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CASE SERIES

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SGLT-2 inhibitors and high-dose acarbose as potential high-risk combinations for ketosis and ketoacidosis in Asian patients with T2DM: A case series

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Key Clinical Message

High-dose acarbose may increase the risk of diabetic ketosis/diabetic ketoacidosis in Asian patients on sodium-glucose cotransporter-2 inhibitors. Healthcare providers and patients should be cautious to avoid this combination.

Abstract

Low-calorie diets should be avoided in patients receiving sodium-glucose cotransporter-2 (SGLT-2) inhibitors to decrease the risk of diabetic ketoacidosis (DKA). High-dose acarbose can decelerate carbohydrate absorption. We detail three cases of diabetic ketosis (DK) following concurrent SGLT-2 inhibitor and high-dose acarbose therapy (acarbose 300 mg/day and dapagliflozin 10 mg/day). Patients, aged 38–63 years with 3–10 years of type 2 diabetes mellitus (T2DM), developed DK, indicated by moderate urinary ketones and high glucose (urine ketone 2+ to 3+ and glucose 3+ to 4+) without acidosis, within 4 days to 1 month post-therapy initiation. Serum glucose was 172.8–253.8 mg/dL; HbA1c was 9.97%–10.80%. The combination therapy was halted, and DK was managed with low-dose intravenous insulin and fluids, followed by intensive insulin therapy. High-dose acarbose with SGLT-2 inhibitors may increase the risk of DK/DKA in Asian patients.

KEYWORDS

acarbose, diabetic ketoacidosis, diabetic ketosis, euglycemic, SGLT-2 inhibitor

1 | INTRODUCTION

Therapeutic options for type 2 diabetes mellitus (T2DM) have broadened, with the emergence of novel antihyperglycemic agents. Glucagon-like peptide-1 receptor (GLP-1R) agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated cardiovascular and renal benefits and are recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for patients with atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), or chronic kidney disease

(CKD).[1] These agents are gaining popularity in China as well. While SGLT-2 inhibitors offer benefits such as cardiovascular and renal protection, weight reduction, and a lower risk of hypoglycemia, they may also induce side effects they are associated with several side effects, notably the rare but severe diabetic ketoacidosis (DKA).[2,3] High-dose acarbose reduces the absorption of dietary carbohydrates particularly in patients with high-carbohydrate diets. The combined use of high-dose acarbose with SGLT-2 inhibitors, which enhance renal glucose excretion, may mimic the metabolic effects of a low-carbohydrate and low-calorie diet, thereby potentially elevating the risk of DKA. This study reports three cases of diabetic ketosis (DK) in patients treated with SGLT-2 inhibitors alongside high-dose acarbose (300 mg/d), juxtaposed with two recently published cases of Chinese patients who experienced DKA with similar treatment.

2 | CASE HISTORY/EXAMINATION

Clinical and laboratory features of the patients are summarized in Table 1.

2.1 | Case 1

A 38-year-old male presented with a 3-year history of T2DM. He had been intermittently taking "Xiaoke pills" a Chinese patent medicine containing glibenclamide. Eighteen days prior to his presentation, he visited the outpatient department (OPD) for polyuria and was found to have a glycated hemoglobin (HbA1c) level of 10.6% (normal range: 4%–6%). He was prescribed acarbose (100 mg three times a day), dapagliflozin (10 mg once daily), and degludec (10 IU/day).

2.2 | Case 2

The patient was a 55-year-old male with a 10-year history of T2DM. He had a sporadic intake of metformin and acarbose, and had a brief period of insulin therapy around 6 years before the current presentation. Approximately 2 months prior to seeking medical attention, he transitioned from metformin to dapagliflozin (10 mg daily) based on a friend's recommendation. Around 1 month prior to the current visit (exact timing not recalled by the patient), he escalated the acarbose dosage to 100 mg three times a day in pursuit of improved glycemic management. Just 2 days before presenting to our hospital with symptoms of polydipsia, he had sought care at another medical facility. At that time, his routine urine analysis exhibited 3+ ketones and 4+ glucose levels.

2.3 | Case 3

The patient was a 63-year-old female with a 7-year history of T2DM. She initially used OADs and transitioned to 2 years of intensive insulin therapy prior to the current presentation. Subsequently, she shifted to "Xiaoke pills". Twenty days before the current visit, she was initiated on insulin detemir (10 units daily), gliclazide (80 mg twice daily), dapagliflozin (10 mg once daily), and acarbose (100 mg three times a day) during OPD visit due to a high HbA1c level of 10.3%. During a routine follow-up appointment, her urine analysis showed 2+ ketones and 3+ glucose. Dapagliflozin was discontinued, and she was hospitalized the following day.

2.4 | Differential diagnosis, investigations, and treatment

Case 1: During his routine subsequent visit on the day of admission, his urine workup revealed ketones at 3+ and glucose at 3+. Physical examination (PE) results were mostly within normal limits, with a body mass index (BMI) of 25.0 kg/m^2. Arterial blood gas analysis showed a pH of 7.350 (normal range: 7.35–7.45), base excess (BE) of −3.0 mmol/L (normal range: −3 to 3 mmol/L), and HCO_3^- of 22.6 mmol/L (normal range: 22–27 mmol/L). Oral antidiabetic drugs (OAD) were discontinued, and low-dose intravenous insulin therapy was initiated alongside fluid infusion. Urine ketone levels became negative after 8 h. Given his elevated HbA1c of 10.6% on admission, intensive insulin therapy was subsequently initiated. His C-peptide levels at 0, 30, and 120 min post breakfast were 1.59, 1.67, and 2.23 ng/mL, respectively. A diagnosis of non-proliferative diabetic retinopathy (NPDR) was confirmed following ophthalmological consultation. He had a urinary microalbumin level of 94.7 mg/24 h, a urinary albumin-creatinine ratio (UACR) of 77.36 mg/g, and an estimated glomerular filtration rate (eGFR) of 285.67 mL/min/1.73 m^2 (normal range: ≥90 mL/min/1.73 m^2), leading to the diagnosis of diabetic nephropathy (DN) (G1A2). Electromyography revealed diabetic peripheral neuropathy (DPN), for which calcium dobesilate, irbesartan, and methylcobalamin were prescribed. Vascular ultrasound of the lower extremities showed atherosclerosis, confirming the diagnosis of diabetic peripheral vascular disease (DPVD) (Figure 1A). Aspirin and atorvastatin were also applied.

TABLE 1 Characteristics of patients who developed DK/DKA on SGLT-2 inhibitors and high dose acarbose.

Patient characteristics	Case 1	Case 2	Case 3	Case 4[22]	Case 5[22]
Age	38	55	63	48	63
Gender	Male	Male	Female	Female	Male
T1/T2DM	T2DM	T2DM	T2DM	T2DM	T2DM
Duration of DM	3 years	10 years	7 years	10 years	10 years
Complication	DN, DR, DPN, DPVD	DN, DR, DPN, DPVD	DPN, DPVD	Complications of T2DM[a]	NA
Comorbidities	CHB	HTN	HTN, CHB, CHC	CHB	HTN, CVD
Family history of DM	Uncle with T2DM	NO	NO	NA	NA
BMI (kg/m^2)	25.0	25.8	23.1	NA	NA
HbA1C(4–6%)	10.60	9.97	10.30	10.8	NA
C-peptide (ng/mL)	1.59 (0 min) 1.67 (30 min) 2.23 (120 min)			0.53 (0 min) 0.95 (30 min) 1.16 (120 min)	
eGFR (>90 mL/min/1.73 m^2)	285.67	111.52	105.90	Left 75.00 right 70.77 mL/min^{-1}[b]	NA
SGLT2 inhibitor (dose)	Dapagliflozin (10 mg/day)	Dapagliflozin (10 mg/day)	Dapagliflozin (10 mg/day)	Dapagliflozin (10 mg/day)	Dapagliflozin (5 mg/day)
α-Glucosidase inhibitors	Acarbose (300 mg/d)	Acarbose (300 mg/d)	Acarbose (300 mg/d)	Acarbose (300 mg/d)	Acarbose (300 mg/d)
Other medications	Degludec (12 u/d)	Irbesartan	Gliclazide Detemir (10 u/d) Nifedipine	Metformin Sitagliptin Detemir (14 u/d)	Metformin Nifedipine Aspirin Atorvastatin
Time to DK/DKA post SGLT-2 inhibitor and α-Glucosidase inhibitor initiation	18 days	Less than 1 month	20 days	9 days	4 days
Symptoms of DKA				Nausea, vomiting	Nausea, vomiting
Mental status	Orited	Orited	Orited	NA	NA
Presenting plasma glucose (mg/dL)	248.4	191.8	237.6	253.8	172.8
Urine routine(−)	Glu3+, Ket3+	Glu4+, Ket3+[c] Glu3+, Ket2+[d]	Glu3+, Ket2+[e] Glu4+, Ket-[d]	Glu4+, Ket4+	Glu4+, Ket3+
Serum ketones	NA	NA	NA	+	+
PH (7.35–7.45)	7.35	7.35	NA	7.07	7.34
PCO_2 (35–45 mmHg)	41	46	NA	15	27

(Continues)

TABLE 1 (Continued)

Patient characteristics	Case 1	Case 2	Case 3	Case 4[22]	Case 5[22]
HCO_3 (22–27 mmol/L)	22.6	24.2	NA	4.3	14.6
Anion gap (−3—3 mmol/L)	−3.0	−0.2	NA	−25.8	−11.2

Abbreviations: BMI, body mass index; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CKD, chronic kidney disease; CVD, cardiovascular disease; DK, diabetic ketosis; DKA, diabetic ketoacidosis; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DPVD, diabetic peripheral vascular disease; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; HT, hypertension; SGLT-2, sodium-glucose co-transporter; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

[a]No detailed information was provided.

[b]Estimated by kidney emission computed tomography (ECT).

[c]2 days prior to admission.

[d]On admission.

[e]1 day prior to admission.

Case 2: Upon admission, the physical examination findings were generally within normal limits (BMI: 25.8 kg/m^2). The urine analysis performed on admission showed 2+ ketones and 3+ glucose levels. Arterial blood gas analysis indicated a pH of 7.35 (normal range 7.35–7.45), BE of −0.2 mmol/L (normal range −3 to 3 mmol/L) and $HCO3^-$ level of 24.2 mmol/L (normal range 22–27 mmol/L). Following 6 h of intravenous insulin and fluid administration, urinary ketone levels normalized. Intensive insulin therapy was initiated due to the patient's elevated HbA1c level of 9.97% (normal range 4%–6%). Subsequent assessments confirmed NPDR, DN stage G1A2, DPN, and DPVD (Figure 1B). Appropriate pharmacological management was prescribed for these diagnoses.

Case 3: Upon admission, the physical examination findings were unremarkable (BMI: 23.1 kg/m^2). Post oral rehydration, urine analysis indicated negative ketone levels and 4+ glucose. Blood gas analysis was not performed. Intensive insulin therapy was initiated. Subsequent evaluations confirmed DPN and DPVD (Figure 1C), leading to appropriate pharmacological management.

2.5 | Outcome

The urine ketone levels became negative and euglycemia were gradually achieved.

3 | DISCUSSION AND CONCLUSIONS

The elevated expression of SGLT-2 on the proximal tubule cells of patients with type 1 diabetes mellitus (T1DM) and T2DM enhances glucose reabsorption in renal tubules. SGLT-2 inhibitors selectively inhibit SGLT-2 on renal proximal tubule epithelial cells, thereby reducing serum glucose levels. This mechanism is insulin secretion-independent and applicable across the spectrum of diabetes. Recognized for their efficacy in CKD, heart failure, weight loss, and hypoglycemia risk reduction,[4,5] SGLT-2 inhibitors are recommended in the joint management guidelines for T2DM by the ADA and the EASD.[1] Additionally, there is a growing trend in the utilization of these agents for T1DM.[6,7]

Despite the various advantages, SGLT-2 inhibitors have been associated with an increased risk of DKA as noted in several reports.[7,8] The underlying mechanism involves the augmentation of urinary glucose excretion, which diminish insulin secretion, elevate glucagon levels, and impair lipolysis control, thus fostering ketone body synthesis. The impaired urinary clearance of ketone bodies may further heightened susceptibility to DKA. Additionally,

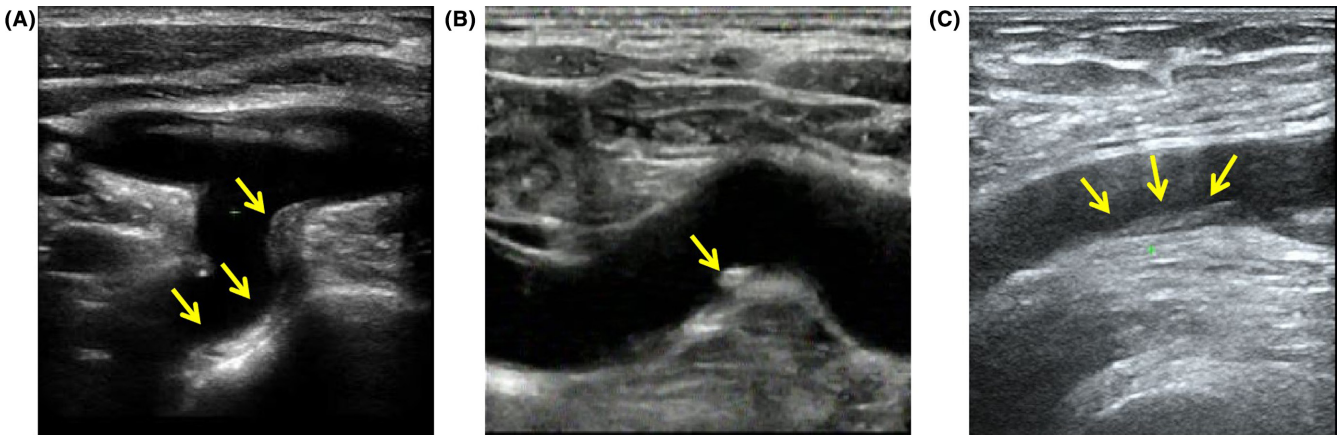

FIGURE 1 Ultrasound of arterial vessels reveals diabetic peripheral vascular disease in the three patients. Atherosclerotic plaques are indicated by arrows (A) for Case 1, (B) for Case 2, and (C) for Case 3.

the escalated urine output associated with SGLT-2 inhibitors could hasten the progression of ketoacidosis.[4,9] Notably, the reduced renal glucose reabsorption threshold can result in euglycemic diabetic ketoacidosis (eDKA), a form of metabolic acidosis (pH <7.3, serum bicarbonate <18 mmol/L) with detectable ketones in urine or serum, yet blood glucose levels remain normal or minimally elevated (< 250 mg/dL, 13.9 mmol/L).[7,10] This characteristic renders DKA induced by SGLT-2 inhibitors elusive for detection.

Currently, specific predictors for DKA with SGLT-2 inhibitors remain unidentified.[11] However, individuals characterized by a lower BMI, prolonged diabetes duration, higher HbA1c levels, and lower estimated eGFRs exhibit an increased risk.[12] The earlier onset of β-cell deficiency in Asian patients compared to Caucasians underscores the need for heightened surveillance, especially among those with diagnosed β-cell dysfunction.[13–15] Tailoring treatment regimens to individual patient profiles is advocated over a universal approach, given the observed link between DKA occurrence and SGLT-2 inhibitor dosages.[7] Since DKA can be precipitated by reduced nutritional intake, it is advisable to eschew low-carbohydrate diets in patients administered SGLT-2 inhibitors who primarily rely on carbohydrates as their main energy substrate.[8]

Acarbose functions by inhibiting α-glucosidase, thereby diminishing the overall absorption of dietary carbohydrates through the delay or prevention of sugars like maltose and sucrose digestion.[16,17] This mechanism is particularly beneficial in East Asian populations where diets are rich in carbohydrates, making acarbose a commonly recommended alternative to metformin for initial T2DM management.[18–20] The impact on carbohydrate absorption becomes more evident with higher doses, and the appetite-suppressing and gastrointestinal effects of high-dose acarbose (100 mg three times daily) can lead to reduced food intake and significant weight loss in some individuals.[21] Although SGLT-2 inhibitors typically induce glucosuria levels of 50–100 g/day, concurrent high-dose acarbose may augment the risk of DK/DKA by emulating a low-carbohydrate diet state. Therefore, the combination should be avoided, particularly in individuals with β-cell insufficiency. Recently, Yuan et al. reported two cases of DKA in Chinese patients treated with this combination.[22] The clinical characteristics of these five patients are summarized in Table 1. All patients initiated this dual therapy at elevated HbA1c levels, with our patients manifesting symptoms of DK within 18 days to a month, contrasted with the rapid progression seen in Yuan's cases, displaying typical severe acidosis symptoms within days. Analysis of the clinical profiles revealed that patients with DKA had a longer T2DM duration, compromised β-cell function (indicated by lower C-peptide levels), and ongoing metformin use, which may have intensified gastrointestinal effects associated with high-dose acarbose and worsened carbohydrate intolerance. However, our patients showed milder impacts on food intake. Notably, four of the five patients received this treatment combination under medical advice, underscoring the need for both healthcare professionals and patients to be vigilant about the associated risks.

A pivotal clinical determination is the identification of an optimal interval following the cessation of SGLT-2 inhibitors before initiating high-dose acarbose therapy. Canagliflozin, dapagliflozin, and empagliflozin exhibit similar half-lives of approximately 13 h,[23] implying potential elimination within approximately 3 days. However, in patients with CKD, an extended half-life and decelerated elimination are observed.[24] Therefore, given the uncertain safety window, the initiation of high-dose acarbose immediately after discontinuing SGLT-2 inhibitors is not recommended, especially in those with renal impairment. Notably, the patients referenced were all treated with dapagliflozin, likely owing to its earlier market introduction

and broader acceptance in China. It is essential to avoid concurrent use of high-dose acarbose with any SGLT-2 inhibitor, including but not limited to dapagliflozin.

The administration of high-dose acarbose to Asian patients receiving SGLT-2 inhibitors may increase the risk of DK/DKA. Healthcare providers must caution against this combination to ensure patient safety.

AUTHOR CONTRIBUTIONS

Wei Qiang: Funding acquisition; writing – original draft. **Fei Yang:** Investigation; writing – review and editing. **Ling Liu:** Investigation; resources. **Ruiqing Dong:** Data curation; visualization. **Yushi Sun:** Investigation; visualization. **Ahona Mondal:** Investigation; visualization. **Hui Guo:** Project administration; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data underlying the results are available as part of the article, and no additional source data are require.

ETHICS STATEMENT

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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