Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9121-21
Intern Med 61: 3699-3702, 2022
http://internmed.jp

【 CASE REPORT 】

Usefulness of Dapagliflozin for Nephrotic Syndrome Secondary to Diabetic Kidney Disease

Ryoko Murashima[1], Eiryu Sai[2], Yumi Tagawa[3], Hiroyuki Yanagawa[4], Sayaki Ishiwata[2], Yuko Kawaguchi[2], Tadashi Miyazaki[2,5] and Katsumi Miyauchi[2,5]

Abstract:
An 81-year-old woman with a medical history of type 2 diabetes mellitus and diabetic nephropathy was admitted with a diagnosis of multiple cerebellar infarctions. Proteinuria and leg edema were observed on the day after admission and diagnosed as nephrotic syndrome. Furosemide and spironolactone were started but showed no diuretic effect, and the renal function deteriorated. These agents were then replaced with dapagliflozin, which resulted in a positive diuretic effect and subsequent improvement of hypoalbuminemia and renal dysfunction. This case report demonstrates the utility of dapagliflozin for nephrotic syndrome to achieve a positive diuretic effect and improve hypoalbuminemia without deteriorating the renal function.

Key words: diabetic nephropathy, nephrotic syndrome, sodium-glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin

(Intern Med 61: 3699-3702, 2022)
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Introduction

Nephrotic syndrome is a disease in which protein is excessively filtered into the urine. This is caused by damage to the clusters of small blood vessels in the kidneys that filter waste and excess water from the blood. The consequences are generalized systemic edema, proteinuria, hypoalbuminemia, and hyperlipidemia (1). Nephrotic syndrome can occur in a variety of diseases. Nephrotic syndrome induced by diseases that specifically target the kidneys are defined as primary nephrotic syndrome, whereas those induced by diseases that involve different parts of the body, such as diabetes, is considered secondary nephrotic syndrome. The treatment for secondary nephrotic syndrome consists of fluid management with diuretics and treatment of the primary disease.

We herein report a patient with nephrotic syndrome that developed into diabetic nephropathy. The use of dapagliflozin allowed for fluid management without deterioration of the renal function.

Case Report

An 81-year-old woman with a medical history of type 2 diabetes mellitus diagnosed 25 years ago and diabetic nephropathy was referred to our hospital. She had a low-grade fever for a week, as well as dysarthria and nausea. When examined in the emergency department, her pulse rate was 107 beats/min, and blood pressure was 158/90 mmHg. Her neck was supple, a cardiovascular examination was normal, her lungs were clear on auscultation, an abdominal examination was unremarkable, and her legs were not edematous. Cohesive and coherent connected speech was detected, and a positive Babinski reflex was recorded in the neurological findings.

A laboratory analysis was notable for a white blood cell count of 16,700/mL with an increased neutrophil count (91.5% white blood cells) and elevated C-reactive protein (CRP) level (29.0 mg/dL). Her glucose profile showed a se-

[1]Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Japan, [2]Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Japan, [3]Department of Medicine, Metabolism, and Endocrinology, Juntendo University Graduate School of Medicine, Japan, [4]Department of Nephrology, Juntendo Tokyo Koto Geriatric Medical Center, Japan and [5]Department of Cardiovascular Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Japan
Received: November 30, 2021; Accepted: March 10, 2022; Advance Publication by J-STAGE: April 23, 2022
Correspondence to Eiryu Sai, eiryu@juntendo.ac.jp

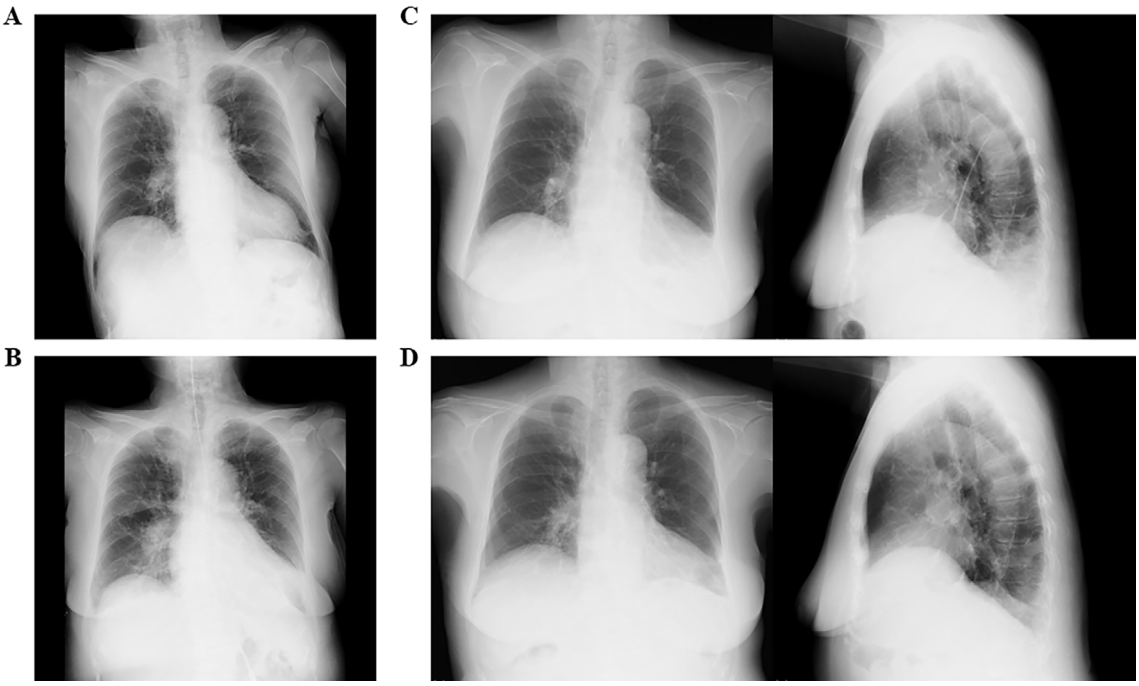

Figure 1. **(A) Chest X-ray on admission. (B) Chest X-ray on development of nephrotic syndrome. (C) Chest X-ray on day 30 after admission at the time of dapaglifrozin initiation. (D) Chest X-ray on day 50 of admission.**

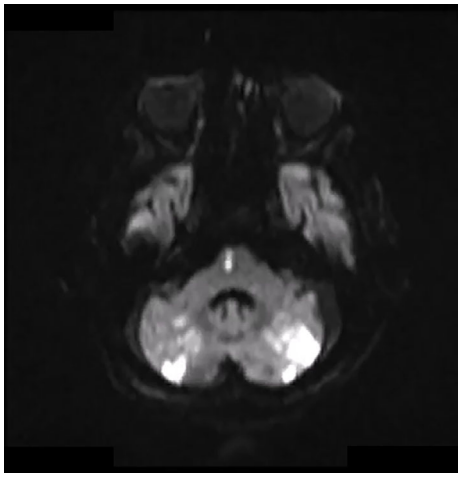

Figure 2. **Diffusion-weighted imaging showing multiple cerebellar infarctions.**

rum glucose level of 380 mg/dL and hemoglobin (Hb) A1c of 9.9% treated with metformin at a dose of 750 mg/day and acarbose at a dose of 300 mg/day. Other laboratory evaluations revealed the following results: Hb, 10.9 g/dL; total protein, 6.1 g/dL; serum albumin, 2.0 g/dL; blood urea nitrogen, 12 mg/dL; creatinine, 0.54 mg/dL; sodium, 136 mmol/L; and potassium, 2.0 mmol/L. The patient's urine contained 70 mg/dL of protein and 300 mg/dL of sugar. Chest X-ray demonstrated no pulmonary consolidation and no obvious infectious pneumonia (Fig. 1A). Cerebral magnetic resonance imaging showed multiple cerebellar infarction (Fig. 2).

Although infective endocarditis had been originally suspected, it was dismissed due to negative blood culture and ultrasound cardiograph findings. Empiric antibiotics, including ampicillin/sulbactam 9 g/day and ceftriaxone 2 g/day, were started on day 1 for a bacterial infection with an unidentified focus. Antibiotics were terminated on day 14 after confirming that CRP had decreased to 0.88 mg/dL. In addition, infusion of mainly glycerol and maintenance transfusion was started for cerebral infarction. The infusion volume was managed at about 1,500 mL/day. During this period, the daily diameter of the inferior vena cava remained between 9 and 13 mm, with appropriate respiratory variability. On day 2, leg edema was observed, and urine protein was positive in a urine qualitative test performed on the same day. The leg edema gradually worsened. On day 4, bilateral pleural effusion appeared on an X-ray image (Fig. 1B), so we started furosemide injections at a dose of 20 mg/day. On day 9, the serum albumin (1.5 mg/dL) and urine protein assay levels (5 g/day) led to the diagnosis of nephrotic syndrome. She was in the acute stage of cerebral infarction and was managed without antihypertensive drugs because her blood pressure was 140-160/60-80 mmHg. However, due to complications associated with nephrotic syndrome and a worsening renal function, azilsartan was started orally at 40 mg/day on day 10, and amlodipine was started at 5 mg/day on day 11.

Plasma serology was negative for antinuclear antibodies, anti-cardiolipin, anti-β2 glycoprotein 1 antibody (<1.2 U/mL), lupus anticoagulant (1.12), protease 3-antineutrophil cytoplasmic antibodies (ANCA) (<1.0 U/mL), and myeloperoxidase-ANCA (<1.0 U/mL). Serum complement levels were within normal limits. The selectivity index was

Table. **Changes of 24-hour Urinary Protein Level, Sodium Excretion, and Volume between Day 30 and Day 35.**

	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Urinary protein, (g/day)	2.3	1.8	3.0	3.3	2.4	2.6
Urinary sodium, (g/day)	1.4	2.0	1.8	1.4	1.3	1.0
Urine volume, (mL/day)	720	1,100	950	850	700	670

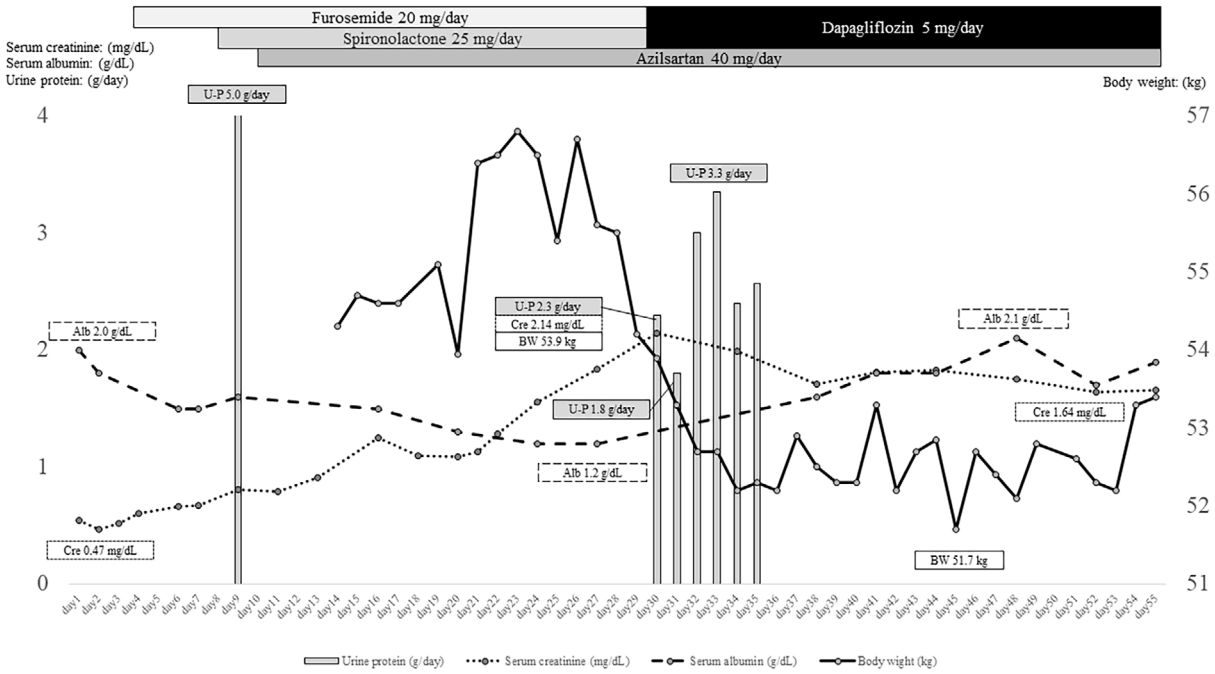

Figure 3. **Changes in values of serum creatinine, serum albumin, body weight, urine protein, and drug dose during the 55-day treatment period.**

less than 0.2, so nephrotic syndrome that had developed due to a bacterial infection in diabetic nephropathy was diagnosed.

Oral furosemide and spironolactone were started at doses of 20 and 25 mg, respectively, for pleural effusion and edema. However, the diuretic effect was poor, and the renal function worsened. On day 30, pleural effusion and edema remained (Fig. 1C), and the serum creatinine levels continued to gradually elevate. Dapagliflozin at 5 mg was started to replace them. On day 31, the 24-h urinary protein levels decreased, and the urinary sodium excretion increased (Table). The patient's body weight decreased with the reduction in systemic edema. Although both the 24-h urinary protein levels and urinary sodium excretion returned to the same values as before dapagliflozin administration on day 35, the pleural effusion and edema disappeared on day 50 (Fig. 1D). However, there was no notable change in the blood pressure after dapagliflozin treatment, which remained at 110-130/60-70 mmHg. Although blood glucose levels were controlled with 40 units of rapid-acting insulin and 12 units of long-acting insulin before dapagliflozin administration, the fasting blood glucose levels remained around 110-130 mg/dL with only 2 units of long-acting insulin after dapagliflozin administration.

In addition, the serum creatinine and albumin levels improved (from 2.14 mg/dL to 1.64 mg/dL, and from 1.2 mg/dL to 2.1 mg/dL, respectively) without the disappearance of proteinuria (Fig. 3). The patient was transferred to another hospital for stroke rehabilitation on day 55.

Discussion

The cause of leg edema in this patient was thought to have been cardiac failure, overflow of fluid due to excessive infusion, or hyponutrition. The patient's cardiac function was preserved, and the fluid infusion was adjusted while monitoring the inferior vena cava diameter, which negated the possibility of overflow. The patient's serum albumin was 2.0 mg/dL at the time of admission, and hyponutrition could not be ruled out. However, when the urinary protein level exceeded 5.0 g on day 9, we concluded that nephrotic syndrome was the main cause of edema.

Nephrotic syndromes, especially secondary nephrotic syndromes, are frequently treated in the field of general medicine. In particular, diabetic nephropathy is the most common cause of secondary nephrotic syndrome (2). The mainstay of

treatment involves proper diet, glycemic control, and antihypertensive therapy. Diuretics are often used to control systemic edema, pleural effusion, and abdominal effusion within nephrotic syndrome. In many cases, several types of diuretics are used in combination to reduce edema. Such edema is sometimes difficult to treat due to diuretic resistance, which can lead to exacerbated prerenal failure (3). As concomitant use of diuretics caused worsening renal failure, the switch from concomitant use of diuretics to a single sodium glucose co-transporter 2 (SGLT2) inhibitor was effective.

Usually, when nephrotic syndrome develops, it is important to identify the cause of the disease based on various tests and a renal biopsy (4). A renal biopsy was also considered in the current case but was not performed due to the patient's paralysis, which made it difficult for her to maintain her posture, and the administration of dual anti-platelet therapy. We therefore used the selectivity index as a surrogate and thus found that a biopsy could actually be avoided in patients with a low selectivity index and diabetic nephropathy.

There are few effective treatments for nephrotic syndrome with underlying diabetic nephropathy apart from diuretic use. However, some recent studies have reported that SGLT2 inhibitors were useful in slowing the progression of diabetic nephropathy and protecting the renal function in patients with type 2 diabetes (5-7). The efficacy of SGLT2 inhibitors for nephrotic syndrome is not yet clear. However, Tanaka et al. reported the therapeutic potential of SGLT2 inhibitors for nephrotic syndrome secondary to diabetic nephropathy by adding a SGLT2 inhibitor to furosemide (8). Since loop diuretics are metabolized after binding to albumin, they may not be effective in the presence of hypoalbuminemia. As our patient's renal function was deteriorating, we switched her to an SGLT2 inhibitor to protect her renal function. SGLT2 inhibitors can be expected to increase the urine volume due to osmotic diuresis associated with urinary glucose excretion, even in the presence of hypoalbuminemia (9). In the present case, a temporary decrease in urinary protein and an increase in urinary sodium were observed. These results suggest that osmotic diuresis led to an increase in urine volume and an improvement in the renal function by releasing renal congestion.

In addition to these effects of dapagliflozin, improvement of the nutritional status with the recovery of the general condition in systemic nursing management improved hypoalbuminemia, enabled good fluid management, and reduced the patient's weight and pleural effusion. Although tolvaptan may be an option, we believe that management with SGLT2 monotherapy is sufficient to avoid polypharmacy in the future.

It is important to obtain a good diuretic effect when treating nephrotic syndrome due to diabetic nephropathy. We herein report a case in which an SGLT2 inhibitor was used to achieve a good diuretic effect and improvement in hypoalbuminemia without deteriorating the renal function.

The authors state that they have no Conflict of Interest (COI).

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