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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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Abstract

Objective: Low-carbohydrate diets should be avoided in patients receiving Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors to reduce the risk of Diabetic Ketoacidosis (DKA). High-dose acarbose has been reported to delay and reduce the absorption of carbohydrates.

Methods: Herein, we present three cases of Diabetic Ketosis (DK) that developed after combined treatment with SGLT-2 inhibitors and high-dose acarbose. Clinical and laboratory features were summarized.

Results: The three patients were aged between 38-63 years old, and have had a history of type 2 diabetes mellitus (T2DM) for 3-10 years. The patients visited the hospital either due to poor glucose control or for regular check-ups. DK (urine ketone 2+ to 3+ and glucose 3+ to 4+) without acidosis was revealed 4 days to <1 month after the initiation of combined therapy including high-dose acarbose (300 mg/d) and dapagliflozin (10 mg/d). No symptoms of DKA were reported and all the patients were fully oriented. Their BMI was 23.1-25.8 kg/m^2. Serum glucose was 172.8-253.8 mg/dl. HbA1c was 9.97-10.80%. Microvascular and macrovascular complications of T2DM were found in patients with normal estimated Glomerular Filtration Rate (eGFR). The combination of acarbose and Dapagliflozin was discontinued. Low-dose intravenous insulin and fluid infusion was administered, as required. Intensive insulin therapy was adopted after the remission of DK.

Conclusion: High-dose acarbose may increase the risk of DK/DKA in Asian patients on SGLT-2 inhibitors. Healthcare providers and patients should be cautious to avoid this combination.

Keywords: SGLT-2 inhibitor; Acarbose; Euglycemic; Diabetic ketoacidosis; Diabetic ketosis.

Abbreviations: SGLT-2: Sodium-Glucose Co-Transporter; GLP-1 RA: Glucagon-Like Peptide-1recptor Agonist; CKD: Chronic Kidney Disease; HF: Heart Failure; DK: Diabetic Ketosis; DKA: Diabetic Ketoacidosis; Eudka: Euglycemic Diabetic Ketoacidosis; T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes; OPD: Outpatient Dispensary; HT: Height; BW: Body Weight; PE: Physical Examination; BMI: Body Mass Index; BE: Base Excess; NPDR: Non-Proliferative Diabetic Retinopathy; UACR: Rurinary Albumin Creatinine Ratio; Egfr: Estimated Glomerular Flitration Rate; HTN: Hypertension; CHB: Chronic Hepatitis B.

Introduction

Treatment options for type 2 Diabetes Mellitus (T2DM) have expanded in recent years. Novel anti-diabetic agents, such as 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]. The use of these novel anti-diabetic agents in China is also on the rise. Despite the advantages of SGLT-2 inhibitors, which include cardiovascular and renal benefits, weight loss, and low hypoglycemic risk, they are associated with several side effects, with Diabetic Ketoacidosis (DKA) being rare but potentially fatal [2,3]. In this study, we present three cases of Diabetic Ketosis (DK) in patients receiving SGLT-2 inhibitors and high-dose acarbose (300 mg/d), and compare them with two other recently reported cases of Chinese patients who developed DKA under a similar regimen.

Case presentation

Clinical and laboratory features of the patients are summarized in Table 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). 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 Anti-Diabetic Drugs (OAD) were discontinued, and low-dose intravenous insulin therapy was initiated alongside fluid infusion. Urine ketone levels became negative after eight hours. Given his elevated HbA1c of 10.6% on admission, intensive insulin therapy was subsequently initiated. His C-peptide levels at 0, 30, and 120 minutes 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 hours, 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). Aspirin and atorvastatin were also applied.

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 six years before the current presentation. Approximately two months prior to seeking medical attention, he transitioned from metformin to dapagliflozin (10 mg daily) based on a friend's recommendation. Around one 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 two 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. Upon admission, the physical examination findings were generally within normal limits (BMI: 25.8 kg/m²). 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 six hours 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. Appropriate pharmacological management was prescribed for these diagnoses.

Case 3: The patient was a 63-year-old female with a 7-year history of T2DM. She initially used OADs and transitioned to two 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. Upon admission, the physical examination findings were unremarkable (BMI: 23.1 kg/m²). 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, leading to appropriate pharmacological management.

Discussion and conclusion

The increased expression of SGLT-2 on the proximal tubule cells of patients with type 1 Diabetes Mellitus (T1DM) and T2DM promotes the reabsorption of glucose in renal tubules. SGLT-2 inhibitors selectively inhibit SGLT-2 on renal proximal tubule epithelial cells, inhibiting urinary glucose reabsorption to reduce serum glucose levels. This mechanism operates independently of insulin secretion by β-cells, making it applicable across the spectrum of diabetes. Due to their established efficacy in CKD, heart failure, weight loss, and hypoglycemia risk reduction [4,5], SGLT-2 inhibitors are endorsed in the collaborative management guidelines for T2DM by the ADA and the EASD [1]. Furthermore, there is a growing trend in the utilization of these agents for T1DM [6,7].

Despite the various advantages of SGLT-2 inhibitors, there are reports indicating an increased risk of DKA [7,8]. The mechanism involves the augmentation of urinary glucose excretion, which in turn leads to reduced insulin secretion, heightened

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	NA
Co-morbidities	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/in/1.73 m^2)	285.67	111.52	105.90	**left75.00 right 70.77 mL min^{-1}	NA
SGLT2 inhibitor (dose)	Dapagliflozin (10 mg/d)	Dapagliflozin (10 mg/d)	Dapagliflozin (10 mg/d)	Dapagliflozin (10 mg /d)	Dapagliflozin (5 mg/d)
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 (12u/d)	Irbesartan	Gliclazide Detemir (10u/d) Nifedipine	Metformin Sitagliptin Detemir (14u/d)	Metformin Nifedipine Aspirin Atorvastatin
Time to DK/DKA post SGLT-2 inhibitor and α-Glucosidase inhibitor initiation	18 days	Less than 1 months	20 days	9 days	4 days
Symtoms 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+	[a]Glu4+, Ket3+ [b]Glu3+, Ket2+	cGlu3+, Ket2+ [d]Glu4+, Ket-	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
HCO_3 (22-27mmol/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

*, no detailed information was provided.**, estimated by kidney Emission Computed Tomography (ECT)
a, 2 days prior to admission; b, on admission; c, 1 day prior to admission; d, on admission
SGLT-2: Sodium-Glucose Co-Transporter; DK: Diabetic Ketosis; DKA: Diabetic Ketoacidosis; DN: Diabetic Nephropathy; DR: Diabetic Retinopathy; DPN: Diabetic Peripheral Neuropathy; DPVD: Diabetic Peripheral Vascular Disease; CHB: Chronic Hepatitis B; CHC: Chronic Hepatitis C; HT: Hypertension; CVD: Cardiovascular Disease; CKD: Chronic Kidney Disease; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus: BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate.

glucagon levels, and the inhibition of lipolysis control, consequently promoting ketone body production. The compromised elimination of ketone bodies through urine may also contribute to the heightened susceptibility to DKA. Additionally, the escalated urine output associated with SGLT-2 inhibitors could hasten the progression of ketoacidosis [4,9]. Notably, due to the decreased renal glucose threshold, DKA triggered by SGLT-2 inhibitors can present as euglycemic ketoacidosis (eDKA), characterized by metabolic acidosis (pH<7.3, serum bicarbonate <18 mmol/L) with positive ketones (either urinary or serum) but normal to slightly elevated blood glucose levels (<250 mg/dL, 13.9 mmol/L) [7,10]. This unique feature makes DKA induced by SGLT-2 inhibitors more challenging to detect.

Currently, specific predictors for DKA with SGLT-2 inhibitors remain unidentified [11]. Nonetheless, individuals with lower BMI, longer diabetes duration, elevated HbA1c levels, and reduced estimated eGFRs are noted to face a heightened risk [12]. Given the earlier β-cell deficiency onset in Asian patients compared to their Caucasian counterparts [13,14], enhanced vigilance is crucial, particularly for those with confirmed β-cell dysfunction [15]. Personalizing the treatment regimen, instead of adopting a standardized approach, is recommended due to the apparent correlation between DKA incidence and SGLT-2 inhibitor dosage [7]. Considering that triggers for DKA encompass factors like surgical procedures, diminished caloric intake, illness, alcohol consumption, and reduced exogenous insulin, it is advisable to steer clear of low-carbohydrate diets in patients prescribed SGLT-2 inhibitors [8].

Acarbose functions by inhibiting α-glucosidase, thereby reducing the overall absorption of dietary carbohydrates through the delay or prevention of sugars like maltose and sucrose digestion [16,17]. Given the carbohydrate-heavy diet typical in East Asian populations, acarbose sees widespread use in these regions and is often recommended as a primary alternative to metformin in the initial management of T2DM [18-20]. The impact on carbohydrate absorption becomes more evident with higher doses, with some individuals experiencing reduced appetite and lower food consumption due to severe gastrointestinal side effects at elevated doses, leading to significant weight loss in patients taking high doses of acarbose (100 mg three times a day) [21]. Although SGLT-2 inhibitors induce glucosuria levels of 50-100 g/day, concomitant high-dose acarbose administration mimics a low-carbohydrate diet and may heighten the risk of DK/DKA. Therefore, combining these two medications should be avoided, particularly in individuals with β-cell insufficiency. Recently, Yuan et al. documented two cases of Chinese patients who developed DKA when treated with a combination of SGLT-2 inhibitors and high-dose acarbose [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 DKA within 18 days to less than 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, potentially exacerbating the gastrointestinal reactions linked with high-dose acarbose and exacerbating carbohydrate intolerance. Conversely, our patients exhibited less pronounced effects on food intake. Noteworthy is that four out 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 critical clinical consideration involves determining the appropriate interval between commencing high-dose acarbose and discontinuing SGLT-2 inhibitors. Canagliflozin, dapagliflozin, and empagliflozin share comparable half-lives of approximately 13 hours [23], suggesting potential elimination within approximately three days. However, the half-life extension and slower elimination process are observed in patients with CKD [24]. Consequently, while the precise safety timeframe remains uncertain, the immediate initiation of high-dose acarbose after ceasing SGLT-2 inhibitors is not recommended, particularly for individuals with renal impairment. Notably, all the cited patients were administered dapagliflozin, likely due to its earlier introduction and wider usage in the Chinese market. It is imperative to avoid high-dose acarbose in conjunction with any SGLT-2 inhibitor, not limited to dapagliflozin.

High-dose acarbose usage among Asian patients on SGLT-2 inhibitors may escalate the risk of DK/DKA. Healthcare professionals and patients should be forewarned to avoid this combination, prioritizing patient safety and well-being.

Declarations

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Authors' contributions: WQ, FY and LL collected patient data, publications, and wrote the first draft of the article. RD and YS participated in the treatment of the patients, obtained consent and provided consultation. BS and HG provided consultation, critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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

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