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Case Presentation

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Benefit or Risk of Dapagliflozin in Type 1 Diabetes Patient, the Key is Appropriate Dosage: A Case Report

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Abstract

Purpose: Dapaglifozin is an oral sodium glucose cotransporter 2 (SGLT2) inhibitors, which provides multiple benefits including glucose-lowering, weight loss, and decreasing the risk of major adverse cardiovascular and renal events. However, a potential side effect had been reported with dapaglifozin in patients with type 2 diabetes (T2D) and particularly when off-label use in type 1 diabetes (T1D) patients is diabetic ketoacidosis (DKA), even dapaglifozin at a dosage of 5 mg/d have been approved in T1D patients. Several randomized controlled clinical trials have evaluated the efficacy and safety of dapaglifozin as an insulin adjuvant in patients with T1D, with divergent conclusions regarding the occurrence of DKA.

Methods: Here we reported a T1D patient presented severe DKA after the first use of dapaglifozin (10 mg/d, FORXIGA, AstraZeneca, Indiana), and DKA occurred again after 3.3 mg/d administration. However, using a small dose of dapaglifozin (1–2 mg/d) achieved a better glycemic control and gradually decreased body weight and daily insulin dosage, without hypoglycemic events and DKA happened. Furthermore, the results of 16S rRNA sequencing demonstrated that potein deficiency befor DKA, and mainly energy supply changed from glucose to fat during the DKA.

Conclusion: The appropriate dose of dapaglifozin is critical for T1D patient therapy in the balance of benefits and risks.

Keywords: Dapagliflozin; Type 1 diabetes; Ketoacidosis; Dosage

Introduction

Type 1 Diabetes (T1D) occurs mainly in adolescents, insulin replacement therapy is the mainstay of therapy for T1D patients [1]. Despite the great progress has been made over the years in insulin delivery and glucose continuous monitoring systems, glycaemic control in T1D patients is often suboptimal, with less than a third of this population achieved optimal glycaemic control [2]. Sodium Glucose Cotransporter 2 (SGLT2) inhibitors are a new type of hypoglycemic drugs that inhibit renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion [3]. Additional benefits include a weight loss and cardiovascular and kidney diseases protection. Dapaglifozin, as SGLT2 inhibitors, have been approved by the US Food and Drug Administration as a new class of glucose-lowering agents for the treatment of Type 2 Diabetes (T2D), either as monotherapy or as add-on treatment [4]. Dapaglifozin have also shown to improve glycemic control and reduce the total daily insulin dose in patients with Type 1 Diabetes (T1D). However, the favourable efficacy profile of dapaglifozin needs to be balanced against possible side-effects, Diabetic Ketoacidosis (DKA) in particular. DKA is a serious and potentially life-threatening acute complication of diabetes, which is characterized by hyperhemoketosis and dehydration [5]. T1D patients are more prone to DKA due to absolutely insulin deficiency. In addition, SGLT2 inhibitors induced DKA usually presents euglycemia (plasma glucose is < 11mmol/L), and therefore challenging to identify and therapy in clinical practice [6]. Since several randomized controlled clinical trials assessing the efficacy and safety of dapaglifozin as adjunct to insulin in individuals with T1D were published [7,8], it has been disputing whether the benefit or risk of this compound in this indication could be optimised. Here, we showed DKA occurred in a patient with T1D after 10mg or 3.3mg dapaglifozin usage, but the small dose of dapaglifozin (1–2 mg/d) could achieve better glycemic control and gradually decrease body weight and daily insulin dosage, without severe hypoglycemic events and DKA happened. We are looking forward to provide more evidence for the improved benefit/risk ratio when using the dapagliflozin in T1D patients.

Case Presentation

A 27-year-old female, underlying T1D for 17 years, was recently admitted to hospital for a better glycemic control. Vital signs at presentation were: temperature 36.1°C, pulse rate 100 beats/ min, respiratory rate was 28 breaths/min, blood pressure was 120/85 mmHg. Past medical history included T1D managed with insulin pump 15 years. In recent years, the dosage of insulin was 45 U/d, and metformin 0.5g (qid) being added to the therapeutic regimen 3 years ago due to weight gain. On admission the following was noted: the body weight was 75.0 kg; BMI was 28.2 kg/m^2; waist circumference was 105.5 cm. Clinical laboratory analysis found urine ketones was positive, fasting blood-glucose was 10.5 mmol/L, and glycated Haemoglobin (HbA1c) was 7.7%. C-peptide < 0.02 ng/mL, Insulin Antibodies (IAA) was 4.96 RU/mL, Islet Cell Antibodies (ICA) was 6.09 IU/mL, Glutamic Acid Decarboxylase antibodies (GAD) was 18.44 IU/mL. Abdominal ultrasound indicated fatty liver. Electrocardiograph (ECG) and auscultation of the lungs showed no significant findings, liver function, renal function, thyroid function did not have obvious abnormality. The patient had no smoking and alcohol intake history, but had history of fracture surgery due to traffic accident and had a family history of diabetes. In order to decrease body weight and achieve a better glycemic control, dagagliazin (FORXIGA, AstraZeneca, Indiana) 10 mg/d was been added as a new therapeutic schedule. After two days dapagliflozin using, she presented with asthenia, dyspnea, nausea, vomiting, and poor oral intake. Arterial blood gases showed

a picture of severe metabolic acidosis with an elevated anion gap (pH 7.285, CO2 31.80 mmHg, HCO3- 15.00 mmol/L, base excess -11.06 mmol/L), but presented a euglycemia (<11 mmol/L) and serum lactate levels were normal (0.80 mmol/L). She was treated with the balanced saline solution and 5% glucose liquid added with insulin infusion (Total 3000 mL/d) through intravenous rehydration for successive five days. Serial blood gas analyses showed gradual resolution of her ketoacidosis with normalized anion gap. She was re-treated with small dosage dapagliflozin (3.3 mg/d) when condition stabilized, after two days, she re-presented with asthenia, dyspnea, and nausea. Arterial blood gases showed the pH was 7.269. Dapagliflozin was permanently discontinued. Clinical features of DKA induced by different dose of dapagliflozin showed in **Table 1.**

Table 1: Comparison of different dosage of dapagliflozin induced DKA.

The dosage	10 mg	3.3 mg	1–2 mg
DKA occurring?	Yes	Yes	No
Days of DKA occurring after drug use	2	2	
Insulin dosage (U/d)	36.2	30.2	22.5
Fasting Blood glucose (mmol/L)	6.0	6.3	
BMI (kg/m^2)	26.84	26.65	22.7
Arterial blood PH	7.285	7.269	
Duration of DKA (Day)	5	4	

The patient was discharged after 4 weeks of hospitalization, the therapeutic schedule was insulin 29.2 U/d and metformin 0.5 g (qid). After two weeks, the patient began self-administration with lower dose of dapagliflozin (1–2 mg/d) to acquire a satisfactory glycemic control, and gradually decreased body weight and insulin dosage. In this period, the dietary structure of her was not adjusted subjectively, and the amount of exercise was not changed.

Changes of body weight and insulin dosage

The patient's body weight at hospitalization was 75.0 kg and BMI was 28.23 kg/m^2, which was defined as overweight. As show in **Figure 1a,** the severe DKA occurred on day 7th after 2 days of 10 mg/d dapagliflozin treated, a rapid body weight loss can be seen. The second DKA also caused a rapid weight loss. At the 45th day, body weight had a gradually decrease after the 1–2 mg/d dapagliflozin was applied. Similarly, as shown in **Figure 1b,** the dosage of insulin had a significant decrease after adding dapagliflozin to the strategy. After discharge, the patient increased her daily insulin because of poor glycemic control (day 28–45th). After treated with 1–2 mg/d dapagliflozin, the insulin dosage had a gradually decreasing. By day 180th, the patient how ever and weighed 60.2 kg and daily insulin dosage was 22.5 U.

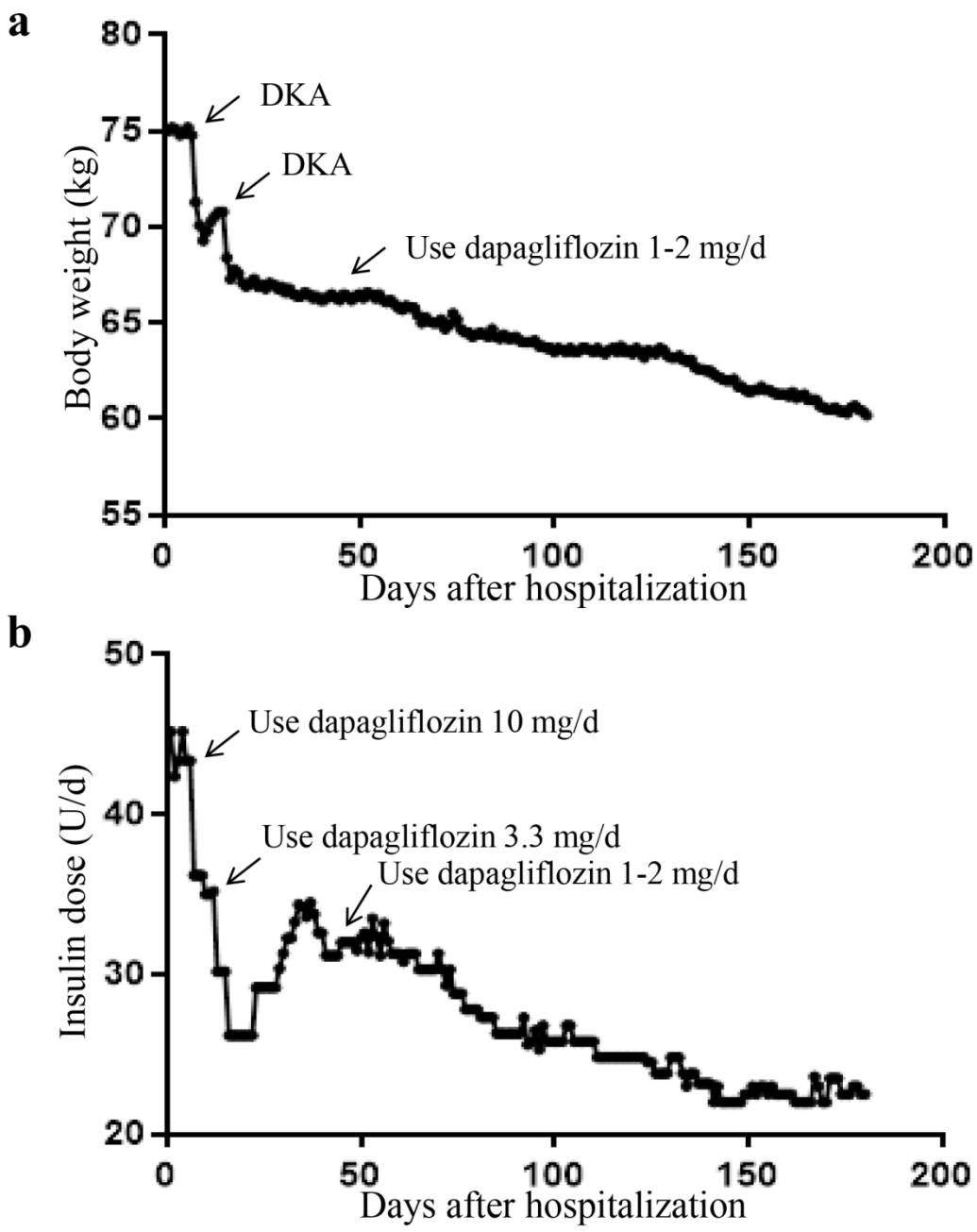

Figure 1: Changes of body weight and daily insulin dosage. a. Change of body weight within 6 months. b. Change of daily insulin dosage within 6 months.

Safety and efficacy

As show in **Table 2,** the BMI, blood glucose, urine ketones, waist circumference and HbA1c had a significant decrease, which indicated a satisfactory glycemic control after 1–2 mg/d dapagliflozin administration. In addition, there was no severe hypoglycemia or DKA occurred during 1–2 mg/d dapagliflozin usage, only with once or twice of urinary ket one overloading twice of urinary ketone overloaded found by urine ketone self-monitoring. Particularly, we noticed that 1–2 mg/d dapagliflozin added accepted an excretion increasing in urinary glucose, indicated the effectiveness of low dose dapagliflozin for her.

Table 2: Safety and efficacy of dapagliflozin on glycemic control.

Parameter	0 month	6 month
BMI (kg/m^2)	28.2	22.7
Waistline (cm)	105.5	88.0
Fasting blood glucose (mmol/L)	7.6	4.9
Postprandial blood glucose (mmol/L)	14.2	9.4
Urine glucose	–	+ + +
Urine ketones	+	+
HbA1c (%)	7.7	6.3
C-peptide (ng/mL)	<0.02	<0.02

Furthermore, Continuous Glucose Monitoring (CGM, Abbott Laboratories) was used to investigate the low dose dapagliflozin for stability of glycemic control. As show in average daily blood glucose graph **(Figure 2),** the average blood glucose was 9.4 mmol/L and estimated HbA1c was 7.5% during hospitalization, while 1–2 mg dapagliflozin added achieved a stabilized and satisfying glycemic control, the average blood glucose was 7.2 mmol/L and estimated HbA1c was 6.2%.

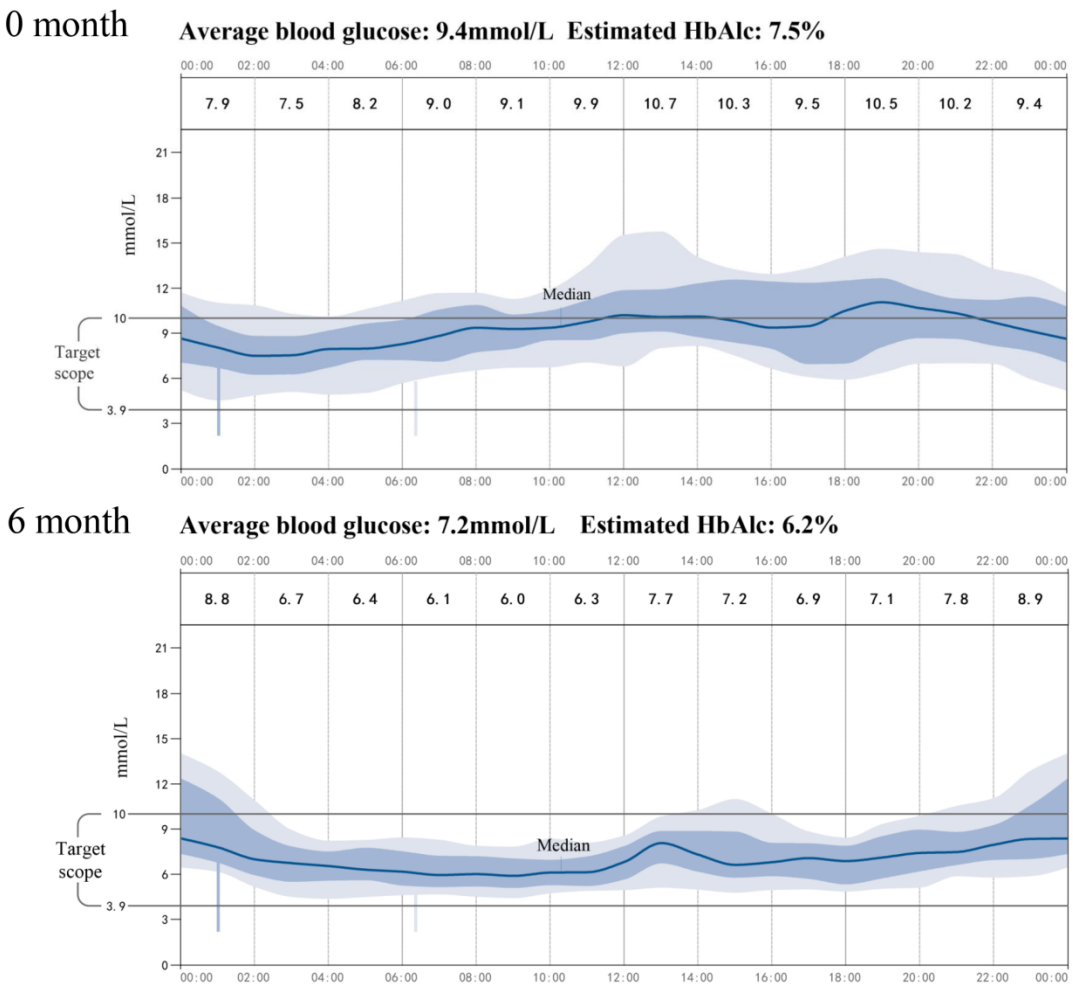

Figure 2: Average daily blood glucose graph. The CGM continued for 14 days, the average daily blood glucose changes graph at day 0 and after 6 months was showed.

16S rDNA sequencing

16S rRNA sequencing was performed to evaluate nutrition metabolism. 3 days before hospitalization and during the first DKA using stool specimens by Shanghai Biozeron Company. For the reason of three major nutrients metabolism is critical in diabetes and ketoacidosis pathology, we mainly analyzed the changes of protein, fat and carbohydrate proportion. The sequencing data were performed function analysis to predict the microbiome related nutrient metabolism using Picrust software. Results showed that the protein ratio was 6.41% before DKA, which was lower than normal range, and the ratio of fat and carbohydrate was not significantly abnormal. When DKA occurred, the balance between carbohydrate and fat shifted to fat metabolism **(Figure 3).**

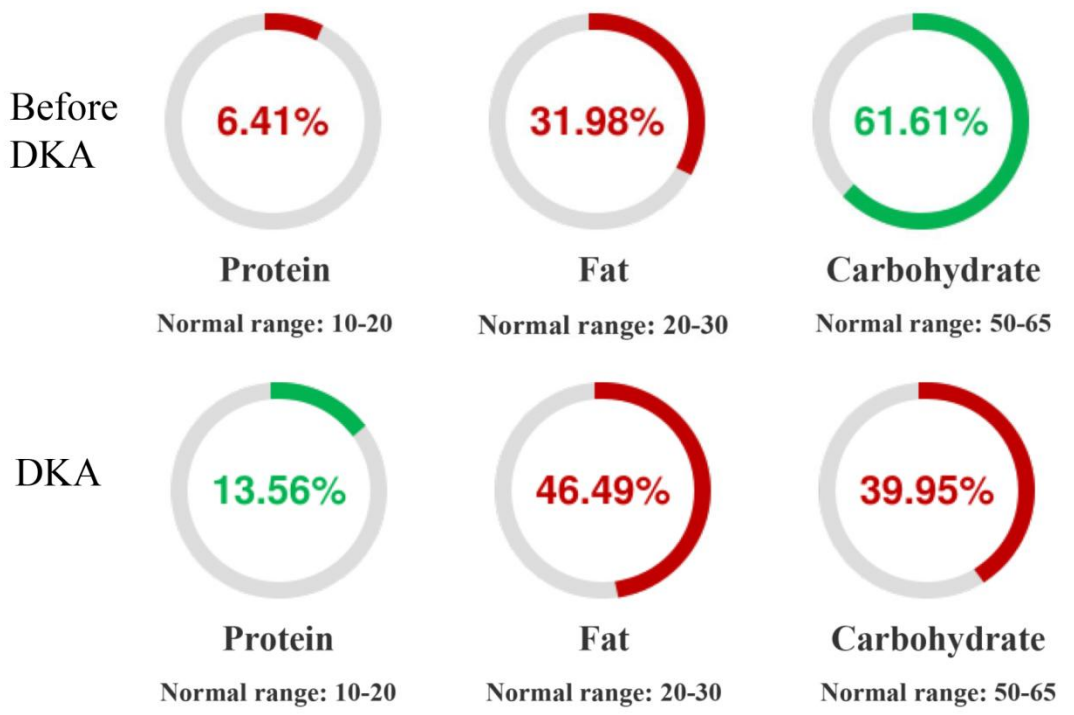

Figure 3: The results of 16S rRNA sequencing. 16S rRNA sequencing of stool specimen was used to analyze metabolism. The predicted proportions of protein, fat and carbohydrate were showed.

Discussion

DKA is one of the most serious and potentially life-threatening complications of diabetes, and it is typically characterized by hyperglycemia, ketosis, and acidosis. The incidence of DKA is between 4.6 to 8.0 cases per 1000 person/years among diabetic patients [9]. It occurs most frequently in patients with T1D who are absolutely insulin deficient but can also occur in patients with T2D. Dapagliflozin is an antidiabetic drug approved for the use of T2D, which by selective inhibiting SGLT2, either as a single treatment or in combination with insulin or other antidiabetics. However, due to its side effects of ketoacidosis, there are still many controversies about dapagliflozin in the treatment of T1D. Reports of SGLT2 inhibitor associated ketoacidosis have been showed in patients with both T1D and T2D. The absence of significant hyperglycemia in many of these patients may delay recognition of the emergent nature of the problem [10]. In a 24 weeks clinical trial about efficacy and safety of dapagliflozin in T1D, treated with daily 5 mg or 10mg dapagliflozin led to improvements in glycemic control and weight loss in patients with T1D, while increasing the risk of DKA (2.6% or 2.2%, 5 mg or 10 mg respectively) [7]. Similarly, a 52 weeks clinical trial demonstrated the same conclusions [11]. However, the results of a 2-week randomized controlled trial evaluating the safety of dapagliflozin in combination with insulin showed that no patient experienced ketoacidosis regardless of the dose (1 mg, 2.5 mg, 5 mg, 10 mg). Here we reported a T1D patient using 1–2 mg dose of dapaglifozin achieved a better glycemic control and decreased body weight and daily insulin dosage, without hypoglycemic events and DKA. In clinical studies, the safety of drug use should be the first concern. In studies, no matter how long the trial period, the dosage of dapagliflozin is relatively higher than our reported case, the patient had severe ketoacidosis even treated with 3.3 mg/d, but 1–2 mg dosage had a well tolerance, indicated that sensitivity and tolerance varies among individuals.

We have known that ketoacidosis is caused by the imbalance of glucose, fat and protein metabolism in patients no matter what types of diabetes **[12].** Under most conditions, glucose is essentially the sole energy source of the body especially in brain. SGLT2 inhibitors could induce a sustained urinary glucose loss of 40–80 g/day under conditions of normal blood glucose **[13].** Thus, when lose excess glucose caused deficiency of cellular glucose acquiring, the brain is forced to use either amino acids or ketone bodies for fuel. Ketone bodies are generated by fat mobilization in the mitochondria of the liver. Insulin lowers ketone levels by inhibiting lipolysis and hepatic ketogenesis as well as increasing the oxidation of ketones in the peripheral tissue. When insulin or carbohydrate deficiency, energy source is converted from glucose to fat, large amounts of fat mobilization produce excess ketone bodies leading to DKA. Thus, the DKA caused by dapagliflozin may be related to the large dosage leading excess glucose lost. The results of 16S rRNA sequencing detection suggested that the patient was severely deficient in glucose when DKA, and energy supply was converted from glucose to fat. Since the function of insulin is to promote protein synthesis. Due to the patient had central obesity and daily insulin dose was 45.2 U before admission, suggested there may be insulin resistance and insulin was relatively insufficient, these could increase the risk of DKA. For this reason, to promote a safer dapagliflozin using for patients with T1D, we considered that assessment of the protein, fat and carbohydrate metabolism of patients used by 16S rRNA sequencing may have extraordinarily helpful in clinical practice. On the other hand, at the time of DKA, the patient had a very low carbohydrate level, indicated a relatively high dose of dapagliflozin leading metabolic disturbances. However, more evidence needed to be collected to support this finding. In addition, there are some views that SGLT2 inhibitors reduce the renal tubular clearance of ketone bodies. An early study showed that the renal tubular capacity to reabsorb acetoacetate was enhanced by phlorizin, a nonselective SGLT2 inhibitor, and was conversely decreased during states of higher renal glucose reabsorption **[14].** This condition increases the blood ketone body concentration and the risk of ketoacidosis.

Furthermore, another important benefit observed was weight loss. Weight loss in the current analysis population may support a decrease in the insulin dose required to maintain optimal glycaemia **[15].** Individuals with T1D always struggle with undesirable weight gain, achieving weight loss and maintaining good glycaemic control is very difficult when receiving intensive insulin therapy, particularly in this group with overweight or obesity (BMI ≥27 kg/m^2) **[16].** Abdominal obesity is a risk factor for non-alcoholic fatty liver disease and insulin resistance **[17].** Interestingly, we noted the decrease in waistline from 105.5 cm to 88.0 cm and decrease in insulin dose, indicated improvement in abdominal obesity and insulin resistance for her. The majority of the steady-state weight loss with SGLT2 inhibitor treatment appears to be due to fat loss rather than fluid loss. The SGLT2 inhibitor enhanced lipolysis and shifted substrate usage from carbohydrates to lipids in patients with T2D **[18].** Dapagliflozin increases in lipolysis is consistent with a clinical observation that reduction in body weight and BMI in patients with T2D in response to 10 mg/day dosage **[19].** In addition, research had shown that in obese rats the reduction in body weight in response to dapagliflozin was associated with increased lipolysis and fatty acid oxidation and lower body fat **[20].** These findings are in accordance with the concept that weight loss associated with SGLT2 inhibition resulted from a reduction in fat tissue content through an increase in fatty acid mobilization. It can also be seen from our report that dapagliflozin can gradually reduce body weight and reach a more satisfactory BMI on the premise of safety, which may be related to dapagliflozin increased fatty acid oxidation and usage. In clinical practice, due to individual differences, clinicians must adjust the dose of dapagliflozin by closely monitoring blood glucose and urinary ketone bodies to reduce the risk of

DKA. In addition, the speed of DKA occurring can also be used as an indicator to determine what the appropriated dosage is. In our case, the patient developed severe DKA only after two days of dapagliflozin administration, indicated that a 10 mg or 3.3 mg dosage is relatively large, and a lower dose may gain a safer clinical practice.

Conclusion

we reported a T1D patient presented DKA as a complication of dapagliflozin (3.3 or 10 mg/d), while a 1–2 mg/d dapagliflozin accepted the reductions in HbA1c and body weight, with improved time in target blood glucose range and no increased risk of hypoglycaemia and DKA. All of above indicated when dapagliflozin was applied to practice of T1D therapy, the key is appropriate dosage.

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Author Contributions

Qun Yan and Bo Feng contributed to the study conception and design. Data collection and analysis were performed by Yan Tian, Weiting Hu, and Qun Yan. The first draft of the manuscript was written by Yan Tian, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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