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Relationship of concomitant anti-diabetic drug administration with sodium-glucose co-transporter 2 inhibitor-related ketosis

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Abstract

Objective: The use of sodium-glucose co-transporter 2 inhibitors (SGLT2is) may be associated with ketoacidosis. Therefore, the associated risk factors should be identified. In particular, information regarding the effects of the co-administration of anti-diabetic drugs is lacking.

Methods: We performed a retrospective study of 68 consecutive patients with diabetes who were taking an SGLT2i and attending a single medical center. After a period of treatment (median 78 days), their circulating ketone concentrations were measured. The concomitant use of other anti-diabetic drugs was analyzed to identify independent risk factors associated with ketosis.

Results: Twenty-five participants were taking empagliflozin, 23 were taking dapagliflozin, and 20 were taking canagliflozin. During the treatment period, no ketoacidotic events were recorded and their mean circulating ketone concentrations at the end of the study period were similar (0.3 mmol/L in the empagliflozin group, 0.26 mmol/L in the dapagliflozin group, and 0.25 mmol/L in the canagliflozin group). After adjustment for the use of anti-diabetic drugs, pioglitazone was found to be independently associated with a risk of high circulating ketone concentration (B value: 0.361, 95% confidence interval: 0.181–0.541).

Conclusion: SGLT2i-associated ketoacidosis was found to be infrequent, but the concomitant use of pioglitazone was associated with a higher risk of ketosis.

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Keywords
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Introduction

Type 2 diabetes is a highly prevalent disease in numerous ethnic groups, which makes it important for physicians to be aware of the possible side effects of the drugs used for its treatment. Sodium-glucose co-transporter 2 inhibitors (SGLT2is) reduces blood glucose concentration by inhibiting SGLT2 in the proximal tubules of the kidneys, which mediate the reabsorption of approximately 90% of the filtered glucose, thereby increasing urinary glucose excretion. In May 2015, the U.S. Food and Drug Administration published a safety warning that the use of SGLT2is might be associated with a higher risk of diabetic ketoacidosis (DKA).[1]

Beyond its effect to increase glucose excretion by the kidneys, SGLT2i also induces the reabsorption of ketone bodies[2] and inhibits SGLT2 in the pancreas, resulting in greater secretion of glucagon by the α-cells,[3] causing an increase in ketone body production and a suppression of insulin secretion.[4] As a result, the use of carbohydrates decreases and metabolism shifts toward lipid oxidation, because the circulating concentrations of fatty acids and lipolysis are increased. The concomitant increase in lipolysis and decrease in the insulin/glucagon ratio results in greater production of ketone bodies in the liver.[2,3]

In practice, only some of the patients who take an SGLT2i develop DKA; therefore, there must be intrinsic risk factors for the manifestation of DKA in patients taking SGLT2is. Previous studies have identified potential risk factors for DKA, which are severe illness or surgical stress, an inadequate dose or the withdrawal of insulin, the restriction of dietary carbohydrate, a history of pancreatitis, alcohol withdrawal, salicylate toxicity, off-label use in patients with type 1 diabetes mellitus, and dehydration.[2,3,5] During treatment with SGLT2is, these risk factors are associated with either altered glucose production or greater lipolysis, which can induce the production of ketone bodies. However, the effects of the co-administration of other anti-diabetic drugs on the incidence of SGLT2i-associated DKA have not been characterized.

It is important for clinicians to identify drugs that pose a risk of DKA events in patients who are being treated with SGLT2is, but observational studies of SGLT2i-associated DKA have yielded conflicting results, possibly because they were limited by modest event sizes.[6–10] Given the limitations of these previous studies, we wished to further characterize the circulating ketone concentrations of patients undergoing SGLT2i therapy in order to better understand this potential drug safety issue, with a focus on the effects of the concomitant use of other anti-diabetic drugs.

Materials and Methods

Participants

Consecutive patients with type 2 diabetes who were undergoing treatment in the

Endocrinology Outpatient Department of Chang Gung Memorial Hospital between July 2016 and September 2020 were recruited. All the participants had been on stable anti-diabetic therapeutic regimens for at least 28 days, either with insulin, a glucagon-like peptide 1 (GLP-1) analog, or an oral anti-diabetic drug other than an SGLT2i, but because of poor glycemic control, an SGLT2i had then been prescribed. All of the participants underwent regular follow-up during the study and none were pregnant or had been diagnosed with end-stage renal disease. In addition, none of the participants had a known risk factor for ketoacidosis (severe illness, surgery, or abnormal fasting behavior). The Institutional Review Board of Chang Gung Memorial Hospital approved the study (No. 202101397B0) and its reporting conforms to the STROBE guidelines.[11] Written informed consent was not required for this retrospective study, in accordance with national legislation and institutional regulations.

Clinical characteristics of the participants

The clinical characteristics of participants, including their age, sex, duration of diabetes, body mass index, smoking and alcohol drinking habits, and the presence of comorbidities such as hypertension, dyslipidemia, coronary heart disease, heart failure, and cerebrovascular accidents were recorded at the clinic visit when their SGLT2i treatment was started. Laboratory measurements to assess glycemic control, circulating lipid profile, circulating liver enzyme activities, and renal function were made on the day of enrolment and after a period of treatment with the SGLT2i (median duration: 78 days; range: 33–162 days). On the last day of this period of treatment, their circulating ketone concentration was measured using an Optium Xceed (Abbott Laboratories, Chicago, IL, USA), which quantifies serum β-hydroxybutyrate concentration with a coefficient of determination of 0.989 ($P<0.001$).[12,13] The other anti-diabetic drugs that were being co-administered during the treatment period were sulfonylureas, metformin, acarbose, a glinide, pioglitazone, a dipeptidyl peptidase-4 inhibitor (DPP4i), a GLP-1 analog, and insulin.

Statistical analysis

Comparisons between participants taking the three groups of SGLT2is were performed using Pearson's chi-square test for categorical data or the Kruskal–Wallis H test for continuous data, as indicated. Paired sample *t*-tests were used to compare the biochemical data across the treatment period. Drug-related factors and the clinical characteristics of the participants were entered into linear regression models to identify independent risk factors for high serum ketone concentration in patients taking an SGLT2i. The B values and 95% confidence intervals for the correlations with circulating ketone concentration associated with the various concomitantly administered anti-diabetic drugs are presented as forest plots. Statistical analyses were performed using SPSS for Windows, version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of the participants taking SGLT2is

Sixty-eight consecutive patients with type 2 diabetes were recruited, all of whom had been on stable anti-diabetic therapeutic regimens for at least 28 days (median: 275.5 days, range: 28–1285 days). Of these participants, 25 were taking empagliflozin, 23 were taking dapagliflozin, and 20 were taking canagliflozin. All the participants

complied well with their medication regimen throughout the study period.

A comparison of the clinical characteristics of the participants taking each SGLT2i is shown in Table 1. The ages of these groups of participants differed; the youngest group were those taking dapagliflozin, with mean age of 49.3 years, followed by the empagliflozin group (mean age 54.21) and the canagliflozin group (mean age 59.61). However, the mean durations of diabetes of these three groups were similar, with a range of 8.03–9.84 years ($P = 0.566$). There was a slight predominance of men in all the groups (50%–69.6%, $P = 0.343$). The prevalence of hypertension was the highest for all the co-morbidities in all three groups, at 68% to 85% ($P = 0.397$), followed by that of coronary heart disease (13%–25%, $P = 0.569$), whereas cerebrovascular accidents and heart failure were rare. The participants in the three groups had similar baseline laboratory data, including signs of inadequate glycemic control, with a pre-meal glucose concentration of 8.451 mmol/L to 8.692 mmol/L ($P = 0.992$) and a glycated hemoglobin (HbA1c) of 8.19% to 8.97% ($P = 0.22$). They had normal estimated glomerular filtration rates (93.37–102.65 mL/minute/1.73 m^2, $P = 0.447$), slightly high alanine aminotransferase (ALT) activity (41.65–53.92 U/L, $P = 0.79$), and dyslipidemia.

Concomitant anti-diabetic drug use

The dosage regimens for the other anti-diabetic drugs administered during the study period did not change and are shown in Table 2. The proportions of the participants that were taking concomitant anti-diabetic drugs were similar among the three groups, with the exception of DPP4is. Approximately 56% to 70% of the participants were taking a sulfonylurea (median: two doses per day, range: 0.5–4 doses; with the doses being glipizide 5 mg, glyburide 5 mg, gliclazide 30 mg, and glimepiride 2 mg), 85% to 100% were taking metformin (median: 1500 mg per day, range: 500–2700 mg), 4.3% to 16% were taking pioglitazone (median: 15 mg per day, range: 15–30 mg), and 30% to 36% were undergoing insulin therapy (median: 20 IU per day, range: 8–114 IU). A DPP4i (dosage: one dose per day of sitagliptin 100 mg, saxagliptin 5 mg, linagliptin 5 mg, or vildagliptin 100 mg) was being administered to 16% of the participants in the empagliflozin group and 35% in the dapagliflozin group, but to none in the canagliflozin group. The other anti-diabetic drugs, including acarbose (median: 100 mg per day, range: 100–300 mg), a glinide (dosage: mitiglinide 30 mg per day), and a GLP-1 analog (dosage: liraglutide 1.2 mg per day), were being used by $\leq$10% of the participants in each of the three groups.

Serum biochemistry

After the treatment period, all the participants showed improvements in glycemic control, with decreases in pre-meal glucose concentration (from 8.569 to 8.061 mmol/L, $P = 0.280$) and HbA1c (from 8.70% to 8.36%, $P = 0.008$), and a trend toward a decrease in ALT activity (from 48.92 to 38.75 U/L, $P = 0.084$). However, their renal function and lipid profiles remained the same (Table 3). The mean serum ketone concentrations at the end of the study were similar (0.3 [0.2, 0.35] mmol/L for the empagliflozin group, 0.26 [0.2, 0.3] mmol/L for the dapagliflozin group, and 0.25 [0.1, 0.38] mmol/L for the canagliflozin group). Seven participants (three in the empagliflozin group, one in the dapagliflozin group, and three in the canagliflozin group) had ketone concentrations above the normal range (<0.6 mmol/L), although none of the participants developed symptoms or signs of DKA during the study (Figure 1).

Table 1. Clinical characteristics and laboratory data for the participants.

Characteristic	Empagliflozin group (n = 25)	Dapagliflozin group (n = 23)	Canagliflozin group (n = 20)	*P*-value
Age (years)	54.21 [43.6, 63.79]	49.3 [41.36, 56.55]	59.61 [48.3, 71]	**0.036**
Male sex	13 (52%)	16 (69.6%)	10 (50%)	0.343
Duration of diabetes (years)	9.84 [5.58, 13.1]	8.51 [3.8, 10.98]	8.03 [3.23, 11.85]	0.566
Body mass index (kg/m^2)	29.71 [25.36, 31.85]	30.87 [27.21, 32.94]	31.56 [26.23, 38.04]	0.682
Alcohol drinker	3 (12%)	3 (13%)	1 (5%)	0.646
Smoker	6 (24%)	5 (21.7%)	4 (20%)	0.949
Hypertension	17 (68%)	18 (78.3%)	17 (85%)	0.397
Coronary heart disease[a]	4 (16%)	3 (13%)	5 (25%)	0.569
Cerebrovascular accident[b]	2 (8%)	0 (0%)	0 (0%)	0.17
Heart failure	1 (4%)	1 (4.3%)	1 (5%)	0.987
Pre-meal glucose (mmol/L)	8.451 [6.619, 8.992]	8.697 [6.647, 9.950]	8.577 [6.883, 8.826]	0.992
HbA1c (%)	8.97 [7.6, 10.3]	8.19 [7.28, 9.13]	8.93 [7.65, 9.93]	0.22
eGFR (mL/minute/1.73m^2)	94.53 [71.52, 122.52]	102.65 [85.03, 119.02]	93.37 [72.72, 118.8]	0.447
ALT (U/L)	53.92 [23.25, 57.5]	49.14 [21.5, 63.25]	41.65 [20.25, 70]	0.79
Cholesterol (mmol/L)	4.625 [4.267, 5.0563]	4.585 [3.970, 5.160]	4.355 [3.621, 4.914]	0.537
Triglyceride (mmol/L)	2.518 [1.432, 3.019]	2.757 [1.271, 2.808]	2.167 [1.650, 2.655]	0.699
HDL-cholesterol (mmol/L)	1.099 [0.963, 1.241]	1.079 [0.866, 1.241]	1.043 [0.879, 1.164]	0.443
LDL-cholesterol (mmol/L)	2.685 [2.108, 3.252]	2.699 [2.244, 3.110]	2.563 [2.069, 3.078]	0.745

Data are mean [first quartile, third quartile] or number (%). [a]Coronary heart disease included a history of ischemic heart disease or coronary artery disease. [b]Cerebrovascular accident included history of embolic, ischemic, or hemorrhagic stroke.

HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase activity; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2. Comparison of the concomitant use of anti-diabetic drugs in the three SGLT2i groups.

Medication	Empagliflozin group (n = 25)	Dapagliflozin group (n = 23)	Canagliflozin group (n = 20)	*P*-value
Sulfonylurea	14 (56%)	15 (65.2%)	14 (70%)	0.608
Metformin	22 (88%)	23 (100%)	17 (85%)	0.175
Acarbose	1 (4%)	2 (8.7%)	2 (10%)	0.712
Glinide	1 (4%)	0 (0%)	1 (5%)	0.579
Pioglitazone	4 (16%)	1 (4.3%)	1 (5%)	0.281
DPP4i[a]	4 (16%)	8 (34.8%)	0 (0%)	**0.011**
GLP-1[b] analog	1 (4%)	0 (0%)	0 (0%)	0.418
Insulin	9 (36%)	7 (30.4%)	7 (35%)	0.912

Data are number (percentage).
[a]DPP4i, dipeptidyl peptidase-4 inhibitor; [b]GLP-1, glucagon-like peptide 1; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Table 3. Biochemical parameters before and after the period of treatment with an SGLT2i.

	Before	After	*P* value
Pre-meal glucose (mmol/L)	8.569 (2.902)	8.061 (2.981)	0.280
HbA1c (%)	8.70 (1.50)	8.36 (1.53)	**0.008**
ALT (U/L)	48.92 (51.65)	38.75 (28.56)	0.084
eGFR (mL/minute/1.73 m^2)	96.50 (30.91)	96.20 (31.79)	0.848
Cholesterol (mmol/L)	4.540 (0.834)	4.539 (0.787)	0.996
Triglyceride (mmol/L)	2.581 (2.450)	2.521 (2.163)	0.695
HDL-cholesterol (mmol/L)	1.079 (0.267)	1.081 (0.261)	0.924
LDL-cholesterol (mmol/L)	2.622 (0.637)	2.642 (0.630)	0.750

N = 68. Data are mean (standard deviation).
HbA1c, glycated hemoglobin; ALT, alanine aminotransferase activity; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Effects of concomitant anti-diabetic drug treatment on the circulating ketone concentration

Figure 2 shows a forest plot of the effects of each anti-diabetic drug on the serum ketone concentration, established using linear regression modeling. After adjustment for the anti-diabetic drug used, pioglitazone was found to be the only concomitantly administered drug that independently increased serum ketone concentration, with a B value of 0.361 and a 95% confidence interval of 0.181 to 0.541. Figure 3 shows the forest plots for the effects of each clinical characteristic and laboratory parameter on the serum ketone concentration, established using linear regression modeling. High-density lipoprotein (HDL)-cholesterol was found to be an independent risk factor for high serum ketone concentration (B value: 0.017, 95% confidence interval: 0.0003–0.0330).

Discussion

We did not identify any ketoacidotic events among the 68 patients with diabetes that we studied, which is consistent with the results of a previous study showing that the incidence of such events in patients taking a SGLT2i in a real-world setting is

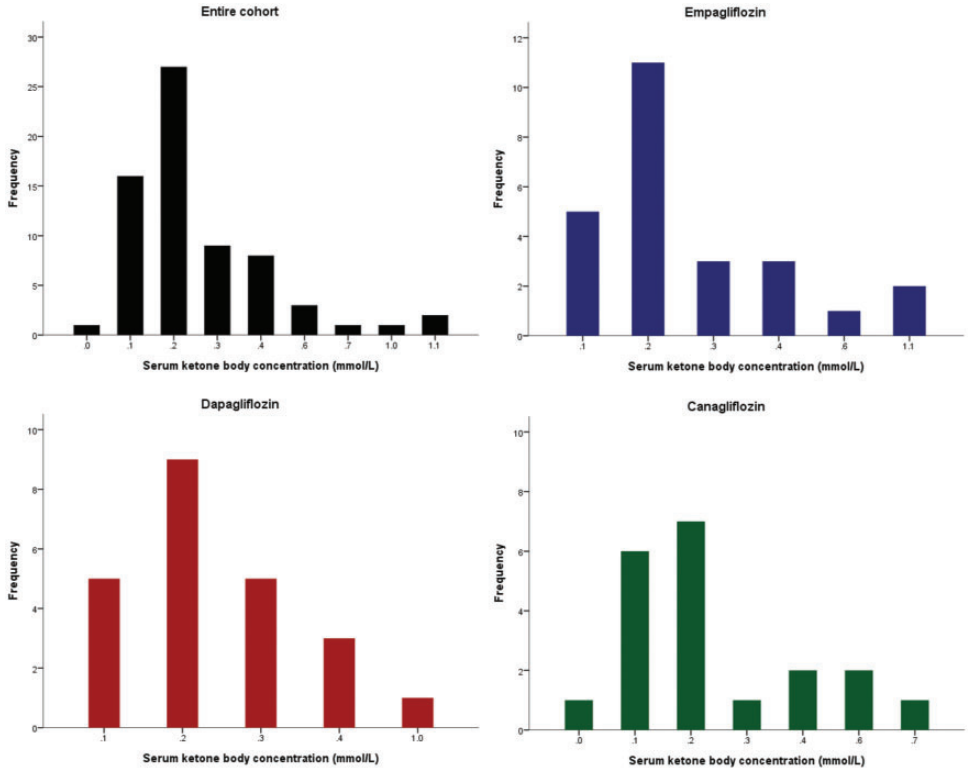

Figure 1. Serum ketone concentrations of participants after treatment with a sodium-glucose co-transporter 2 inhibitor. The frequencies of each concentration are shown for participants who were taking empagliflozin, dapagliflozin, or canagliflozin, and the entire cohort. Three patients taking empagliflozin, one taking dapagliflozin, and three taking canagliflozin had serum ketone concentrations above the normal range (<0.6 mmol/L).

rare (0.18%).[14] Previous studies regarding DKA in patients taking SGLT2is have aimed to quantify the incidence, rather than the actual ketone body concentrations. To the best of our knowledge, the present study is the first to evaluate the relationship of the serum ketone concentration of patients taking an SGLT2i with the use of concomitant anti-diabetic drugs. In addition, we directly measured β-hydroxybutyrate concentration, rather than using the conventional nitroprusside test, which provides a semiquantitative estimate of the acetoacetate and acetone concentrations but does not recognize β-hydroxybutyrate, the main contributor to DKA, and therefore this represents a superior diagnostic test for DKA. Only a few of the participants had serum β-hydroxybutyrate concentrations above the normal range, and no differences in concentration were identified among participants taking each of the three SGLT2is.

In the present study, we aimed to identify concomitantly used anti-diabetic drugs that represent risk factors for ketosis in patients taking an SGLT2i. Of the medications considered, only pioglitazone was shown to be associated with a significantly greater risk of high serum ketone concentration and none of the other drugs were associated with lower risk. Although it has been suggested that insulin and GLP-1 might reduce

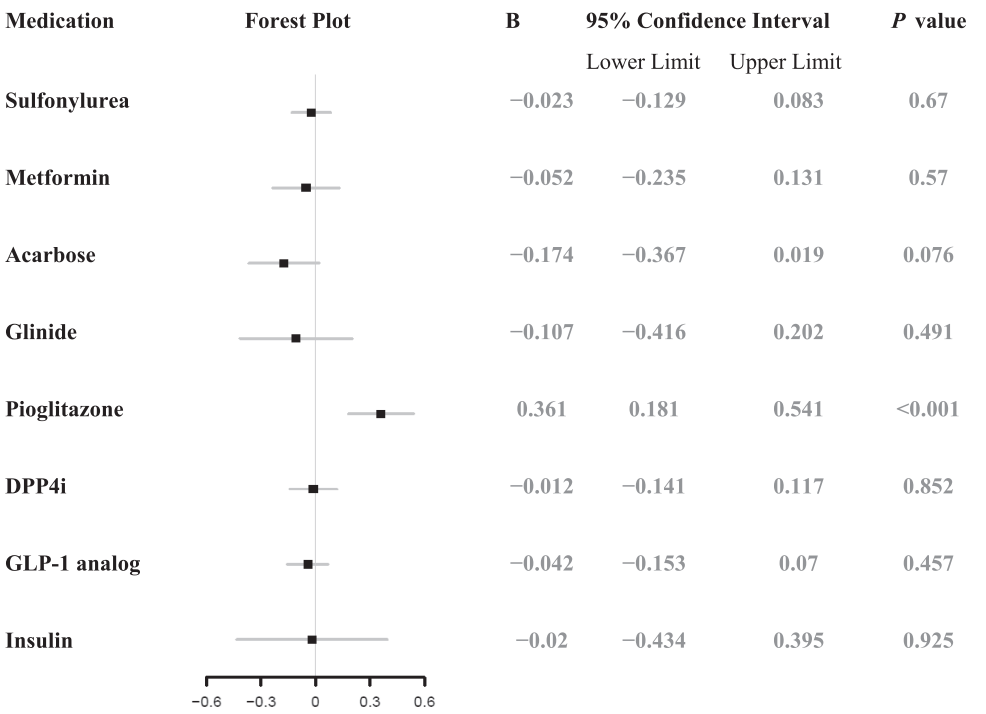

Figure 2. Forest plot of the effects of each anti-diabetic drug on the serum ketone concentration of the participants, determined using linear regression modeling. Pioglitazone had an independent effect on the ketone body concentration (B value 0.361, 95% confidence interval 0.181–0.541).
GLP-1, glucagon-like peptide 1.

ketone body production, because of their counter-regulatory effect on glucagon,[15] we found no significant effects of insulin, a sulfonylurea, a DPP4i, or a GLP-1 analog.

The mechanism of the association between high ketone body concentration and pioglitazone use remains unclear. However, a role for peroxisome proliferator-activated receptors (PPARs) in the regulation of ketone body metabolism has previously been shown.[16] In addition, adipocyte triglyceride lipase (ATGL) may also be involved in the identified ketosis. SGLT2is mirror the effects of the fasting state, even if patients do not substantially restrict their food intake.[17] In the fasting state, ATGL activity is high; therefore, larger amounts of triglyceride are hydrolyzed in adipocytes, releasing free fatty acids into the circulation.[18] Pioglitazone activates PPARγ, and to a lesser extent PPARα,[19] and in *in vivo* and *in vitro* studies, PPARγ agonists have been shown to increase ATGL mRNA and protein levels in pre-adipocytes and mature adipocytes.[20–22] In addition, another study showed that adipose ATGL expression is increased by pioglitazone treatment in humans.[23] Therefore, the co-administration of an SGLT2i and pioglitazone would facilitate the release of fatty acids into the circulation of patients, and these could be metabolized to form acetyl-CoA, which can undergo mitochondrial β-oxidation, ultimately generating ketone bodies.[24] Furthermore, the hepatic expression of ATGL and hormone-sensitive lipase

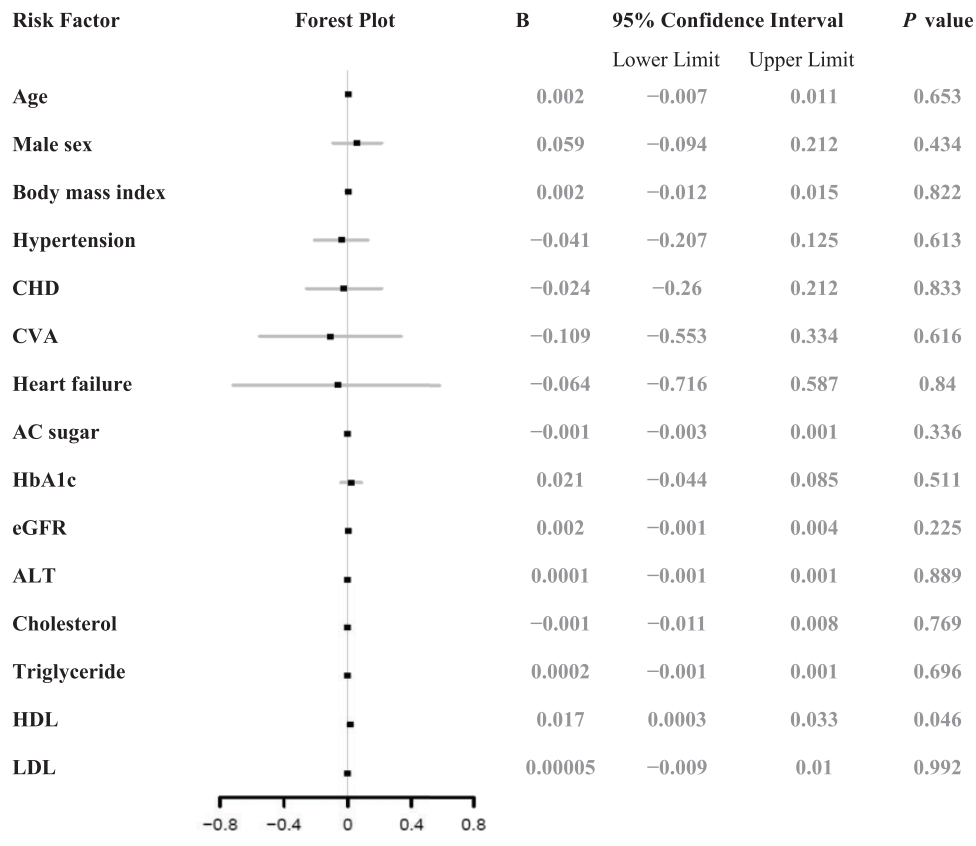

Figure 3. Forest plot of the effects of each clinical characteristic and biochemical parameter on the serum ketone concentration of the participants, determined using linear regression modeling. HDL-cholesterol had an independent effect on the ketone body concentration (B value 0.017, 95% CI 0.0003–0.0330). CHD, coronary heart disease; CVA, cardiovascular accident; AC sugar, *ante cibum* (pre-meal) glucose concentration; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase activity; HDL, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol.

and β-oxidation have been shown to be significantly increased by pioglitazone,[25] which would facilitate the production of ketone bodies.

The effects of concomitant anti-diabetic drug administration on SGLT2i-associated ketoacidosis had not previously been investigated. In the previous small studies of SGLT2i-associated ketoacidosis, some of the participants were taking pioglitazone, but there was no analysis of potential drug-drug interactions.[26,27]

Another interesting but problematic explanation of the present findings is that there was a high HDL-cholesterol concentration in association with the high serum ketone concentration. A previous *in vivo* study showed that the administration of β-hydroxybutyrate affected the lipid profile of the animals, notably by increasing HDL-cholesterol concentration and reducing the low-density lipoprotein-cholesterol/HDL-cholesterol ratio, which suggests that ketones may have similar effects to niacin

on these parameters;[28] in another animal study, an association was identified between the low HDL-cholesterol and ketone body concentrations that characterize mice deficient in ATGL function.[29] We have not identified a mechanism to explain the association of high HDL-cholesterol with ketosis, and this represents a limitation of the present study. However, the association between the concentrations of ketone bodies and HDL-cholesterol in the present study was significant but weak (B value: 0.017, 95% confidence interval: 0.0003–0.0330), and further investigation is required to validate and dissect the mechanism underlying this association.

The present study was limited by its small size and the lack of measurement of baseline serum ketone concentration, which would have permitted a comparison of the longitudinal changes. In addition, the high ketone body concentration identified does not necessarily imply an adverse reaction to the co-administration of an SGLT2i and pioglitazone. There is still disagreement regarding the implications of high ketone body concentrations: some investigators have shown that ketone bodies are used as an energy source in the diabetic or function-impaired heart instead of glucose.[30,31] Furthermore, to determine whether the co-administration of other oral anti-diabetic drugs and SGLT2is can cause ketoacidosis, the conditions in which this type of ketoacidosis is likely to occur must be replicated for the study to be valid. Therefore, we chose circulating ketone concentration as the endpoint of the study, rather than the incidence of ketoacidotic events, in order to identify risk factors for SGLT2i-related ketosis.

In conclusion, this is the first study to investigate the relationship between concomitant anti-diabetic drug use and SGLT2i-related ketosis in patients with type 2 diabetes. Pioglitazone was found to be associated with high ketone body concentrations in patients who were also administered an SGLT2i.

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Author Contributions

CWL conceived the study. SYH performed the data curation. IWC undertook the formal data analysis. CWL wrote the original draft of the manuscript. All the authors reviewed the manuscript and approved the final version.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

References

1. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. 15 May 2015. Accessed at https://wayback.archive-it.org/7993/20170112031553/http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm.
2. Palmer BF and Clegg DJ. Euglycemic Ketoacidosis as a Complication of SGLT2 Inhibitor Therapy. *Clin J Am Soc Nephrol* 2021; 16: 1284–1291.

3. Somagutta MR, Agadi K, Hange N, et al. Euglycemic Diabetic Ketoacidosis and Sodium-Glucose Cotransporter-2 Inhibitors: A Focused Review of Pathophysiology, Risk Factors, and Triggers. *Cureus* 2021; 13: e13665.
4. Liljenquist JE, Bomboy JD, Lewis SB, et al. Effects of glucagon on lipolysis and ketogenesis in normal and diabetic men. *J Clin Invest* 1974; 53: 190–197.
5. Goldenberg RM, Berard LD, Cheng AYY, et al. SGLT2 Inhibitor-associated Diabetic Ketoacidosis: Clinical Review and Recommendations for Prevention and Diagnosis. *Clin Ther* 2016; 38: 2654–2664 e2651.
6. Fralick M, Schneeweiss S and Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. *N Engl J Med* 2017; 376: 2300–2302.
7. Wang Y, Desai M, Ryan PB, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract* 2017; 128: 83–90.
8. Kim YG, Jeon JY, Han SJ, et al. Sodium-glucose co-transporter-2 inhibitors and the risk of ketoacidosis in patients with type 2 diabetes mellitus: A nationwide population-based cohort study. *Diabetes Obes Metab* 2018; 20: 1852–1858.
9. Ueda P, Svanstrom H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ* 2018; 363: k4365.
10. Wang L, Voss EA, Weaver J, et al. Diabetic ketoacidosis in patients with type 2 diabetes treated with sodium glucose co-transporter 2 inhibitors versus other antihyperglycemic agents: An observational study of four US administrative claims databases. *Pharmacoepidemiol Drug Saf* 2019; 28: 1620–1628.
11. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
12. Chiu RW, Ho CS, Tong SF, et al. Evaluation of a new handheld biosensor for point-of-care testing of whole blood beta-hydroxybutyrate concentration. *Hong Kong Med J* 2002; 8: 172–176.
13. Bektas F, Eray O, Sari R, et al. Point of care blood ketone testing of diabetic patients in the emergency department. *Endocr Res* 2004; 30: 395–402.
14. Liu J, Li L, Li S, et al. Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2020; 22: 1619–1627.
15. Garg M, Ghanim H, Kuhadiya ND, et al. Liraglutide acutely suppresses glucagon, lipolysis and ketogenesis in type 1 diabetes. *Diabetes Obes Metab* 2017; 19: 1306–1311.
16. Grabacka M, Pierzchalska M, Dean M, et al. Regulation of Ketone Body Metabolism and the Role of PPARalpha. *Int J Mol Sci* 2016; 17: 2093.
17. Osataphan S, Macchi C, Singhal G, et al. SGLT2 inhibition reprograms systemic metabolism via FGF21-dependent and -independent mechanisms. *JCI Insight* 2019; 4: e123130.
18. Nielsen TS, Vendelbo MH, Jessen N, et al. Fasting, but not exercise, increases adipose triglyceride lipase (ATGL) protein and reduces G(0)/G(1) switch gene 2 (G0S2) protein and mRNA content in human adipose tissue. *J Clin Endocrinol Metab* 2011; 96: E1293–E1297.
19. Yki-Jarvinen H. Thiazolidinediones. *N Engl J Med* 2004; 351: 1106–1118.
20. Gerhold DL, Liu F, Jiang G, et al. Gene expression profile of adipocyte differentiation and its regulation by peroxisome proliferator-activated receptor-gamma agonists. *Endocrinology* 2002; 143: 2106–2118.
21. Kershaw EE, Schupp M, Guan HP, et al. PPARgamma regulates adipose triglyceride lipase in adipocytes in vitro and in vivo. *Am J Physiol Endocrinol Metab* 2007; 293: E1736–E1745.
22. Shen WJ, Patel S, Yu Z, et al. Effects of rosiglitazone and high fat diet on lipase/esterase expression in adipose tissue. *Biochim Biophys Acta* 2007; 1771: 177–184.

23. Yao-Borengasser A, Varma V, Coker RH, et al. Adipose triglyceride lipase expression in human adipose tissue and muscle. Role in insulin resistance and response to training and pioglitazone. *Metabolism* 2011; 60: 1012–1020.
24. Newman JC and Verdin E. Ketone bodies as signaling metabolites. *Trends Endocrinol Metab* 2014; 25: 42–52.
25. Hsiao PJ, Chiou HC, Jiang HJ, et al. Pioglitazone Enhances Cytosolic Lipolysis, Beta-oxidation and Autophagy to Ameliorate Hepatic Steatosis. *Sci Rep* 2017; 7: 9030.
26. Sharma PV, Jobanputra YB, Lewin K, et al. Diabetic Ketoacidosis in Patients with Type 2 Diabetes on Sodium-Glucose Cotransporter-2 Inhibitors – A Case Series. *Rev Recent Clin Trials* 2018; 13: 156–160.
27. Yehya A and Sadhu A. Sodium-Glucose Cotransporter 2 Inhibitor-Associated Prolonged Euglycemic Diabetic Ketoacidosis in Type 2 Diabetes: A Case Report and Literature Review. *Clin Diabetes* 2020; 38: 112–116.
28. Caminhotto RO, Komino ACM, De Fatima Silva F, et al. Oral beta-hydroxybutyrate increases ketonemia, decreases visceral adipocyte volume and improves serum lipid profile in Wistar rats. *Nutr Metab (Lond)* 2017; 14: 31.
29. Wang Y, Zhang Y, Qian H, et al. The g0/g1 switch gene 2 is an important regulator of hepatic triglyceride metabolism. *PLoS One* 2013; 8: e72315.
30. Mizuno Y, Harada E, Nakagawa H, et al. The diabetic heart utilizes ketone bodies as an energy source. *Metabolism* 2017; 77: 65–72.
31. Voros G, Ector J, Garweg C, et al. Increased Cardiac Uptake of Ketone Bodies and Free Fatty Acids in Human Heart Failure and Hypertrophic Left Ventricular Remodeling. *Circ Heart Fail* 2018; 11: e004953.