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Case Report

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Renal Function Improvement With Glucagon-Like Peptide-1 Receptor Agonist in a Patient With Type 2 Diabetes

Hidekatsu Yanai

Abstract

Diabetic kidney disease (DKD) includes hypertensive nephrosclerosis, aging, obesity, and atherosclerosis-related renal diseases, in addition to classical diabetic nephropathy. Sodium-glucose co-transporter 2 inhibitors (SGLT2is) have been approved for diabetic and non-diabetic patients at risk of chronic kidney disease progression. As the main mechanism for SGLT2i-mediated improvement of renal function, the normalization of tubulo-glomerular feedback (TGF) has been proposed. Enhanced TGF and resulting glomerular hypertension are observed in diabetic patients, and SGLT2is normalize TGF, reducing the intraglomerular pressure, which may reduce albuminuria and improve renal function. A type 2 diabetic patient with DKD complicated with hypertensive nephrosclerosis, whose renal function was deteriorated by SGLT2i and improved by glucagon-like peptide-1 receptor agonists (GLP-1RAs), was presented. In patients with hypertensive nephrosclerosis such as this case, the normalization of TGF by SGLT2i may further reduce afferent arteriolar blood flow which may worsen glomerular ischemia, resulting in deterioration of renal function. GLP-1RAs have no effect on TGF and have multiple effects to improve vascular endothelial function, which may be associated with an improvement in renal function in this patient.

Keywords: Diabetic kidney disease; Glucagon-like peptide-1 receptor agonist; Hypertensive nephrosclerosis; Sodium-glucose co-transporter 2 inhibitor; Tubulo-glomerular feedback

Introduction

The natural history of typical and classical "diabetic nephropathy" has been described as high levels of albuminuria and subsequent declined renal function. However, in recent decades, the diabetic cases, who show the reduced estimated glomerular filtration rate (eGFR) without the progression of albuminuria, have been increased [1], which may be explained by that diabetic kidney disease (DKD) includes hypertensive nephrosclerosis, aging, obesity, and atherosclerosis-related renal diseases, in addition to classical diabetic nephropathy. According to the American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines, sodium-glucose co-transporter 2 inhibitors (SGLT2is) are now recommended the first-line agents for patients with type 2 diabetes, chronic kidney disease (CKD), and eGFR $\geq$ 20 mL/min/1.73 m^2 with urinary albumin > 200 mg/g creatinine (grade A recommendation) [2]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are the first line of recommended anti-hyperglycemic medications by the ADA, particularly in patients with overweight or obesity, and in patients who have kidney disease without proteinuria such as hypertensive nephrosclerosis [3].

The effective drugs for DKD with classical diabetic nephropathy and effective drugs for DKD with hypertensive nephrosclerosis may be different. A type 2 diabetic patient with hypertensive nephrosclerosis-dominant DKD, whose renal function was deteriorated by SGLT2i and improved by GLP-1RA, was presented.

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Case Report

Investigations

A 51-year-old man was referred to our hospital because hemoglobin A1c (HbA1c) was high (13.5%; normal range, 4.6-6.2%), in March 2015. Body height, weight, body mass index and abdominal circumference were 162.8 cm, 63 kg, 24.6 kg/m^2, and 83.5 cm, respectively. This patient was diagnosed as having type 2 diabetes. Systolic and diastolic blood pressures were 106 (normal range < 120 mm Hg) and 66 mm Hg (normal range < 80 mm Hg), respectively. Serum levels of triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), creatinine and eGFR were 231 mg/dL (normal range < 150 mg/dL), 48 mg/dL (normal range > 40 mg/dL), 141 mg/dL (normal range < 140 mg/dL), 0.8 mg/dL (normal range, 0.61 - 1.04 mg/dL) and 80.1 mL/min/1.73 m^2 (normal range > 60 mL/min/1.73 m^2), respectively. The urinalysis showed no proteinuria.

Sitagliptin, one of dipeptidyl peptidase 4 inhibitors (DPP4is), was started to treat type 2 diabetes. Changes in the treatments for type 2 diabetes, eGFR and HbA1c and body weight are shown in Figure 1. Metformin (500 mg/day) was started

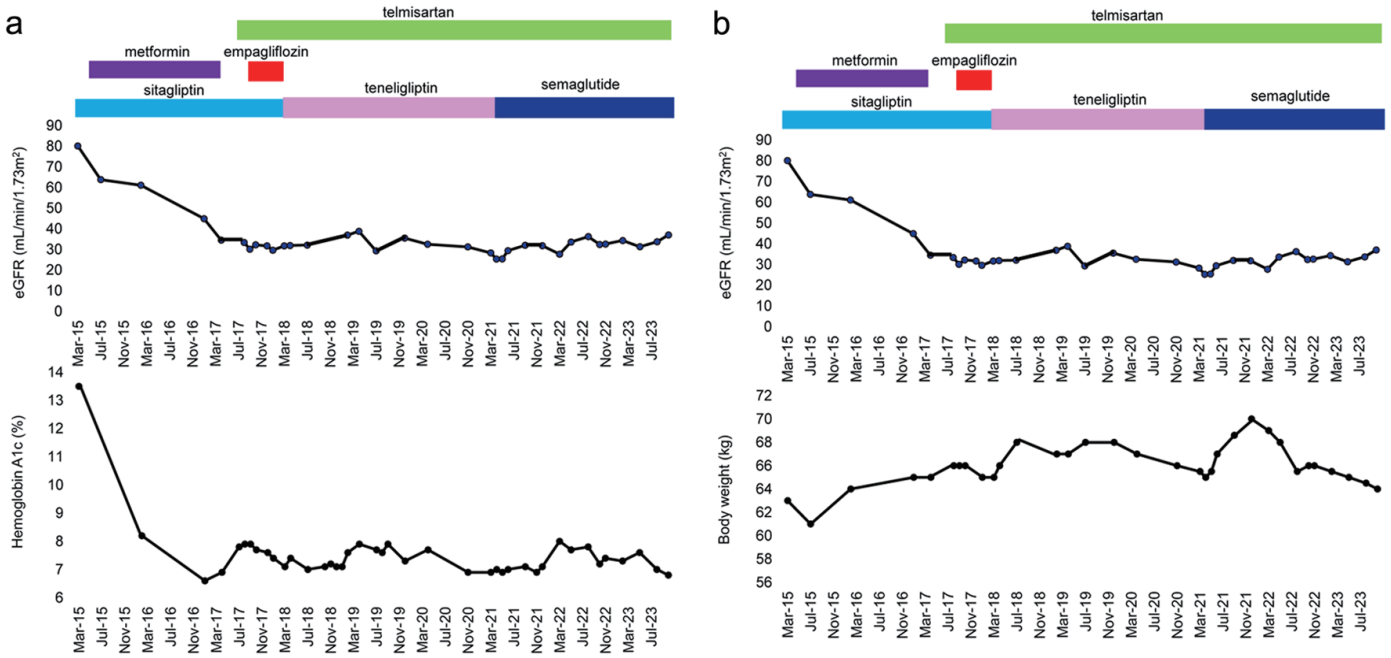

Figure 1. Changes in the treatments for type 2 diabetes, estimated glomerular filtration rate (eGFR) and hemoglobin A1c (a) and body weight (b).

in May 2015, and serum TG (139 mg/dL), HDL-C (40 mg/dL) and LDL-C (124 mg/dL) levels were improved to normal range due to an improvement in plasma glucose.

Diagnosis

eGFR gradually decreased after March 2016; eGFR decreased to 34.5 mL/min/1.73 m^2 in April 2017 and metformin was discontinued. Systolic and diastolic blood pressures at the outpatient clinic were 120 and 74 mm Hg. At this time, microalbuminuria was not detected. This patient had continued to monitor and record body weight and blood pressure from 2015, and showed the records in July 2017. Home systolic and diastolic blood pressures were frequently over 140 and 90 mm Hg, respectively, from 2015, and the diagnosis of hypertension was missed due to normal office blood pressure. In short, this patient had masked hypertension which was previously called as "reverse white-coat hypertension" [4]. Auto-antibodies such as anti-neutrophil cytoplasmic antibody and drugs which induce renal injury were not detected. This type 2 diabetic patient was diagnosed as having hypertensive nephrosclerosis. Angiotensin II receptor blocker (ARB) telmisartan (20 mg) was started in July 2017.

Treatment

The use of SGLT2i empagliflozin (10 mg/day) decreased eGFR from 33.4 to 30.1 mL/min/1.73 m^2 after 2 months, and kept it at low levels (32.2 and 31.7 mL/min/1.73 m^2 at 3 and 5 months after the start of empagliflozin). An increase in daily dose of empagliflozin from 10 to 25 mg further decreased eGFR from 31.7 to 29.6 mL/min/1.73 m^2 after 1 month, and kept it at a low level of 31.7 mL/min/1.73 m^2 at 3 months after the start of daily 25 mg of empagliflozin. Empagliflozin was stopped and switched to DPP4i teneligliptin. After the switching to teneligliptin, eGFR increased to a maximum of 38.3 mL/min/1.73 m^2 in April 2019. During the treatment using empagliflozin, reduction in both HbA1c and body weight was obtained.

eGFR decreased to 27.7 mL/min/1.73 m^2 in March 2022, and oral semaglutide (3 mg) instead of teneligliptin was started. HbA1c decreased from 8.0% to 7.7%, and eGFR increased from 27.7 to 33.6 mL/min/1.73 m^2 (Fig. 2). Daily 14 mg of oral semaglutide remarkably reduced HbA1c to 6.8% and increased eGFR to 37 mL/min/1.73 m^2, respectively. Albuminuria was not detected during the entire observation period.

Changes in body weight, systolic and diastolic blood pressures, postprandial glucose, the peak of daily glucose and average value of daily glucose are shown in Figure 3. Body weight decreased simultaneously with an increase in the daily dose of oral semaglutide. Systolic blood pressure seemed to decrease after the start of daily 14 mg of oral semaglutide. The postprandial glucose, the peak of daily glucose and average value of daily glucose remarkably decreased after the start of daily 14 mg of oral semaglutide.

Follow-up and outcomes

Approximately 10 months passed after the start of oral semaglutide, body weight and glucose control have been stable and eGFR has been kept to be around 35 mL/min/1.73 m^2.

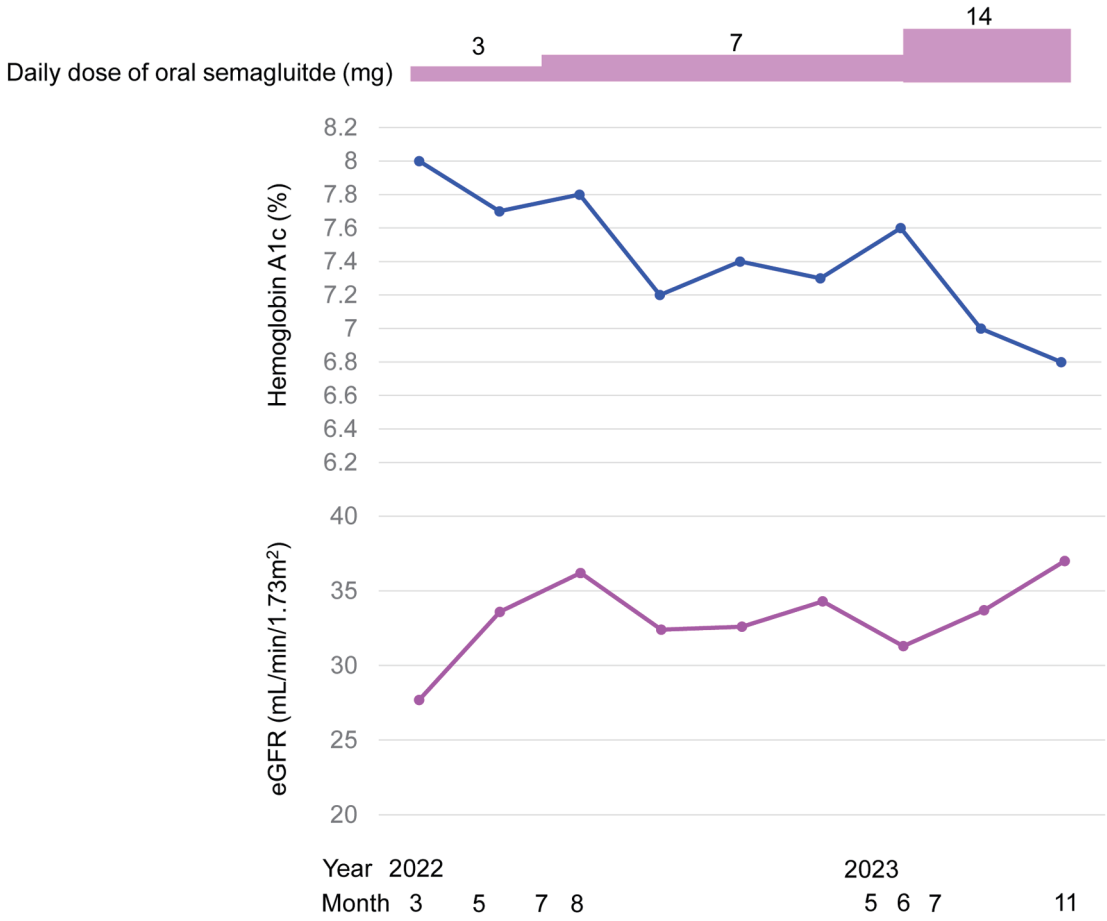

Figure 2. Changes in hemoglobin A1c and estimated glomerular filtration rate (eGFR) after the start of oral semaglutide.

Discussion

DKD is a concept widely recognized as the pathophysiological changes induced by diabetes as the onset and progressive factor of renal injury and declined renal function, regardless of the level of albuminuria [5]. DKD includes hypertensive nephrosclerosis, aging, obesity, and atherosclerosis-related renal diseases, in addition to classical diabetic nephropathy. To choose the appropriate treatment that should be prioritized in the clinical setting, we should determine whether patients' DKD is classical diabetic nephropathy-dominant or hypertensive nephrosclerosis-dominant.

SGLT2is have been approved for diabetic and non-diabetic patients at risk of CKD progression. SGLT2is have shown renal benefits in many conditions that affect the kidneys including hypertensive nephrosclerosis. Twenty-two percent of patients in EMPA-Kidney had hypertensive kidney disease [6]. SGLT2is are known to cause an initial dip in eGFR after initial implementation but the slope of deterioration of renal function over time is reduced with SGLT2is. SGLT2is have reduced cardiovascular morbidity and mortality in type 2 diabetic patients with established cardiovascular disease (CVD) and in patients with heart failure [7, 8]. Thus, there are additional benefits on the CV system from implementation of SGLT2is that start shortly after the initiation of their use especially in diabetic patients with CVD or patients with heart failure [7, 8].

Therefore, a continuous use of SGLT2i was desirable in this case as well. However, eGFR continued to decline and did not show any upward trend for 8 months after the start of SGLT2i. Therefore, SGLT2i was discontinued. As the main mechanism for SGLT2i-mediated improvement of renal function, the normalization of tubulo-glomerular feedback (TGF) has been proposed. Renal protective effects of SGLT2i-mediated normalization of TGF in patients with classical diabetic nephropathy are shown in Figure 4. The sodium-related physiological effects of SGLT2i have been reported to impact on kidney protection [9, 10]. An increased SGLT2 mRNA expression increased the renal NaCl reabsorption in the proximal tubule, leading to a marked reduction in distal NaCl delivery to the macula densa [11]. According to the tubular hypothesis for glomerular hyperfiltration, the decline in macula densa NaCl delivery is sensed as a reduction in the circulating plasma volume by the juxtaglomerular apparatus, and leads to maladaptive glomerular afferent arterial vasodilatation which is called TGF, increasing intraglomerular pressure [12]. SGLT2 inhibition increased distal renal NaCl delivery, causing an increased afferent tone, thereby reducing the intraglomerular pressure

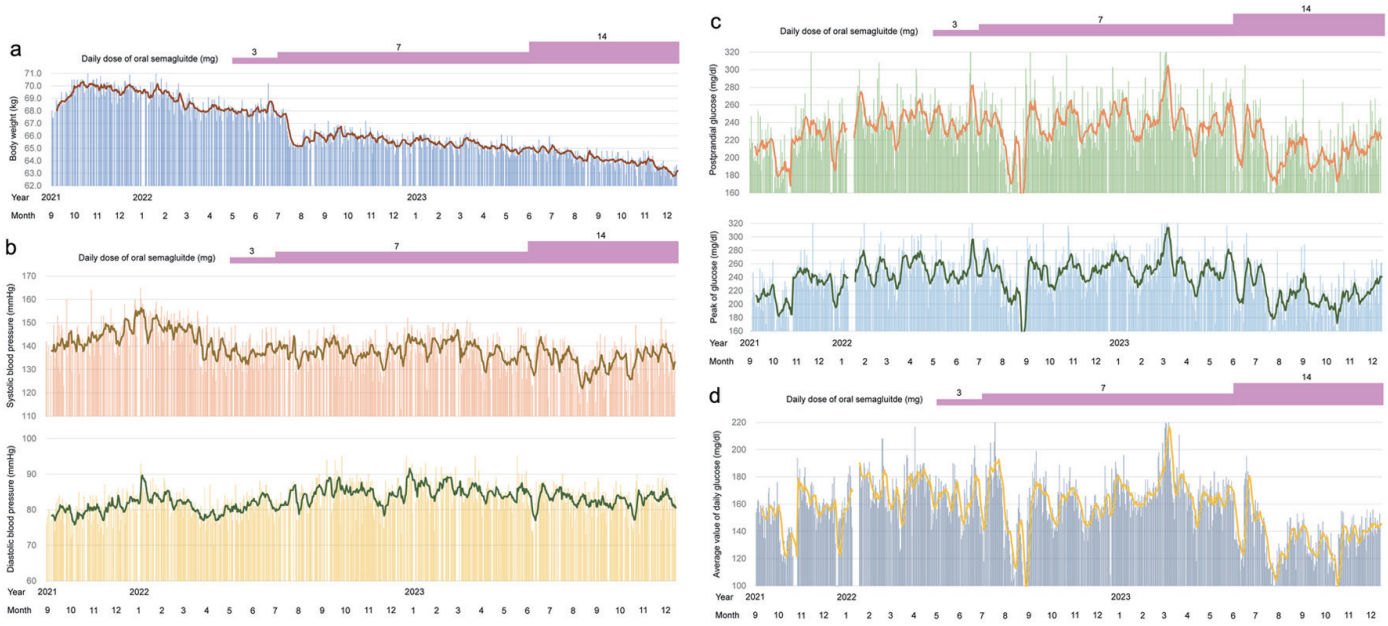

Figure 3. Changes in body weight (a), systolic and diastolic blood pressures (b), postprandial glucose, the peak of daily glucose (c) and average value of daily glucose (d) after the start of oral semaglutide. Thin vertical lines and continuous lines indicate daily values and average values of 1 week, respectively.

and glomerular hyperfiltration [13], which may improve renal function.

The histological lesion of hypertensive nephrosclerosis is well recognized: myo-intimal hyperplasia of interlobular and afferent arteriolar vessels, hyaline arteriolosclerosis, and global glomerulosclerosis, which are believed to result from "glomerular ischemia" due to afferent arteriolar narrowing [14]. Unfavorable effects of SGLT2i-mediated normalization of TGF on renal function in patients with hypertensive nephrosclerosis are shown in Figure 5. Type 2 diabetic patients with hypertensive nephrosclerosis have glomerular ischemia due to afferent arteriolar narrowing. The normalization of TGF

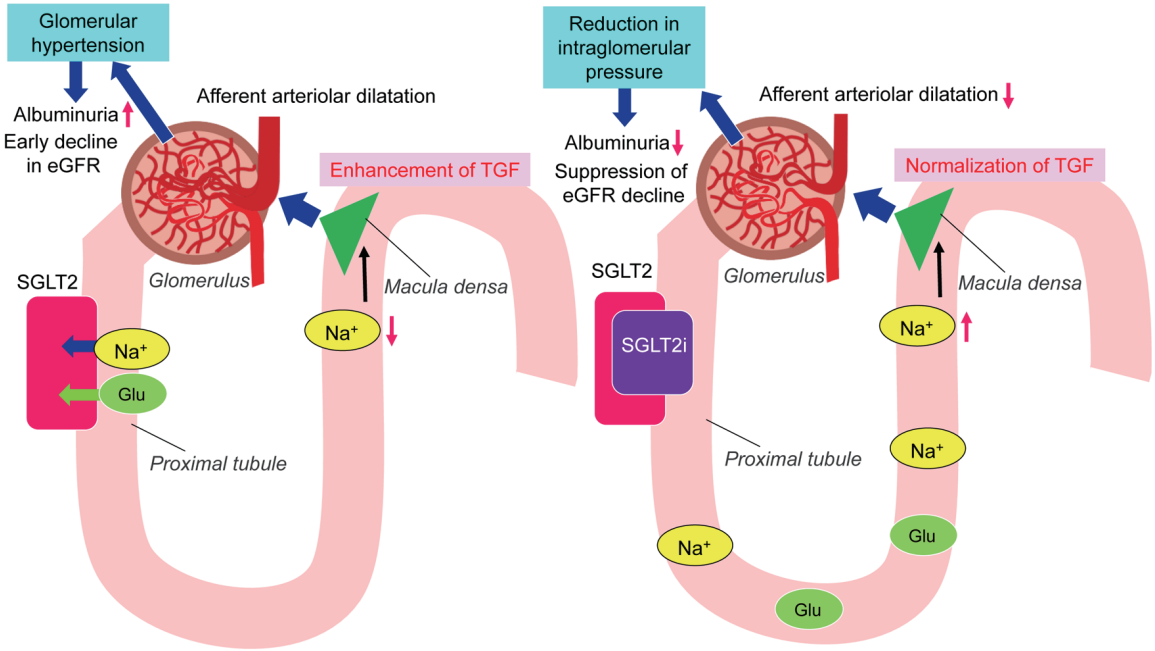

Figure 4. Renal protective effect of SGLT2i-mediated normalization of tubulo-glomerular feedback in patients with classical diabetic nephropathy. eGFR: estimated glomerular filtration; Glu: glucose; SGLT2i: sodium-glucose co-transporter 2 inhibitor; TGF: tubulo-glomerular feedback.

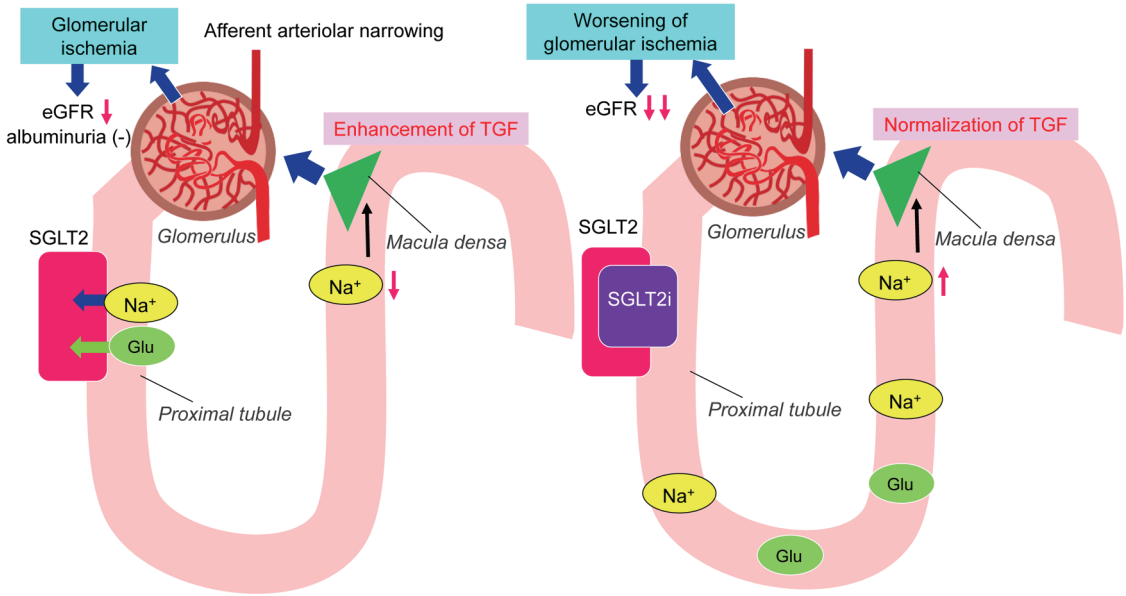

Figure 5. Unfavorable effect of SGLT2i-mediated normalization of tubulo-glomerular feedback on renal function in patients with hypertensive nephrosclerosis. eGFR: estimated glomerular filtration; Glu: glucose; SGLT2i: sodium-glucose co-transporter 2 inhibitor; TGF: tubulo-glomerular feedback.

by SGLT2i reduces afferent arteriolar blood flow which may further worsen glomerular ischemia, resulting in a decline of eGFR.

GLP-1RAs are a promising therapeutic option for patients with DKD. The renal protective effects of GLP-1RA likely result from their direct actions on the kidney such as inhibition of oxidative stress and inflammation and induction of natriuresis, in addition to their indirect actions such as reducing blood glucose levels, blood pressure, and body weight [15]. At least, indirect actions of GLP-1RA were all observed in this patient. Endothelial release of nitric oxide (NO) is significantly associated with the development of glomerular ischemia due to afferent arteriolar narrowing in hypertensive nephrosclerosis [16]. GLP-1RAs have multiple effects to improve endothelial function [17], which may be associated with an improvement in renal function in this patient.

Hypertensive nephrosclerosis is the second most common cause of end-stage renal disease (ESRD) after diabetes. Hypertensive nephrosclerosis has been focused on the afferent arterioles and glomerular damage and the involvement of the renin angiotensin system [18]. Recently, novel evidence has demonstrated that persistent high blood pressure injures tubular cells, leading to epithelial-mesenchymal transition (EMT) and renal fibrosis [18]. Renal fibrosis is recognized as the common route of all CKD progressing to ESRD. Additionally, accumulating evidence suggests that EMT plays a significant role in the process of renal fibrogenesis. GLP-1RAs such as liraglutide have been reported to attenuate the EMT [19].

As far as I know, there are no studies that have investigated the effects of GLP-1RA on renal function in patients with hypertensive nephrosclerosis. At present, the only effective treatments for hypertensive nephrosclerosis are anti-hypertensive drugs or salt intake restriction. GLP-1RA can be a promising therapeutic option that may halt the progression of hypertensive nephrosclerosis.

The limitation of this case report should be mentioned. An acute decline in eGFR after SGLT2i use over background of ARB could at times be a hemodynamic effect, and also in part, due to natriuresis. In this patient, the decline in eGFR after SGLT2i use may not be unexpected, but it may be rather expected. The change in eGFR may be modest, and such change can be acceptable. The patient lost weight subsequently by about 5 kg after semaglutide use. Reduced muscle weight might have affected eGFR values. eGFR rapidly decreased before starting SGLT2i. The worsening course of renal function might have been unrelated to SGLT2i.

Conclusion

A type 2 diabetic patient with DKD complicated with hypertensive nephrosclerosis, whose renal function was deteriorated by SGLT2i and improved by GLP-1RA, was presented. Furthermore, I proposed possible mechanisms for such different effect of SGLT2i and GLP-1RA on renal function.

Learning points

The learning points from this article include that DKD includes hypertensive nephrosclerosis, aging, obesity, and atherosclerosis-related renal diseases, in addition to classical diabetic nephropathy. Although SGLT2is act reno-protectively in patients having glomerular hypertension with proteinuria, they have an unfavorable effect on renal function in patients having glomerular ischemia without proteinuria such as hypertensive ne-

phrosclerosis. GLP-1RA can be a promising therapeutic option that may halt the progression of hypertensive nephrosclerosis.

Acknowledgments

None to declare.

Financial Disclosure

Author has no financial disclosure to report.

Conflict of Interest

None to declare.

Informed Consent

Informed consent for publication was obtained from the patient.

Author Contributions

HY collected and analyzed data. HY wrote and approved the final paper.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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