

COMMENTARY

Intestinal SGLT1 as a therapeutic target in COVID-19-related diabetes: A “two-edged sword” hypothesis

Theocharis Koufakis¹  | Symeon Metallidis²  | Pantelis Zebekakis^{1,2}  | Kalliopi Kotsa¹ 

¹Division of Endocrinology and Metabolism and Diabetes Center, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece

²Infectious Diseases Division, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece

Correspondence

Kalliopi Kotsa, Division of Endocrinology and Metabolism and Diabetes Center, First Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, 1 St. Kiriakidi Street, 54636, Thessaloniki, Greece.
Email: kalmanthou@yahoo.gr

Emerging data are linking coronavirus disease 2019 (COVID-19) with an increased risk of developing new-onset diabetes. The gut has been so far out of the frame of the discussion on the pathophysiology of COVID-19-induced diabetes, with the pancreas, liver, and adipose tissue being under the spotlight of medical research. Sodium-glucose co-transporters (SGLT) 1 represent important regulators of glucose absorption, expressed in the small intestine where they mediate almost all sodium-dependent glucose uptake. Similar to what happens in diabetes and other viral infections, SGLT1 upregulation could result in increased intestinal glucose absorption and subsequently promote the development of hyperglycaemia in COVID-19. Considering the above, the question whether dual SGLT (1 and 2) inhibition could contribute to improved outcomes in such cases sounds challenging, deserving further evaluation. Future studies need to clarify whether putative benefits of dual SGLT inhibition in COVID-19 outweigh potential risks, particularly with respect to drug-induced euglycaemic diabetic ketoacidosis, gastrointestinal side effects, and compromised host response to pathogens.

KEYWORDS

COVID-19, diabetes, SGLT1, SGLT2

1 | BACKGROUND

Emerging data are linking coronavirus disease 2019 (COVID-19) with an increased risk of developing new-onset diabetes and severe diabetic complications, including diabetic ketoacidosis (DKA). Whether this type of diabetes resembles type 1 (T1D) type 2 (T2D) or comprises a new form of the disorder remains vague. In a recently published observational study from Scotland, McGurnaghan et al.¹ demonstrated substantially increased risk of fatal or critical care unit-treated COVID-19 in people with both type of diabetes compared with the background population. Among patients with diabetes and after adjustment for age, sex, diabetes type, and duration, those with poor glycaemic control, presence of complications (retinopathy and renal disease), previous history of hospitalization due to hypoglycaemia or DKA, and being on treatment with multiple antidiabetes agents and other medication were found to be at greater risk for severe COVID-19 than individuals who didn't have the above-

mentioned characteristics. Obesity, a major risk factor for the development of T2D, has been also linked to poor outcomes, including severe pneumonia, intensive care unit admission, and mortality during COVID-19, probably related to increased viral entry into cells and defects in immune response.² COVID-19-related DKA seems to manifest peculiar—still interesting—characteristics, including the occurrence in people without a previous diagnosis of diabetes, or in those with non-insulin-dependent diabetes and adequate metabolic control prior to infection. In addition, hyperglycaemia without diabetes and new-onset diabetes have been both linked to a poorer prognosis in the context of COVID-19.³

The development of hyperglycaemia in COVID-19, either being genuinely new or the unmasking of a previously existing occult diabetes, is the result of a pathophysiological interplay between impaired insulin secretion and action. Up to now, putative explanations for the underlying pathophysiological mechanisms through which the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can induce

severe hyperglycaemia and subsequent DKA have mainly focused on two directions: first, a direct viral attack against beta-cells and, second, an exacerbation of insulin resistance (IR), as a result of systemic inflammation.⁴

In this paper, we discuss a novel hypothesis according to which, intestinal sodium-glucose transport proteins might be implicated in the pathogenesis of COVID-19-induced diabetes and could represent a therapeutic target for the disorder in the future.

2 | HYPOTHESIS

The angiotensin-converting enzyme 2 (ACE2), which is the entry point for the virus into the cells, has been shown to be expressed in the pancreatic tissue. In line with what is already known from studies conducted with other coronaviruses, it has been demonstrated that SARS-CoV-2 exerts cytotoxic effects that cause islet cell injury and impair insulin production.⁵ Moreover, downregulation of ACE2 following the endocytosis of the virus complex results in increased angiotensin II concentrations, which are known to impede insulin secretion.^{6,7} Similar to what happens with other viral infections, an immune-mediated beta-cell destruction triggered by the SARS-CoV-2 infection has been also suggested.^{4,7} In a parallel way, COVID-19-related cytokine storm leading to overproduction of proinflammatory molecules, predominantly interleukin (IL)-6 and tumour necrosis factor- α (TNF- α), further aggravates beta-cell dysfunction and induces IR.

Over the past few years, the importance of the gut in the regulation of glucose homeostasis has been greatly recognized by identifying its multiple roles in modulating nutrient absorption, satiety, systemic and adipose tissue inflammation and insulin secretion and action. Although patients with COVID-19 mainly present with respiratory symptoms, a recent meta-analysis proved that approximately 12% of SARS-CoV-2-infected individuals will manifest gastrointestinal (GI) symptoms, with diarrhoea, nausea, or vomiting being the most commonly reported among them.⁸ While the exact mechanisms through which the virus attacks the GI tract are still under investigation, it is believed that following the infection of the lung tissue by SARS-CoV-2, effector CD4⁺ T-cells move to the small intestine through the gut-lung axis and cause intestinal immune damage. However, the gut has been so far out of the frame of the discussion on the pathophysiology of COVID-19-induced diabetes, with the pancreas, liver, and adipose tissue being under the spotlight of medical research. Only recently, alterations in the gut microbiome have been proposed to contribute to the pathogenesis, severity, and disease course of COVID-19, potentially leading to an upregulated systemic inflammatory state, negatively affecting this way insulin production and sensitivity.⁷

Sodium-glucose co-transporters (SGLT) 1 and 2 represent important regulators of glucose uptake across apical cell membranes. SGLT1 are particularly expressed in the small intestine where they mediate almost all sodium-dependent glucose uptake, whereas they are also located in other tissues, including heart and kidneys. High expression

of ACE2 in mucosal cells of the intestine renders the organ vulnerable to SARS-CoV-2 invasion and replication. Previous research has highlighted that ACE2-mediated downregulation of SGLT1 in the intestinal epithelium has the potential to improve glycaemic status in an experimental model of T1D.⁹ Inversely, ACE2-mediated SGLT1 upregulation occurs in diabetes and diabetes-related diseases, which results in increased intestinal glucose absorption and subsequently to the development of hyperglycemia.⁶ In support of the perspective that SGLT1 might be implicated in the metabolic disarrangement observed in some patients with COVID-19, Dai et al.¹⁰ have demonstrated that infection with transmissible gastroenteritis virus—another coronavirus—results in augmented glucose uptake through enhanced SGLT1 expression in porcine intestinal columnar epithelial cells.

On the other hand, recent studies have suggested an important role of SGLT1 activation in the host response against specific pathogens. Sharma et al.¹¹ have showed that genetic knockout of SGLT1 in a murine model of *Listeria* infection increased bacterial load in liver, spleen, kidney, and lung and significantly upregulated the hepatic expression of IL-12 a and TNF- α , resulting in the death of SGLT1-deficient mice, in contrast with the wild-type animals which survived the infection. In a similar way, SGLT1 inhibition with phlorizin was correlated with a decreased survival rate in a rat model of bronchial inflammation and sepsis.¹²

SGLT activation has recently been a key therapeutic target in T2D, where excessive glucose reabsorption by the kidneys is observed.¹³ Available drugs mainly inhibit SGLT2, located in the early segment of the proximal renal tube, thus leading to reduced renal glucose reabsorption.¹⁴ However, specific agents within the class, namely, sotagliflozin and canagliflozin, present only 20- and 250-fold higher inhibitory activity for SGLT2 compared with SGLT1, respectively, and are considered “dual inhibitors,” manifesting their glucose-lowering actions by reducing—apart from renal—intestinal glucose absorption, as well¹⁵ (Table 1). Interestingly, dual inhibition has been questionably linked to a greater risk of adverse events, including lower extremity amputations and euglycaemic DKA, compared with the more selective SGLT2 inhibitors.^{14,15} Although the exact mechanisms that could explain these differences are still debatable, they may be related to the volume depletion-mediated increased ketone body reabsorption in the distal tubules, which, in turn, could amplify the magnitude of ketonemia already observed with SGLT2 inhibition.¹⁶ GI adverse events, such as osmotic diarrhoea, are also more common with dual inhibitors, attributable to their effects on the brush border of the small intestine.^{14–16}

Relevant to their remarkable cardiorenal protective properties in people with or without diabetes, previous research has highlighted the potential of SGLT2 inhibitors to decrease the concentrations of proinflammatory cytokines, reduce oxidative stress, downregulate sympathetic activity and improve cell autophagy, leading to amelioration of both systemic and adipose-tissue inflammation.¹⁷ These seem to be class effects and not related either to SGLT1 or SGLT2 inhibition alone. In this context, dapagliflozin, a molecule with a 1200-fold higher potency for SGLT2 compared with SGLT1, is currently being tested in clinical trials as a potential treatment for acute respiratory

TABLE 1 Pharmacological characteristics of different SGLT inhibitors

	Drug	SGLT2 over SGLT1 selectivity	Site of action	Glucose-lowering action by	HbA1c reduction (%) ^a	Anti-inflammatory potency	Effects on heart failure and kidney disease outcomes
SGLT2 inhibitors	Empagliflozin	2500-fold	Almost exclusively kidney	Reducing renal glucose reabsorption	0.7–0.9	Similar	Beneficial
	Ertugliflozin	2000-fold			0.5		
	Dapagliflozin	1200-fold			0.5–0.7		
Dual inhibitors	Canagliflozin	250-fold	Mostly in kidney and small intestine	Reducing renal glucose reabsorption and dietary absorption of glucose and galactose	0.91–1.16		
	Sotagliflozin	20-fold			0.52–0.92		

Abbreviations: HbA1c, glycated haemoglobin; SGLT, sodium-glucose co-transporters.

^aData refer to individual and not to head-to-head trials.

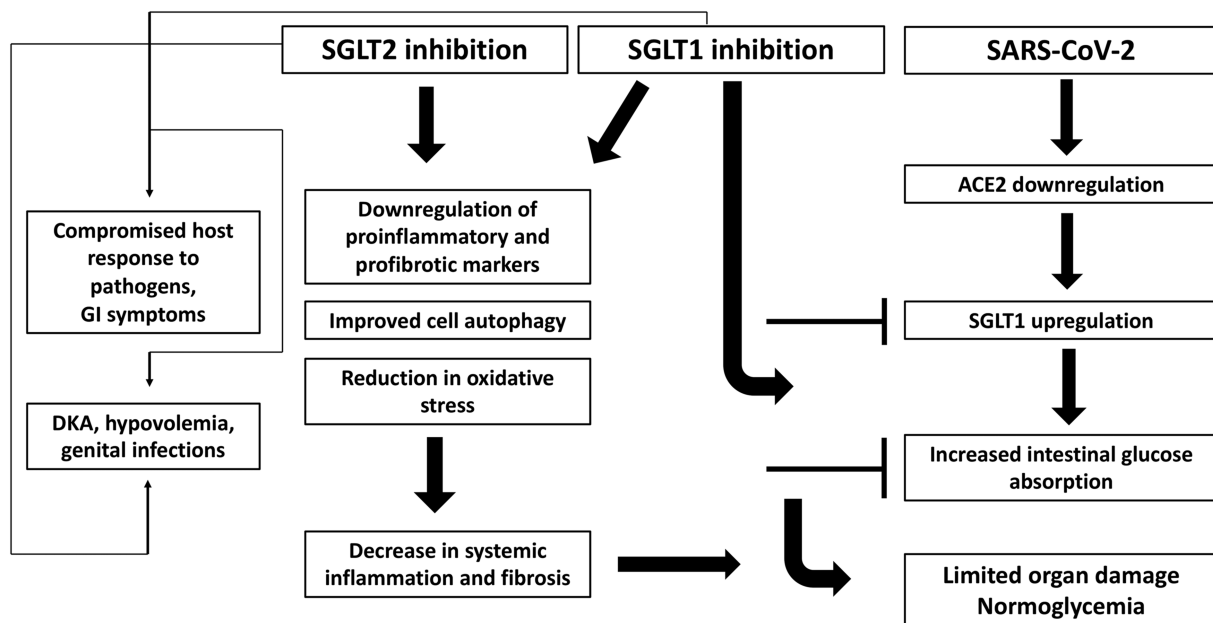


FIGURE 1 Potential harms and benefits of dual SGLT (1 and 2) inhibition in COVID-19-induced diabetes. Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; GI, gastrointestinal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGLT, sodium-glucose co-transporters

COVID-19 disease,¹⁷ and their results are anticipated in order to clarify whether the class could represent an additional weapon in the therapeutic arsenal against SARS-CoV-2. Considering the hypothesis that ACE2-mediated intestinal SGLT1 dysregulation is implicated in the development of COVID-19-related hyperglycaemia, the question whether dual SGLT (1 and 2) inhibition could contribute to improved outcomes in such cases sounds challenging, deserving further evaluation in clinical studies (Figure 1).

3 | CONCLUSION

In conclusion, there is indirect evidence linking ACE2-mediated SGLT1 upregulation to the development of hyperglycaemia and diabetes-

related adverse outcomes in COVID-19. Thus, the excessive activation of SGLT1 could be a potential therapeutic target for COVID-19-induced diabetes. The testing of the hypothesis seems to be relatively feasible, considering that dual SGLT inhibitors are already widely used in daily clinical practice for the management of T2D.

On the other hand, it should be noted that available data are still very limited. Therefore, the development of animal models for the mechanistic study of the key molecular mechanisms implicated in the SARS-CoV-2 binding receptor ACE2 mediated dysregulation of intestinal nutrient transporters is needed.⁶ Moreover, the great heterogeneity of the clinical presentation of COVID-19 implies complex underlying interactions between genetic and environmental components that determine inter-individual variations in disease severity and possibly in response to various treatments. Clinical studies are hence

required to investigate the potential of a tailored approach in the therapeutic management of COVID-19, but also to clarify whether putative benefits of dual SGLT inhibition outweigh potential risks, particularly with respect to drug-induced euglycaemic DKA, GI side effects, and compromised host response to pathogens.

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CONTRIBUTORS

T.K. reviewed the literature and drafted the first version of the manuscript. S.M., P.Z., and K.K. reviewed the literature and edited the manuscript. All authors have read and approved the final version of the manuscript.

ORCID

Theocharis Koufakis  <https://orcid.org/0000-0002-5853-1352>

Symeon Metallidis  <https://orcid.org/0000-0002-3869-5341>

Pantelis Zebekakis  <https://orcid.org/0000-0001-8821-406X>

Kalliopi Kotsa  <https://orcid.org/0000-0003-2376-740X>

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