Case Report

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Use of dapagliflozin in patients with advanced diabetic kidney disease

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Sodium-glucose cotransporter-2 (SGLT2) inhibitors are effective for overweight diabetic patients through the induction of glucosuria. However, SGLT2 inhibitors are not recommended for patients with advanced chronic kidney disease (CKD) because they may aggravate renal function and thus become less effective in controlling blood glucose in this patient population. We suggest that adequate hydration would be helpful to prevent the side effects of SGLT2 inhibitors in diabetic patients with advanced CKD. In this study, we review five cases of SGLT2 inhibitor therapy, specifically with dapagliflozin, for the treatment of diabetes mellitus in patients with advanced CKD. The patients experienced dramatic weight reduction, improved glucose control, and further benefits without aggravation of renal function.

Keywords: Albuminuria, Chronic kidney disease, Dapagliflozin, Hyperuricemia, Obesity

Introduction

Weight control is an important issue for patients with diabetic nephropathy, especially for those who are obese. In a secondary analysis of a multicenter randomized clinical trial, the effects of intensive lifestyle modification suggested that weight loss could delay the onset of chronic kidney disease (CKD) in obese diabetic patients [1]. Several small studies have also reported that weight reduction can improve proteinuria, glomerular filtration, and hypertension [2,3]. In addition, sodium-glucose cotransporter-2 (SGLT2) inhibitors are particularly helpful in obese diabetic patients. SGLT2 is present in the proximal tubules of nephrons and primarily functions to reabsorb glucose; accordingly, inhibition of SGLT2 causes urinary glucose excretion and natriuresis and results in serum glucose control, weight reduction, and diuresis [4].

The effectiveness of SGLT2 inhibitors in patients with stage 3 or higher CKD has not been demonstrated. Although SGLT2 inhibitors can induce a renoprotective effect in CKD patients with improvement of proteinuria, they have a reduced glucosuric effect and pose a renal risk through aggravation of the glomerular filtration rate (GFR) [5–7]. The GFR aggravation can be explained by glucosuria and natriuresis, leading to blood volume depletion through osmotic diuresis. Furthermore, proximal tubular natriuresis induces tubuloglomerular feedback, resulting in reduced intraglomerular pressure [6,7]. Based on this mechanism, we aimed to offset the impact of tubuloglomerular feedback by providing adequate hydration. Hydration might increase renal blood flow and maintain both GFR and the glucosuric effect. We suggest that SGLT2 inhibitors can be used safely in adequately hydrated CKD patients. In the following cases, the use of SLGT2 inhibitors was necessary because either the

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maximum dose of other hypoglycemic agents resulted in no improvement, the patients were too resistant to insulin, or management of volume overload failed because diuretics were contraindicated for fear that they would aggravate azotemia. We report five cases in which the SLGT2 inhibitor dapagliflozin induced significant weight reduction and edema control in patients with advanced CKD.

Case reports

Case 1

A 68-year-old male patient with type 2 diabetes, Churg-Strauss syndrome, and interstitial lung disease visited our emergency center. He complained of aggravated dyspnea and hyperglycemia. The patient reported a history of oral steroid use resulting in progressive obesity, which exacerbated his chronic interstitial lung disease and pulmonary congestion. Oxygen saturation was 88% on room air. Azotemia had developed and subsequently deteriorated to serum blood urea nitrogen (BUN) of 40 mg/dL and creatinine (Cr) of 2.54 mg/dL. The echocardiogram was identical to the previous one, with normal ejection fraction and moderate aortic valve stenosis observed. Because of the worsened renal function and pulmonary congestion it was difficult to adequately hydrate the patient or use high-dose diuretics. The azotemia worsened with even a slight increase in furosemide dose. Although insulin therapy was needed to control hyperglycemia, the patient strongly refused this treatment. As the patient was already taking high doses of glimepiride and vildagliptin we cautiously administered dapagliflozin at 10 mg per day without any other diuretics. At that time, fasting blood glucose and 2-hour post-prandial plasma glucose were 192 and 413 mg/dL, respectively. From the third day after initiation of treatment the edema improved and dyspnea was resolved. On the fourth day, the patient was hydrated with 1 L of half-normal saline to facilitate the glucosuric effect, and we expected to see weight reduction as well as volume control. Blood sugar gradually improved and vildapliptin was discontinued. Dapagliflozin was stopped after a total of 4 days of administration. The serum BUN and Cr levels improved to 11.3 and 1.99 mg/dL, respectively (Table 1). The serum uric acid level decreased from 8.2 to 6.6 mg/dL in 4 days. His body weight decreased to 63.5 kg (body mass index [BMI], 24.2 kg/m^2) compared with 67 kg at the start of treatment. Despite the remarkably short treatment duration of dapagliflozin, the patient experienced great improvement in edema and hyperglycemia. After 6 months, he still weighs 65 kg and maintains serum BUN/Cr levels of 22.9 mg/dL/1.96 mg/dL and serum uric acid of 7.1 mg/dL.

Case 2

An obese (BMI, 30 kg/m^2) 72-year-old man with type 2 diabetes was taking 30 international units (IU) of detemir, vildagliptin, metformin (500 mg, once a day), and glimepiride. Due to poor compliance, insulin was injected inconsistently and he experienced repeated episodic hyperglycemic and hypoglycemic events. At presentation he had CKD stage IV with GFR 28 mL/min/1.73 m^2 and was exhibiting a slight elevation of glycated hemoglobin (HbA1c) to 7.6%. He was admitted for diabetic control and appeared to be euvolemic. He displayed strong insulin resistance and complained of aggravated arthralgia with weight gain. We felt that attempting dapagliflozin for weight reduction and glycemic control was worthwhile. We started dosing with 10 mg of dapagliflozin, vildagliptin was withdrawn, and hydration was maintained with half-normal saline at 1 L per day to maxi-

Table 1. Changes in patient data during the treatment period

Case	Dapagliflozin treatment duration	Body weight (kg)		Spot urine protein/Cr ratio		Serum Cr (mg/dL)/GFR*		Serum uric acid (mg/dL)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	4 d	67.0	63.5	No data		2.5/25	1.99/35	8.2	6.6
2	10 wk	81.0	72.0	0.15	No change	2.3/28	1.88/35	7.2	6.2
3	2 wk	67.4	62.0	2.92	2.86	3.3/16	3.0/18	7.8	5.3
4	More than 1 yr	82.4	66.4	2.12	1.27	3.5/18	No change	7.2	5.4
5	3 mo	80.0	71.0	5.35	4.0	3.0/20	No change	6.1	5.7

*Estimated GFR by CKD-EPI creatinine equation (mL/min/1.73 m^2).

Cr, creatinine; GFR, glomerular filtration rate.

mize the glucosuric effect. After 2 days of dapagliflozin administration insulin was initially reduced to 20 IU, and then further reduced to 10 IU on the following day and stopped on day 4. The patient was hospitalized for a total period of 11 days, and 1 L of half-normal saline per day was administered for 8 days. Three days before discharge, half-normal saline administration was stopped and the patient was instructed to orally hydrate by drinking 2 L per day. Dapagliflozin was reduced to a half-dose per day 6 weeks after initiation and stopped after a total of 10 weeks. During the period of treatment his blood glucose levels were well controlled without episodes of hypoglycemia. During the treatment his body weight decreased from 81 to 72 kg (BMI, 27 kg/m^2) (Table 1). Proteinuria was unchanged with spot urine protein Cr ratio 0.15, and serum Cr gradually recovered to 1.88 from 2.27 mg/dL. In addition, his need for blood pressure medications was reduced. After 6 months he still weighs 72 kg, maintains serum BUN/Cr level of 20.1 mg/dL/2.06 mg/dL, and urinalysis reveals no proteinuria.

Case 3

An 85-year-old man was hospitalized for chest discomfort and poor glucose control. At that time, CKD was stage 4 (Cr, 3.31 mg/dL; GFR, 16 mL/min/1.73 m^2), and insulin was administered at 60/40 IU with a 70/30 premix pen from the endocrinology service together with linagliptin. Abdominal obesity was particularly severe and was accompanied by 1+ pitting edema. He complained of anginal symptoms and ischemic heart disease was suspected. He was recommended to undergo coronary angiography; however, there was a risk of progression to end-stage renal disease due to the contrast media. The patient refused the test and wanted only control of his blood sugar with subsequent discharge. High-dose insulin treatment increased his obesity, which meant that he required an even higher dose of insulin. We suggested that weight loss would attenuate CKD progression and decrease his insulin requirement. We administered dapagliflozin with half-normal saline at 1 L per day. During the treatment period, insulin was gradually reduced over 2 weeks to 16/14 IU in the morning and evening. After 2 weeks, serum Cr was changed from 3.31 to 3.0 mg/dL, accompanied by weight loss from 67.4 to 62 kg (Table 1). The spot urine protein/Cr ratio exhibited no significant change (from 2.92 to 2.86), and serum uric acid decreased from 7.8 mg/dL to 5.3 mg/dL. Pitting edema was improved without the need for any other diuretics. There was no elevation in liver function tests or additional chest pain during the period of dapagliflozin treatment; in fact, the chest pain was improved. After 6 months his body weight is maintained at 62 kg, his serum BUN/Cr level is 41.4 mg/dL/3.0 mg/dL, and insulin in the evening has been discontinued.

Case 4

A 69-year-old man with diabetic CKD stage 4 visited the emergency center for exacerbated edema and New York Heart Association class IV dyspnea. While in the outpatient clinic long term, the patient suffered from chronic severe pitting edema, which was improved slightly by the use of furosemide but the azotemia worsened. His laboratory results were serum BUN 55.2 mg/dL, serum Cr 3.52 mg/dL, HbA1c 6.4%, and urine protein Cr ratio 2.1. There were no events or medication changes during this period. Weight gain was 20 kg over 15 days. Both legs exhibited 3+ pitting edema. Chest X-ray showed pulmonary congestion. Diastolic dysfunction was reported on his echocardiography, but there were no cardiac changes compared to the previous record. Renal function and proteinuria were similar to recent laboratory work; however, serum glucose had increased. Intravenous furosemide was not helpful, and albumin-furosemide 40 mg combination helped only temporarily. Dialysis was considered for edema control. A 70/30 premix insulin dose was taken in the morning at 20 IU and in the evening at 10 IU. Dapagliflozin was attempted cautiously for edema and glycemic control; if this was unsuccessful dialysis would be unavoidable. With administration of dapagliflozin, urine volume increased from 1,100 to over 2,000 mL/day. As the urine volume increased, the edema improved and body weight decreased. In addition, serum glucose reached the normal range. To maximize the glucosuric effect, we reduced the insulin dose gradually. After the edema improved, we expected that dapagliflozin would reduce his weight. We suggested that oral hydration, as well as intravenous hydration, would be helpful for a prolonged glycosuric effect and renal protection and we forced him to drink over 1 L of free water per day. Dapagliflozin was administrated for 33 days during his hospital stay and

has been continued since. Body weight was 82.4 kg (BMI, 29.5 kg/m^2) at the time of treatment initiation and later decreased to 66.45 kg (BMI, 23.8 kg/m^2) (Table 1). In the course of treatment, the requirement for 70/30 premix insulin decreased from 20 IU in the morning and 10 IU in the evening to only 15 IU in the morning. Urine protein Cr ratio improved from 2.1 (before admission) to 1.2 (after discharge), serum uric acid was decreased from 7.2 to 5.4 mg/dL, and serum Cr showed no change, staying at approximately 3.5 mg/dL. Six months later his body weight is maintained at 67 to 69 kg and serum Cr level is still unchanged at 3.5 mg/dL; however, there is some fluctuation depending on the amount of drinking water consumed. Currently, his urine protein Cr ratio is 3.9 and hemoglobin is 11.3 g/dL without erythropoietin. Prior to admission, he had to take methoxy polyethylene glycol-epoetin beta 120 μg once a month to manage anemia. More than 1 year later, he maintains use of both dapagliflozin and insulin. His health has improved with no edema or any other health problem. Bone mineral densitometry revealed no osteoporosis.

Case 5

An overweight 76-year-old man with diabetic CKD stage 4 (Cr, 3.0 mg/dL) visited the outpatient clinic. He had chronic, 2+ pitting edema. Whenever furosemide was added to his medications the azotemia worsened. Dapagliflozin was prescribed for 2 weeks in the outpatient clinic but failed due to insufficient hydration, which resulted in thirst, hyperglycemia, and hyperkalemia due to volume depletion. Because of severe weight gain caused by obesity and edema we decided to administer dapagliflozin again with fluid supplementation. We provided education to encourage consumption of 2 L of water every day and administered dapagliflozin 10 mg with follow-up in the outpatient clinic over 5 weeks. Diuretics were not prescribed. Body weight was 80 kg (BMI, 28.6 kg/m^2) when he initially began treatment and decreased to 71 kg (BMI, 25 kg/m^2) at the end of treatment. Several changes occurred during the treatment: long-acting insulin administration was stopped, short-acting insulin dose was decreased, urine protein Cr ratio decreased from 5.35 to 4.0, and serum uric acid decreased from 6.1 to 5.7 mg/dL. Serum Cr showed no change and was maintained at 3.0 mg/dL.

Discussion

Although these five patients had type 2 diabetes with moderate to severe renal impairment, they all showed a dramatic improvement in renal function, weight reduction, and glucose control.

According to Dr. Bernstein's Diabetes Solution endocrinology textbook [8], body fluid and serum glucose levels are closely related. High glucose levels can promote dehydration through glucosuria, and dehydration leads to contraction of peripheral blood vessels resulting in insulin resistance and markedly low glucose utilization. As a result of this vicious cycle, hyperglycemia and volume depletion are inseparable. If natriuresis and glucosuria are maintained by use of a SGLT2 inhibitor, the patient will develop insulin resistance from volume depletion, in addition to worsened GFR.

In previous studies, SGLT2 inhibitors were shown to be less effective at glycemic control and unsafe to continue when the GFR indicates advanced CKD compared with normal or mildly impaired renal function [5–7]. In almost all of the previous studies evaluating SGLT2 inhibitors, the researchers did not address the volume status of individual patients and did not consider the role of adequate hydration. Without volume status assessment and supplementation it might be impossible to achieve positive clinical results from SGLT2 inhibitor therapy in CKD patients. These experiences highlight the importance of knowing how to use a medication properly.

The renal proximal tubule contains two glucose reabsorption transporters: sodium-glucose co-transporter-1 (SGLT1) and SGLT2. More than 90% of the filtered glucose is reabsorbed by SGLT2 in a 1:1 ratio with sodium [4]. When SGLT2 is inhibited, SGLT1 is upregulated and functions to decrease glucosuria in a euglycemic state [9]. Correspondingly, serum glucose levels greater than the normal range would be required to maximize the glucosuric effect over the treatment period. We proposed that hydration matched to individual needs and decreased doses of oral hypoglycemic agents or insulin would help maintain excretion of large amounts of urine glucose. Although the use of isotonic or hypertonic fluids for hydration would be more effective for increasing renal blood flow, older patients do not tolerate this salt loading and must consume sufficient salt from their diet. Accordingly, we administered half-normal saline for intravenous

hydration.

There is another benefit of SGLT2 inhibitors. Many patients complain of weight gain after the initiation of insulin. According to Henry et al [10], who investigated this issue in 1993 through statistics, insulin causes a dose-related weight gain. SGLT2 inhibitors can overcome the problem of weight gain by increasing excretion of glucose and reducing the required insulin dose. As a result, the patients might experience further weight loss compared with the average reduction of 2 kg with SGLT2 inhibitors alone [11]. A dramatic weight reduction can improve a patient's quality of life, in addition to achieving glucose control. Also, a recent study reported that even a short-term intensive weight reduction intervention resulted in improvements of GFR, glucose control, and physical activity [2].

Our cases were all negative or 1+ for urine glucose before using dapagliflozin. After administering dapagliflozin urine glucose increased to 3+, and with adequate hydration the daily urine output was greater than 2 L. In our experience, urine glucose positivity can be a useful predictor of the effect of dapagliflozin therapy. Certain patients who initially had 3+ glucosuria experienced difficulty with hyperglycemic episodes and thirst after using dapaliglifozin. We suggest that chronic glucosuria can induce non-symptomatic volume depletion and insulin resistance, and a SGLT2 inhibitor would not be tolerated in this situation. Glucose positivity indicated by urine analysis can be easily overlooked, but might be helpful in predicting the efficacy and effect of SGLT2 inhibitors.

Improvement of proteinuria was observed in only cases 4 and 5 among our described patients, and these patients were given dapagliflozin over a relatively long treatment period. If hydration decreases tubuloglumerular feedback, improvement of proteinuria is influenced by weight reduction rather than a reduction of intraglomerular pressure. These two patients also experienced a decrease in serum uric acid with the expanded uricosuric effect of dapagliflozin. However, the patients did not undergo 24-hour urine test or measurement of urinary uric acid level.

Lastly, there are concerns regarding genitourinary tract infection, but our patients did not have complications from infection. However, in case 3 the patient had voiding difficulty due to benign prostate hypertrophy and a Foley catheter was inserted only during hospitalization. We made every effort to avoid urinary tract obstruction in order to make the patients comfortable with the increased urine output.

All of the patients were able to either reduce or stop other oral hypoglycemic agents or insulin. Overall, our cases showed improved physical activity and arthralgia and back pain improved after the dramatic weight loss. We suggest that these changes are class effects of SGLT2 inhibitors, rather than specific to dapagliflozin.

SGLT2 inhibitors can be multipotent drugs that offer increased benefit when they are managed appropriately. For nephrologists who are skilled and experienced in volume control, these agents can safely provide various beneficial stable effects in patients with CKD. However, these benefits may not be applicable to all patients, especially in the context of CKD. Further research of volume states with close monitoring of CKD patients is required.

Conflicts of interest

All authors have no conflicts of interest to declare.

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