NADPH oxidase 1 (Nox1) and 2 (Nox2) enzyme expressions were reduced. In another study, dapagliflozin downregulated Nox4 expression in renal cells and reduced macrophage infiltration and interstitial fibrosis in kidneys in a murine type 2 diabetes model. Furthermore, in Type 1 diabetic rats, a 12-week treatment with SGLT-2 inhibitor ipragliflozin not only reduced oxidative stress in the liver but also reduced IL-6, TNF-α, MCP-1, and TGF-β levels.

Figure 1. Summary of reported effects of SGLT-2 inhibitors on inflammatory responses. Abbreviations: IL-1β, interleukin 1β; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; NF-κB, Nuclear factor κB; NLRP3, NLR family; pyrin domain-containing 3; Nox4, NADH oxidase isoform; RAS, renin-angiotensin system; TGF-β, transforming growth factor-beta.
TNF-α and MCP-1 inflammatory markers. Preclinical studies also show that SGLT-2 inhibitors improve mitochondria function and lower oxidative stress levels through advanced glycation end products (AGEs).

Sodium-glucose co-transporter-2 inhibitor and possible anti-inflammatory effect – clinical evidence

There is also emerging evidence from human studies on the underlying mechanisms of reno-cardiovascular protective effects of SGLT-2 inhibitors. In a recent controlled trial involving patients with T2D, canagliflozin treatment resulted in a decrease in plasma IL-6 and an increase in TNF-α levels compared to glimepiride. Similarly, in another study, both empagliflozin and canagliflozin were shown to reduce the inflammatory cytokines IL-6 and Interferon-β (IFN-β) levels in plasma. After 6 months of treatment with empagliflozin in patients with T2D, expression of NFκB-p65 protein together with adhesion molecules in leukocytes were dramatically reduced, highlighting the effect of SGLT-2 inhibitors on inflammatory response. The most recent potential cardioprotective mechanism of SGLT-2 inhibitors was proposed to involve modulation of insulin, uric acid, and ketone body β-hydroxybutyrate levels. Empagliflozin was found to suppress IL1β-mediated NLRP3 inflammasome activation by increasing serum β-hydroxybutyrate levels in type 2 diabetes at high risk of CVD.

While only a few clinical trials to date have examined the role of SGLT-2 inhibitors in the inflammatory response and therefore, definitive conclusions regarding underlying reno-cardiovascular protective mechanisms cannot be reached; nevertheless, the findings are promising and pave the way to unravelling the underlying pathogenic mechanism of SGLT-2 inhibitors in renal and cardiovascular health and disease.

Current clinical recommendations: use of sodium-glucose co-transporter-2 inhibitors in COVID-19 infection

The application of SGLT-2 inhibitors during the acute phase of illness or infection must be balanced with the issue of volume depletion, lowering of blood pressure and the likelihood of developing diabetic ketoacidosis (DKA). With this in mind, healthcare providers, have provided advice on the risks of using SGLT2 inhibitors and the potential for DKA in patients with diabetes who are suffering from a COVID-19 infection. They have defined patients with a history of high blood pressure, type 2 diabetes, atherosclerotic CVD, heart failure, or estimated GFR <25 mL/min/1.73 m² as high risk, and as such, they recommend that SGLT-2 inhibitors are not used in this group of patients. Furthermore, COVID-19 patients may consume less food, develop diarrhoea, have higher respiratory and fever-based fluid loss.

DKA has been identified in three of 658 positive cases of COVID-19. This study however has shown increased risks associated with using SGLT-2i with the severity of acute COVID-19 illness. In another hand, DARE_19 reported two non-severe cases of DKA of 613 positive cases of COVID-19. Both cases had type 2 diabetes at baseline. Thus, due to the risk of DKA, the potential for SGLT-2 inhibitors to cause serious harm might need to be balanced against any benefits they confer, even in high-risk patients, who ordinarily would be the ones who would benefit most from these drugs.
Any use of SGLT-2 inhibitors should therefore be adopted on an individual approach, and patients should be closely monitored for symptoms indicative of blood pressure or volume loss. Frequent blood ketones monitoring is crucial during an acute episode of COVID. To prevent renal dysfunction or DKA, treatment should cease if a symptom of a rise in blood ketones is detected.

**Discussion**

Balancing the risk and benefits of SGLT-2 inhibitors in patients with COVID-19 is crucial. Reduction of cardiovascular risk factors, for example, hypertension, ambient glucose levels, body mass index and cardiac function, in conjunction with a level of anti-inflammatory action, could potentially tackle several parameters that may predict undesirable clinical endpoints in patients with COVID-19. In addition, a theoretical anti-viral action of SGLT-2 inhibitors has been postulated since it can elevate lactate levels and diminish intracellular pH, thus lowering the viral burden.

Another controversy regarding SGLT-2 inhibitors is that this drug class amplifies angiotensin-converting enzyme 2 (ACE2) expression. Hypothetically, this could heighten the likelihood of viral entry, although this may not be a uniform effect owing to the restricted accessibility of Transmembrane Serine Protease 2 (TMPRSS2), a serine protease essential for viral attachment. Moreover, despite women and younger individuals exhibiting greater ACE2 concentrations, publications have revealed an elevated death rate in men and the more aged population, implying that elements in addition to ACE2 amplification contribute to the underlying disease process associated with COVID-19. Clinical trial results from the BRACE CORONA study have demonstrated that there is no medical advantage in automatically withdrawing Angiotensin-converting enzyme inhibitors (ACEI) and Angiotensin receptor blockers (ARB) from in-patients with COVID-19 infection of a mild to moderate severity.

Few studies have documented clinical endpoints related to SGLT-2 inhibitors in individuals with COVID-19. All have consistently shown a significant reduction in death amongst SGLT2 inhibitors users as compared to non-users in patients with COVID-19. Additionally, the use of SGLT-2 inhibitors compared with DPP-4 inhibitors was associated with a significantly lower mortality risk associated with COVID-19. It is conceivable that the benefits of SGLT-2 inhibitor in people with type 2 diabetes are driven predominantly by improvements in heart failure status rather than its anti-inflammatory effects. Evidence derived from DARE-19, although did not show statistical evidence of benefits due to small numbers provided important reassurance regarding the safety profile of SGLT-2 inhibitor provided appropriate measures are taken to reduce risks of DKA. Table 1 summarises the effects of SGLT-2 inhibitors in patients with diabetes with COVID-19.

**Conclusion**

The anti-inflammatory effects of SGLT-2 inhibitors add to their cardioprotective effect, suggesting that they could be suitable drugs for COVID-19 infections that can damage cardiac functions. However, before using SGLT-2 inhibitors on critically ill diabetic COVID-19 patients, a risk-benefit analysis must be performed, as this cohort is particularly at risk of DKA.

**Transparency**

**Declaration of funding**

This paper was not funded.

**Declaration of financial/other relationships**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

**Acknowledgements**

None.

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