CORRESPONDENCE

Association of common variant rs9934336 of *SLC5A2* (*SGLT2*) gene with SARS-CoV-2 infection and mortality

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Abstract

COVID-19 has its life-threatening complications more pronounced in people with underlying health conditions such as diabetes, cardiovascular disease and kidney disease. Inhibition of the sodiumglucose cotransporter 2 (SGLT2), which primarily increases urinary glucose excretion, is shown to be beneficial in patients with type 2 diabetes mellitus (T2D) and other comorbidities. SGLT2 is encoded by *SLC5A2* gene, and of the several genetic variants, SNP rs9934336 is gaining importance for being associated with reduced HbA1c level and lower incidence of T2D. Since a complex bidirectional relationship exists between COVID-19 and hyperglycaemia, we conducted a worldwide association study to investigate the effect of rs9934336 on COVID-19 outcomes. Worldwide prevalence data of *SLC5A2* SNP rs9934336 were obtained from relevant published articles and databases for genomic variants. COVID-19 data procured from the Worldometer website were used for conducting Spearman's correlation analysis with minor allele frequency data of rs9934336. Significant positive correlation was observed between rs9934336 and COVID-19 incidence ($p < 0.0001$, $r = 0.6225$) as well as deaths ($p < 0.0001$, $r = 0.5837$). The present finding of significant association of *SLC5A2* variant rs9934336 with COVID-19 risk has to be validated by case–control studies in diverse populations along with other variants regulating the expression and function of SGLT2.

Keywords COVID-19, *SLC5A2* gene, rs9934336, Type 2 diabetes, Sodium–glucose cotransporter 2, Sodium–glucose cotransporter 2 inhibitor

Introduction

The devastating pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has its life-threatening complications more pronounced in people with underlying health conditions or comorbidities, such as diabetes, cardiovascular disease and kidney disease [1]. Of these, a complex bidirectional relationship seems to exist between COVID-19 and diabetes. While hyperglycaemia in diabetes predisposes to severe disease and adverse outcomes including death and long-term COVID-19 sequelae, SARS-CoV-2 infection is described to induce new-onset hyperglycaemia and diabetes in COVID-19-infected individuals as well as poor glycaemic control in pre-existing diabetes [2]. Kidney plays an important role in glucose homoeostasis. Specifically, of the two sodium–glucose cotransporters (SGLTs-SGLT1 and SGLT2) expressed in the kidneys, approximately 90% of glucose reabsorption from the glomerular ultra-filtrate occur via SGLT2, which would have otherwise excreted out through urine [3]. Interestingly, inhibition of SGLT2 renders excellent blood glucose lowering potential in an insulin-independent manner via glucosuria, and SGLT2 inhibitors (SGLT-2is) are being widely used for the control of type 2 diabetes (T2D). Moreover, SGLT-2is are

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shown to have cardio- and reno-protective effects, which have been confirmed in clinical trials [3]. SGLT-2is are also presently gaining importance in the treatment of heart failure [4] and chronic kidney disease [5] even in patients without diabetes.

SGLT2 is encoded by *SLC5A2* (Solute Carrier Family-5 Member-2) gene, which is located on chromosome 16 of humans. Common genetic variants of *SLC5A2*, primarily SNP rs9934336: G > A, perhaps have a role in the regulation of glucose homoeostasis and may influence the risk of T2D including treatment response with SGLT-2is in T2D patients [3]. Since a complex bidirectional relationship seems to exist between COVID-19 and hyperglycaemia and that *SLC5A2* variant rs9934336 is likely to affect glucose homoeostasis, we conducted a worldwide association study to investigate the effect of this genetic variant on SARS-CoV-2 infection and mortality.

Materials and methods
Prevalence of *SLC5A2* variant rs9934336 data
The present study is a worldwide retrospective cohort study. Genotype and/or allele frequency data of rs9934336 were obtained from relevant published articles through literature search (PubMed, Google scholar) and databases for genomic variants, such as ALFRED (Allele frequency database) (https://alfred.med.yale.edu/alfred/ or https://alfred.med.yale.edu/alfred/index.asp) and 1000 Genomes Project (https://www.internationalgenome.org or https://www.ensembl.org/index.html) to acquire the maximum possible data across worldwide human populations. Though ALFRED lacked genotype data and also had no information about Hardy–Weinberg equilibrium (HWE), inclusion of its data will probably not affect the reliability of the study dataset as intensive curation and data integrity checks are performed preceding any data upload into the database [6]. The minor allele frequency (MAF) data obtained from ALFRED was compared with the MAF data in gnomAD (genome aggregation database) (https://gnomad.broadinstitute.org). The data were merged only for countries with more than one study/report by both including and excluding data from ALFRED separately.

COVID-19 data
COVID-19 worldwide data were obtained from the Worldometer website (https://www.worldometers.info/coronavirus/) and WHO (World Health Organization) website (https://covid19.who.int/). In order to nullify the possible confounding effect due to disparity of COVID-19 vaccinations across countries, we used COVID-19 data (total cases/million of population and deaths/million of population) of 16th January, 2021, i.e. before massive vaccination drive started.

Statistical analysis
Countrywide incidence (total cases/million of population) and mortality (deaths/million of population) data of COVID-19 were used for conducting Spearman's correlation analysis with MAF data of *SLC5A2* rs9934336 in GraphPad Prism, version 5.0. A p value ≤ 0.05 was considered to be statistically significant. In the absence of patient-wise data of rs9934336 polymorphism and COVID-19 outcome data, our association study correlating countrywide COVID-19 outcomes with their respective country-wise rs9934336 MAF data from people of all age groups and gender minimises the possible bias due to disparity in race, age and gender. Besides, data obtained from more than one study/report for a country being merged together, and studies lacking sufficient data and/or those deviating from the HWE being excluded from the analysis, the correlation results seem to be convincing.

Results
A total of 105 reports with genotype and/or allele frequency data of *SLC5A2* variant rs9934336 across worldwide human populations were obtained from relevant published articles and databases for genomic variants (ALFRED and 1000 Genomes Project) after systematic and vigorous literature search. Some reports obeying HWE in 1000 Genomes Project database were also found in ALFRED. Moreover, the MAF data obtained from ALFRED matched with the data in gnomAD, indicating that ALFRED is a reliable source of MAF data though it lacks information about HWE. Countrywide COVID-19 data obtained from the two sources (Worldometer and WHO websites) were comparable.

Thirty reports obtained from published articles and 1000 Genomes Project database had information about HWE. Among these 30 studies, three studies—one each from India, Italy and the Gambia—were omitted as they deviated from the HWE. After merging MAF data for countries with more than one report (each obeying HWE), data from 21 countries were finally obtained. After considering the MAF data of rs9934336 acquired from ALFRED, data from 20 more countries were attained. Finally, data from 41 countries were taken into consideration for the present study (Table 1). Thus, among these 41 countries, some had data obeying HWE (from published articles and 1000 Genomes Project database) as well as data from ALFRED which had no information about HWE.

MAF data [which ranged from 0.081 (Vietnam) to 0.302 (UK) (Table 1)] obeying HWE were available from 21 countries (Table 1). Significant positive correlation of the minor allele (A) of rs9934336 with COVID-19 incidence

Table 1 Countrywide COVID-19 data (January 16, 2021) and MAF data of rs9934336 of *SLC5A2* gene from worldwide human populations

Sl. no.[#]	Country*	Cases/million	Deaths/million	Obeying HWE		Unknown HWE		Combined MAF	Data sources
				Sample size	MAF	Sample size	MAF		
1	India	7600	110	102	0.167	–	–	0.167	1000 genomes database, ALFRED
2	Sri Lanka	2420	12	102	0.186	–	–	0.186	1000 genomes database, ALFRED
3a	China (Worldometer website)	61	3	301	0.120	192	0.150	0.135	1000 genomes database, ALFRED
3b	China (WHO website)	68	3						
4	South Korea	1400	24	–	–	53	0.083	0.083	ALFRED
5	Japan	2449	34	104	0.135	239	0.163	0.149	1000 genomes database, ALFRED, [7]
6	Israel	58,173	425	–	–	95	0.18	0.18	ALFRED
7	Bangladesh	3183	48	86	0.140	–	–	0.14	1000 genomes database, ALFRED
8	Pakistan	2315	49	96	0.177	175	0.25	0.2135	1000 genomes database, ALFRED
9	Afghanistan	1370	59	–	–	24	0.28	0.28	ALFRED
10	Palestine	29,346	329	–	–	51	0.18	0.18	ALFRED
11	Kazakhstan	8843	124	–	–	45	0.178	0.178	ALFRED
12	Russia	24,283	446	–	–	509	0.192	0.192	ALFRED
13	Kyrgyzstan	12,608	210	–	–	28	0.179	0.179	ALFRED
14	Uzbekistan	2310	18	–	–	39	0.192	0.192	ALFRED
15	Cambodia	26	NO DATA	–	–	11	0.09	0.09	ALFRED
16	Vietnam	16	0.4	99	0.081	–	–	0.081	1000 genomes database, ALFRED
17	Germany	24,132	555	3355	0.256	–	–	0.256	[8–10]
18	Finland	7231	111	99	0.212	–	–	0.212	1000 genomes database, ALFRED
19	Spain	48,160	1140	107	0.276	–	–	0.276	1000 genomes database, ALFRED
20	Austria	43,447	781	1284	0.262	–	–	0.262	[15]
21	France	43,961	1070	–	–	53	0.28	0.28	ALFRED
22	Italy	38,939	1346	–	–	49	0.213	0.213	ALFRED
23	UK	48,708	1282	91	0.302	290,053	0.264	0.283	1000 genomes database, ALFRED, [12]
24	Belarus	23,661	166	–	–	28	0.429	0.429	ALFRED
25	Estonia	27,649	241	–	–	1000	0.25	0.25	ALFRED
26	Ukraine	26,490	475	–	–	29	0.224	0.224	ALFRED
27	USA	72,592	1210	160	0.244	–	–	0.244	1000 genomes database, ALFRED
28	Mexico	12,415	1072	64	0.156	50	0.2	0.178	1000 genomes database, ALFRED
29	Colombia	36,544	935	94	0.277	13	0.27	0.2735	1000 genomes database, ALFRED
30	Brazil	39,340	976	–	–	45	0.295	0.295	ALFRED
31	Peru	31,789	1164	85	0.141	–	–	0.141	1000 genomes database, ALFRED
32	Nigeria	514	7	207	0.186	25	0.23	0.208	1000 genomes database, ALFRED

Table 1 (continued)

Sl. no.[#]	Country*	Cases/million	Deaths/million	Obeying HWE		Unknown HWE		Combined MAF	Data sources
				Sample size	MAF	Sample size	MAF		
33	Kenya	1821	32	99	0.227	12	0.13	0.1785	1000 genomes database, ALFRED
34	Sierra Leone	367	10	85	0.182	–	–	0.182	1000 genomes database, ALFRED
35	Democratic Republic of the Congo	227	7	–	–	15	0	0	ALFRED
36	Algeria	2335	64	–	–	30	0.22	0.22	ALFRED
37	Namibia	11,650	109	–	–	7	0.33	0.33	ALFRED
38	Central African Republic (CAR)	1020	13	–	–	56	0.035	0.035	ALFRED
39	Barbados	3603	24	96	0.177	–	–	0.177	1000 genomes database, ALFRED
40	Puerto Rico (WHO website)	29,647	591	104	0.221	–	–	0.221	1000 genomes database, ALFRED
41	Papua New Guinea	92	1	–	–	36	0.09	0.09	ALFRED

MAF minor allele frequency, *HWE* Hardy–Weinberg equilibrium, *ALFRED* allele frequency database,

Link for 'ALFRED': https://alfred.med.yale.edu/alfred/ or https://alfred.med.yale.edu/alfred/index.asp,

Link for '1000 genomes project' database: https://www.internationalgenome.org or https://www.ensembl.org/index.html,

Countrywide COVID-19 data: https://www.worldometers.info/coronavirus/ and https://covid19.who.int

*All COVID-19 data are from Worldometer website unless otherwise mentioned

[#] Serial no.

($p = 0.0012$, $r = 0.6569$) and deaths ($p = 0.0072$, $r = 0.5679$) were observed (Fig. 1). After considering ALFRED data, MAF data were available from 41 countries, which ranged from 0.035 (Central African Republic) to 0.429 (Belarus) (Table 1). Consistently, the 'A' allele in combination data (i.e. data obeying HWE plus ALFRED data of unknown HWE information) also revealed significant positive correlation with COVID-19 incidence ($p < 0.0001$, $r = 0.6225$) and deaths ($p < 0.0001$, $r = 0.5837$) (Fig. 1).

Discussion

The present findings of significant association of COVID-19 occurrence and mortality with *SLC5A2* variant rs9934336 across worldwide human populations suggest possible deleterious impact of *SLC5A2* expression on the disease. Upregulation of SGLT2 along with downregulation of apelin and angiotensin-converting enzyme 2 followed by severe inflammation, oxidative stress, endothelial damage and fibrosis have been demonstrated to contribute to the adverse cardio-renal injury in COVID-19 patients [13]. Renal SGLT2 expression is also increased in T2D patients [14]. Though rs9934336 likely provides some protection from the development of T2D [7, 12, 15] and heart failure [16] in few populations of the world, other studies investigating its association with susceptibility to T2D show inconsistent results [8, 9]. However, the association of rs9934336 with poor glycaemic control and higher risk of diabetic retinopathy in T2D

patients in a Slovenian study [11] as well as with COVID-19 risk in our study is interesting. Being located in deep intronic position, it is suggested that rs9934336 possibly has no functional effect [7]. Since the exact role of this variant with regard to SGLT2 expression is still unclear, in such case it is possible that another variant associated with rs9934336 might actually affect the function of SGLT2, which requires to be examined.

Currently dapagliflozin (DAPA), empagliflozin, canagliflozin and ertugliflozin are the primary commercially available SGLT-2is [3]. They possess anti-inflammatory properties and reduce mRNA expression of some cytokines and chemokines (TNF-α, IL-6, MCP-1) and other inflammatory markers (C-reactive protein) [17, 18]. Besides being cardio- and reno-protective [3, 5, 14], SGLT-2is also protect the lungs by decreasing oxidative stress, tissue hypoxia and inflammation [14]. Moreover, DAPA has been reported to reduce lactate levels and is proposed to protect against the severe course of SARS-CoV-2 infection by preventing the lowering of cytosolic pH and reducing the viral load [19]. SGLT-2is usage was also associated with reduced hospitalisation, severity and mortality in COVID-19 patients with T2D [20, 21], and no increased risk of developing COVID-19 was observed [22], which assured safe use of the drug for primary care of diabetes during COVID-19 pandemic. Though euglycemic diabetic ketoacidosis was reported in some COVID-19 patients with T2D using SGLT2-is
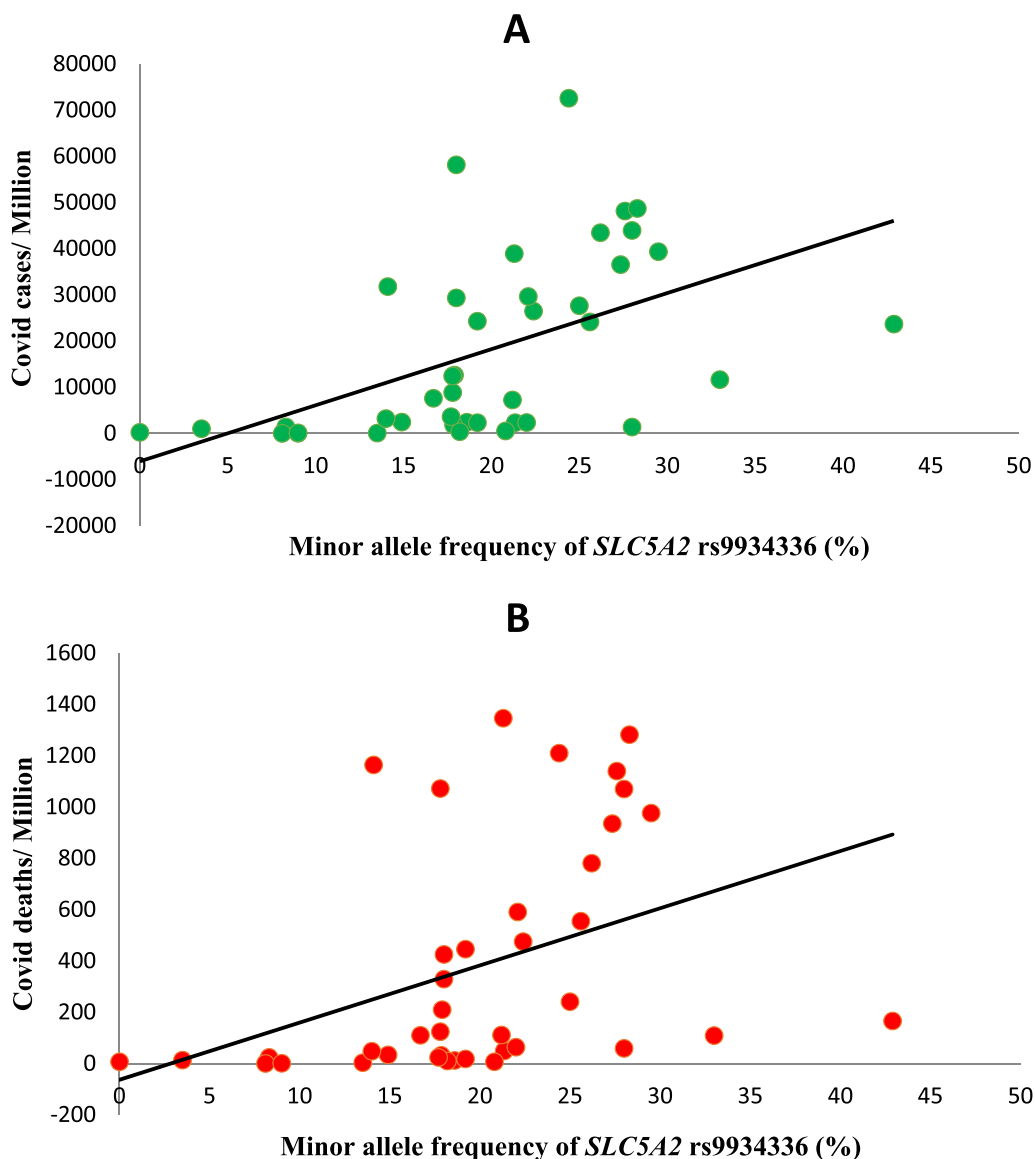
Fig. 1 Correlation of minor allele frequency (MAF) of *SLC5A2* rs9934336 with COVID-19 incidence and mortality. Data from 41 countries were analysed. Each circle in the figure represents a country. Spearman's correlation analysis showed that MAF of *SLC5A2* variant rs9934336 was positively associated with COVID-19 incidence (cases/million of population) ($p < 0.0001$, $r = 0.6225$) (**A**) and COVID-19 mortality (deaths/million of population) ($p < 0.0001$, $r = 0.5837$) (**B**). The countries enrolled in the study are specified in Table 1

[23], DAPA was found to be safe in a randomised, phase 3 trial (DARE-19 study) [24]. Hence, discontinuation of DAPA was discouraged in these patients as long as they were monitored [24]. It seems that the benefits of using SGLT-2is in COVID-19 patients with pre-existing diabetes and/or cardio-renal conditions outweigh the rare side-effects found in a minority of patients. Recent study documents upregulated expression of SGLT2 induced by plasma from COVID-19 patients disrupt vascular homoeostasis, which gets restored upon treatment with SGLT2-is [25]. It is also documented that

individuals with *SLC5A2* rs9934336 minor allele in both homozygous (AA) and heterozygous (GA) conditions excrete higher level of urinary glucose [7, 15]. However, better response to SGLT-2is is predicted in individuals who excrete lower level of glucose in the urine [26] and thus, individuals carrying the G allele of rs9934336 may respond better to the SGLT2-is than individuals with the minor allele A [7]. Though the exact mechanism behind the positive correlation between rs9934336 A allele and COVID-19 detected in our study remains unclear, it proposes poor treatment response to

SGLT-2is in COVID-19 patients carrying the variant, whose frequency is, however, found to be lower in T2D [7]. Additional studies to validate this observation are necessary.

The present study is the first study reporting the association of *SLC5A2* variant rs9934336 with COVID-19 risk. However, the finding has to be validated by case–control studies in diverse populations along with other variants regulating the expression and function of SGLT2. Moreover, treatment response studies involving the use of SGLT-2is in COVID-19 patients having different rs9934336 genotypes as well as other functional genetic variants might help to provide some insight regarding the utility of SGLT-2is in COVID-19 patients with T2D or other comorbidities.

Abbreviations

A	Adenine
ALFRED	Allele frequency database
COVID-19	Coronavirus disease 2019
DAPA	Dapagliflozin
G	Guanine
gnomAD	Genome aggregation database
HbA1c	Haemoglobin A1c (glycated haemoglobin)
HWE	Hardy–Weinberg equilibrium
IL-6	Interleukin 6
MAF	Minor allele frequency
MCP-1	Monocyte chemoattractant protein 1
p	Probability
r	Correlation coefficient
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGLT2	Sodium–glucose cotransporter 2
SGLT-2is	Sodium–glucose cotransporter 2 inhibitors
SLC5A2	Solute carrier family-5 member-2 gene
SNP	Single-nucleotide polymorphism
T2D	Type 2 diabetes
TNF-α	Tumour necrosis factor alpha
WHO	World Health Organization

Author contributions
AD searched the literature as well as genomic databases for acquiring data for the study, analysed and interpreted the data, and prepared the final draft of the manuscript; GD conceived and designed the study, analysed and interpreted the data, and prepared the first draft of the manuscript. Both the authors read and approved the final version of the manuscript.

Availability of data and materials
Data were extracted from published research articles and genomic databases, all of which are available and accessible. The data generated and analysed in the current study are available in Table 1.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P et al (2020) Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med 2:1069–1076. https://doi.org/10.1007/S42399-020-00363-4
2. Unnikrishnan R, Misra A (2021) Diabetes and COVID19: a bidirectional relationship. Eur J Clin Nutr 75:1332–1336. https://doi.org/10.1038/S41430-021-00961-Y
3. Klen J, Dolzan V (2021) Treatment response to SGLT2 inhibitors: from clinical characteristics to genetic variations. Int J Mol Sci 22:9800. https://doi.org/10.3390/ijms22189800
4. Shah KS, Fang JC (2022) Sodium–glucose cotransporter 2 inhibitors in heart failure. Annu Rev Pharmacol Toxicol 62:109–120. https://doi.org/10.1146/annurev-pharmtox-052120-014725
5. Heerspink HJ, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF et al (2020) Dapagliflozin in patients with chronic kidney disease. N Engl J Med 383:1436–1446. https://doi.org/10.1056/NEJMoa2024816
6. Rajeevan H, Soundararajan U, Kidd JR, Pakstis AJ, Kidd KK (2012) ALFRED: an allele frequency resource for research and teaching. Nucleic Acids Res 40:D1010–D1015. https://doi.org/10.1093/nar/gkr924
7. Monobe K, Noso S, Babaya N, Hiromine Y, Taketomo Y, Niwano F et al (2021) Clinical and genetic determinants of urinary glucose excretion in patients with diabetes mellitus. J Diabetes Investig 12:728–737. https://doi.org/10.1111/jdi.13417
8. Enigk U, Breitfeld J, Schleinitz D, Dietrich K, Halbritter J, Fischer-Rosinsky A et al (2011) Role of genetic variation in the human sodium–glucose cotransporter 2 gene (*SGLT2*) in glucose homeostasis. Pharmacogenomics 12:1119–1126. https://doi.org/10.2217/pgs.11.69
9. Zimdahl H, Haupt A, Brendel M, Bour L, Machicao F, Salsali A et al (2017) Influence of common polymorphisms in the *SLC5A2* gene on metabolic traits in subjects at increased risk of diabetes and on response to empagliflozin treatment in patients with diabetes. Pharmacogen Genom 27:135–142. https://doi.org/10.1097/FPC.0000000000000268
10. Ordelheide AM, Bohm A, Kempe-Teufel D, Wagner R, Machicao F, Heni M et al (2017) Common variation in the sodium/glucose cotransporter 2 gene *SLC5A2* does neither affect fasting nor glucose-suppressed plasma glucagon concentrations. PLoS ONE 12:e0177148. https://doi.org/10.1371/journal.pone.0177148
11. Klen J, Goricar K, Dolzan V (2020) Genetic variability in sodium–glucose cotransporter 2 influences glycemic control and risk for diabetic retinopathy in type 2 diabetes patients. J Med Biochem 39:276–282. https://doi.org/10.2478/jomb-2019-0040
12. Wang S, Said MA, Groot HE, van der Most PJ, Thio CH, van de Vegte YJ et al (2021) Search for a functional genetic variant mimicking the effect of SGLT2 inhibitor treatment. Genes 12:1174. https://doi.org/10.3390/genes12081174
13. Li X-T, Zhang M-W, Zhang Z-Z, Cao Y-D, Liu X-Y, Miao R et al (2021) Abnormal apelin-ACE2 and SGLT2 signaling contribute to adverse cardiorenal injury in patients with COVID-19. Int J Cardiol 336:123–129. https://doi.org/10.1016/j.ijcard.2021.05.029
14. Fernandez-Fernandez B, D'Marco L, Gorriz JL, Jacobs-Cacha C, Kanbay M, Luis-Lima S et al (2020) Exploring sodium glucose co-transporter-2 (SGLT2) inhibitors for organ protection in COVID-19. J Clin Med 9:2030. https://doi.org/10.3390/jcm9072030
15. Drexel H, Leiherer A, Saely CH, Brandtner EM, Geiger K, Vonbank A et al (2019) Are SGLT2 polymorphisms linked to diabetes mellitus and cardiovascular disease? Prospective study and meta-analysis. Biosci Rep 39:BSR20190299. https://doi.org/10.1042/BSR20190299
16. Katzmann JL, Mason AM, Marz W, Kleber ME, Niessner A, Bluher M et al (2021) Genetic variation in sodium–glucose cotransporter 2 and heart failure. Clin Pharmacol Ther 110:149–158. https://doi.org/10.1002/cpt.2153

17. Bonnet F, Scheen AJ (2018) Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: the potential contribution to diabetes complications and cardiovascular disease. Diabetes Metabol 44:457–464. https://doi.org/10.1016/j.diabet.2018.09.005
18. Alshnbari A, Idris I (2022) Can sodium–glucose cotransporter-2 (SGLT-2) inhibitor reduce the risk of adverse complications due to COVID-19?—targeting hyperinflammation. Curr Med Res Opin 38:357–364. https://doi.org/10.1080/03007995.2022.2027141
19. Cure E, Cure MC (2020) Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes Metab Syndr Clin Res Rev 14:405–406. https://doi.org/10.1016/j.dsx.2020.04.024
20. Dalan R, Ang LW, Tan WY, Fong S-W, Tay WC, Chan Y-H et al (2020) The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. Eur Heart J Cardiovasc Pharmacother 7:e48-51. https://doi.org/10.1093/ehjcvp/pvaa098
21. Khunti K, Knighton P, Zaccardi F, Bakhai C, Barron E, Holman N et al (2021) Prescription of glucose-lowering therapies and risk of COVID-19 mortality in people with type 2 diabetes: a nationwide observational study in England. Lancet Diabetes Endocrinol 9:293–303. https://doi.org/10.1016/S2213-8587(21)00050-4
22. Sainsbury C, Wang J, Gokhale K, Acosta-Mena D, Dhalla S, Byne N et al (2021) Sodium–glucose co-transporter-2 inhibitors and susceptibility to COVID-19: a population-based retrospective cohort study. Diabetes Obes Metab 23:263–269. https://doi.org/10.1111/dom.14203
23. Vitale RJ, Valtis YK, McDonnell ME, Palermo NE, Fisher ND (2021) Euglycemic diabetic ketoacidosis with COVID-19 infection in patients with type 2 diabetes taking SGLT2 inhibitors. AACE Clin Case Rep 7:10–13. https://doi.org/10.1016/j.aace.2020.11.019
24. Kosiborod MN, Esterline R, Furtado RH, Oscarsson J, Gasparyan SB, Koch GG et al (2021) Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 9:586–594. https://doi.org/10.1016/S2213-8587(21)00180-7
25. Mroueh A, Fakih W, Carmona A, Trimaille A, Matsushita K, Marchandot B et al (2024) COVID-19 promotes endothelial dysfunction and thrombogenicity: role of proinflammatory cytokines/SGLT2 prooxidant pathway. J Thromb Haemost 22:286–299. https://doi.org/10.1016/j.jtha.2023.09.022
26. Hwang Y-C, Kim JH, Lee BW, Lee WJ (2019) A lower baseline urinary glucose excretion predicts a better response to the sodium glucose cotransporter 2 inhibitor. Diabetes Metab J 43:898–905. https://doi.org/10.4093/dmj.2018.0257

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