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Case Report

Therapeutic potential of tofogliflozin on nephrotic syndrome secondary to diabetic nephropathy

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ABSTRACT

Diabetic nephropathy (DN) is a critical complication in patients with type 2 diabetes and regarded as a progressive disorder with a poor prognosis. The degree of albuminuria is associated closely with worse renal and cardiovascular outcomes. It is therefore important to achieve remission of proteinuria to avoid progression of DN and improve outcomes. Although a recent clinical trial demonstrated that a sodium glucose cotransporter 2 (SGLT2) inhibitor could improve cardiovascular and renal outcomes in cardiovascular high risk patients with type 2 diabetes, little is known whether SGLT2 inhibitors have favorably renal effects in patients with nephrotic syndrome associated with DN. Herein, we report a 54-year-old patient with refractory nephrotic syndrome accompanied by diabetic nephropathy. Tofogliflozin, a SGLT2 inhibitor, successfully increased urine volume, and reduced body weight, HbA1c, and urinary protein excretion (10.8 to 2.6 g/day) during 24 weeks. His severe edema also was diminished after administration of tofogliflozin. This case indicates that an SGLT2 inhibitor may be a useful choice in the treatment of patients with diabetic nephropathy and the nephrotic syndrome.

<**Learning objective:** Little is known whether SGLT2 inhibitor can attenuate nephrotic-range of proteinuria in patients with diabetic nephropathy. The present case is the first to demonstrate that tofogliflozin markedly reduced urinary protein excretion, body weight, and relevant markers in patient with nephrotic syndrome secondary to diabetic nephropathy. Thus, it is suggested that SGLT2 inhibitor has a therapeutic potential to attenuate nephrotic syndrome-related symptoms and markers as well as glycemic control.>

Introduction

Diabetic nephropathy (DN) affects one-third of diabetes patients and is associated with considerably worse cardiovascular morbidity and mortality. Although the exact cause of DN remains unclear, several mechanisms have been postulated including hyperglycemic-induced renal hyperfiltration and renal injury, increased oxidative stress, increased production of cytokines, and different inflammatory and apoptotic signals [1]. Proteinuric diabetic kidney disease frequently progresses to end-stage renal disease. Accumulated evidence suggests that aggressive treatment against hypertension and resultant remission of nephrotic-range albuminuria in patients with type 2 diabetes and DN markedly improves renal outcome and survival [2].

Kidney diseases other than diabetic nephropathy can also occur in patients with type 2 diabetes and are known as non-diabetic renal diseases, either isolated or superimposed on DN [3]. While DN is difficult to reverse, certain non-diabetic renal diseases are often treatable or even remittable. Accordingly, the treatment and prognosis of DN and non-diabetic renal disease are quite different and a renal biopsy is therefore essential in patients with DM to obtain a precise diagnosis of nephropathy.

Sodium glucose cotransporter 2 (SGLT2) inhibitors are novel glucose-lowering agents that modulate selective inhibition of SGLT2 in the proximal renal tubule, leading to an increase in glycosuria and natriuresis. A number of studies have suggested that SGLT2 inhibitors may potentially have nephron and renal protective effects in patients with type 2 diabetes [4]. However, the treatment effect of SGLT2 inhibitors on the nephrotic syndrome secondary to DN has yet to be fully investigated. This paper is the first to report that tofogliflozin, a SGLT2 inhibitor, greatly reduced urinary protein excretion and improved clinical symptoms in a

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patient with the nephrotic syndrome secondary to DN, suggesting promising renal protection of tofogliflozin.

Case report

A 54-year-old Japanese male was referred to our hospital with severe lower limb edema, dyspnea, and abdominal distension. At 40 years of age, he had been diagnosed with type 2 diabetes with an HbA1c level of 7.6%. However, he refused administration of drugs and had never been to a hospital since his first visit. Three months before admission, he visited another clinic and was diagnosed with hypertension (170/100 mmHg), hypercholesterolemia [low-density lipoprotein cholesterol (LDL-C): 220 mg/dL, triglyceride (TG): 210 mg/dL], high level of HbA1c (9.2%) and high level of urinary protein excretion in a spot urine of 100 mg/dL. Despite induction of a nutrition support therapy (total energy 2000 Kcal/day, NaCl 7 g/day, and protein 50 g/day) and co-administration of furosemide (80 mg/day), anagliptin (200 mg/day), telmisartan (40 mg/day) and pitavastatin (2 mg/day) treatment for 3 months, the patient's generalized edema persisted. He was therefore transferred to our hospital three months after these initial treatments. At admission, clinical examination revealed the following: body height 174 cm, weight 86 kg (weight gain of about 12 kg in 6 months), body temperature 36.8 °C, blood pressure 150/94 mmHg, and heart rate 80/min. Auscultation revealed decreased breath sounds. Laboratory data showed a high level of HbA1c (8.8%), hyperglycemia (fasting blood sugar 240 mg/dL), severe proteinuria (10.8 g/day), no hematuria, hypoproteinemia (serum total protein 4.4 g/dL, albumin 2.4 g/dL), hyperuricemia (uric acid 8.2 mg/dL) and dyslipidemia (LDL-C 188 mg/dL, TG 198 mg/dL), but normal renal function (serum creatinine 0.76 mg/dL, 24-h creatinine clearance 92.2 mL/min). Plasma serology was negative for antinuclear antibody, anti-glomerular basement membrane antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA), proteinase 3-ANCA, hepatitis C antibody, and hepatitis B antigen. Serum complement and immunoglobulin (G, A, M) levels were within normal limits. The patient had no history of major diseases, no smoking habit, and no family history of renal disease.

A renal biopsy was performed on the third day of admission. Renal histopathology showed thickening of the glomerular and tubular basement membranes, mesangial expansion, global glomerular sclerosis, nodular sclerosis (arrow), tubular atrophy, fibrotic changes, and cell infiltration in the interstitium indicating advanced stage (Fig. 1). On immunohistochemistry, there was linear positivity of IgG in the peripheral capillary loops, while IgA and IgM were negative. Electron microscopy showed broad

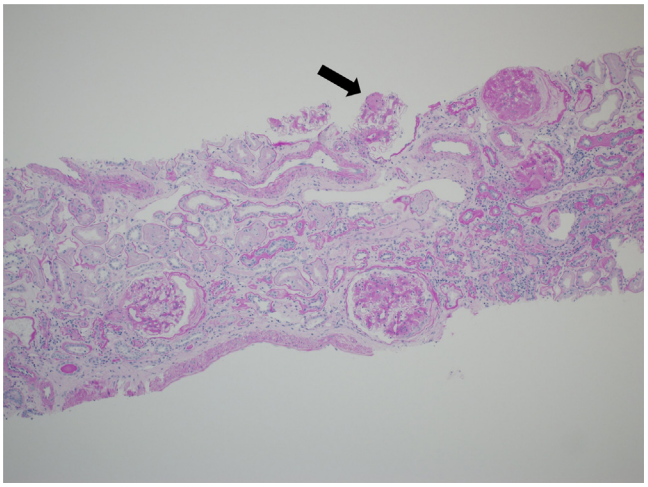

Fig. 1. Renal biopsy specimen. (PAS X 200).
Renal histopathology showing thickening of the glomerular and tubular basement membranes, mesangial expansion, global glomerular sclerosis, nodular sclerosis (arrow), tubular atrophy, fibrotic changes, and cell infiltration in the interstitium.

disappearance of the foot processes in the glomerular basement membrane, glomerular basement membrane thickening, mesangial matrix expansion, and nodular sclerosis. The patient was diagnosed with typical diabetic nephropathy. Despite further nutrition support therapy (total energy 1600–1800 Kcal/day, NaCl 5 g/day, and protein 70 g/day) for a week, his glycemic parameters and generalized edema were poorly controlled. Therefore, we decided to add-on tofogliflozin 20 mg once daily to the background treatments. The serial changes in clinical parameters were well controlled as follows (Table 1): body weight decreased continuously from 92.2 kg to 80.4 kg at 24 weeks, with his weight returning to that observed before onset of edema. Both systolic and diastolic blood pressure decreased continuously from 150/94 mmHg to 130/84 mmHg at 24 weeks, while HbA1c decreased from 8.8% to 8.2% at 4 weeks, 7.4% at 12 weeks, and 6.8% at 24 weeks. Other metabolic parameters relating to lipid profiles and insulin resistance also improved. Immediate increase of urinary sodium and glucose excretion was observed after initiation of tofogliflozin treatment (Table 2). After 4 weeks, urine volume had increased from 800 mL/day to 2400 mL/day and remained at that level up to 24 weeks (Fig. 2). Following the increase in urine volume caused by administration of tofogliflozin, the dose of

Table 1 Serial changes in clinical and laboratory parameters.

	Pre-tofogliflozin	4 weeks	12 weeks	24 weeks
Body weight (kg)	92.2	88.2	84.8	80.4
Systolic blood pressure (mmHg)	150	138	132	130
Diastolic blood pressure (mmHg)	94	90	86	84
HbA1c (%)	8.8	8.2	7.4	6.8
Low-density lipoprotein cholesterol (mg/dL)	188	180	152	116
Triglyceride (mg/dL)	198	166	132	110
Uric acid (mg/dL)	8.2	7.8	7.4	7.0
Total protein (g/dL)	4.4	4.8	5.2	6.8
Serum albumin (g/dL)	2.4	2.6	3.2	4.0
Urine volume (mL/day)	800	2400	2200	2300
Serum creatinine (mg/dL)	0.76	0.78	0.76	0.74
24-h creatinine clearance (mL/min)	92.2	91.8	92.4	93.8
24-h urinary protein excretion (g/day)	10.8	7.2	4.4	2.6
Urinary liver-type fatty acid binding protein (μg/g.Cr) (Reference: below 7.4 μg/g.Cr)	220.8	98,8	54.8	38.8
Serum insulin (μu/mL)	2.62	–	–	2.04
HOMA-IR	4.24	–	–	2.54

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