



SGLT2 Inhibition in Patients With Type 2 Diabetes Mellitus Post-Nephrectomy: A Single-Center Case Series

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Abstract

Background: Nephrectomy is the mainstay of treatment for many kidney cancers, but has been correlated with increased incidence of acute kidney injury (AKI) and chronic kidney disease (CKD). Recently, sodium-glucose cotransporter-2 (SGLT2) inhibition has been shown to decrease the incidence of end-stage kidney disease and death in people with type 2 diabetes mellitus (T2D). However, at present, there has been no description of the use of SGLT2 inhibition in patients with T2D and solitary kidney despite the high risk of CKD progression.

Objective: To characterize the use of SGLT2 inhibition and kidney function in a series of patients with T2D with prior nephrectomy for renal cell carcinoma (RCC).

Design: Retrospective case series.

Setting: University hospital outpatient onco-nephrology clinic.

Patients: Patients post-nephrectomy for RCC with T2D who were prescribed an SGLT2 inhibitor.

Measurements: Serum creatinine, albumin to creatinine ratio (ACR), HgA1c, and blood pressure measurements.

Methods: Patients post-nephrectomy with incident use of SGLT2 inhibitor were identified from an existing registry of patients followed in the Onco-Nephrology Clinic at our institution from May 2019 to March 2021. Demographics, medication use, time since nephrectomy, cancer diagnosis, serum creatinine, ACR measurements, and blood pressure measurements were extracted from electronic medical records.

Results: Five patients were identified who had initiated SGLT2 inhibition post-nephrectomy. All patients were male, had T2D, and a prior history of hypertension. Renal cell carcinoma was the clinical indication for nephrectomy in all patients. None of patients were prescribed diuretics, and all were receiving renin-angiotensin system (RAS) inhibition therapies. The time from nephrectomy to SGLT2 inhibitor initiation ranged from 5 to 74 months. Baseline mean estimated glomerular filtration rate (eGFR) values were 49 mL/min/1.73 m² (95% confidence interval [CI]: 31.5-66.5), and mean ACRs were 8.7 mg/mmol (95% CI: 0.6-16.9). After 6 months of SGLT2 inhibition, the mean eGFR and ACR values were 58 mL/min/1.73 m² (95% CI: 29.7-86.2) and 23.8 mg/mmol (95% CI: 0-60), respectively. After 16 to 18 months of follow-up (4 patients), the mean eGFR was 56 mL/min/1.73 m² (95% CI: 37.3-74.7), and mean ACR was 10.5 (95% CI: 0-30.5), similar to baseline values before SGLT2i therapy initiation. At baseline, mean systolic blood pressure was 128 mm Hg (95% CI: 118.3-140.9) and remained similar after 12 months of treatment (mean 131 mm Hg [95% CI: 112.3-149.7]). There were no adverse events related to AKI, electrolyte disturbances, ketoacidosis, or genitourinary infections during the 18-month follow-up period.

Limitations: Small sample size, lack of a comparison group, and the variable timing of clinical data collection, including eGFR levels following initiation of SGLT2 inhibition.

Conclusions: SGLT2 inhibition is becoming a standard component of nephrology care to reduce kidney function decline, cardiovascular risk, and mortality. To our knowledge, our report is the first to provide longitudinal data on SGLT2 inhibitor usage in patients with T2D and solitary kidneys post-nephrectomy. Larger prospective studies are needed to determine the efficacy and safety of SGLT2 inhibition strategies for kidney protection in patients post-nephrectomy.

Abrégé

Contexte: La néphrectomie est le traitement de référence pour de nombreux cancers rénaux, mais elle est corrélée à une incidence accrue d'insuffisance rénale aiguë (IRA) et d'insuffisance rénale chronique (IRC). On a récemment montré que l'inhibition du cotransporteur sodium-glucose de type 2 (SGLT2) réduisait l'incidence de l'insuffisance rénale terminale et la



mortalité chez les personnes atteintes de diabète de type 2 (DB2). À l'heure actuelle, malgré le risque élevé de progression vers l'IRC, il n'existe aucune description de l'utilisation des inhibiteurs du SGLT2 chez les patients DB2 ayant un seul rein.

Objectif: Caractériser la fonction rénale et l'utilisation des inhibiteurs du SGLT2 chez une série de patients atteints de DB2 ayant subi une néphrectomie pour traiter un carcinome rénal (CR).

Type d'étude: Série de cas rétrospective.

Cadre: Clinique externe d'onconéphrologie d'un hôpital universitaire.

Sujets: Patients atteints de DB2 ayant subi une néphrectomie pour un CR et à qui on a prescrit un inhibiteur du SGLT2.

Mesures: Créatinine sérique, rapport albumine/créatinine (RAC), HgA1c et mesures de la pression artérielle.

Méthodologie: Les patients ayant subi une néphrectomie et ayant utilisé un inhibiteur du SGLT2 ont été identifiés dans le registre des patients suivis à la clinique d'onconéphrologie de notre établissement entre mai 2019 et mars 2021. Les données suivantes ont été extraites des dossiers médicaux: données démographiques, consommation de médicaments, temps écoulé depuis la néphrectomie, diagnostic du cancer, taux de créatinine sérique, mesures du RAC et de la pression artérielle.

Résultats: Cinq patients avaient amorcé l'inhibition du SGLT2 après la néphrectomie. Tous les sujets étaient des hommes atteints de diabète de type 2 et présentant des antécédents d'hypertension. Le CR était dans tous les cas l'indication clinique pour la néphrectomie. Aucun des patients n'avait reçu une prescription de diurétiques et tous suivaient un traitement avec un inhibiteur du système rénine-angiotensine (SRA). Le délai entre la néphrectomie et l'amorce de l'inhibition du SGLT2 variait entre cinq et soixante-quatorze mois. Le DFGe initial moyen s'établissait à 49 ml/min/1,73 m² (IC 95 %: 31,5-66,5) et le rapport albumine/créatinine moyen (RAC) à 8,7 mg/mmol (IC 95 %: 0,6-16,9). Après six mois d'inhibition du SGLT2, les valeurs moyennes de DFGe et de RAC s'établissaient respectivement à 58 ml/min/1,73 m² (IC 95 %: 29,7-86,2) et à 23,8 mg/mmol (IC 95 %: 0-60). Après 16-18 mois de suivi (quatre patients), le DFGe moyen était de 56 ml/min/1,73 m² (IC 95 %: 37,3-74,7) et le RAC moyen de 10,5 mg/mmol (IC 95 %: 0-30,5); des valeurs semblables aux valeurs mesurées avant le début du traitement par inhibiteur du SGLT2. La pression artérielle systolique (PAS) moyenne initiale était de 128 mmHg (IC 95 %: 118,3-140,9) et elle est demeurée quasi inchangée après douze mois de traitement (moyenne de 131 mmHg [IC 95 %: 112,3-149,7]). Aucun événement indésirable lié à l'insuffisance rénale aiguë, à des perturbations électrolytiques, à une acidocétose ou à des infections génito-urinaires n'a été observé au cours des 18 mois de suivi.

Limites: Échantillon de petite taille, absence d'un groupe de comparaison et synchronisation variable de la collecte des données cliniques, notamment du DFGe, après le début de l'inhibition du SGLT2.

Conclusion: L'inhibition du SGLT2 devient une partie intégrante des soins néphrologiques visant à réduire le déclin de la fonction rénale, les risques cardiovasculaires et la mortalité. À notre connaissance, notre rapport est le premier à fournir des données longitudinales sur l'utilisation des inhibiteurs du SGLT2 chez les patients atteints de diabète de type 2 ayant subi une néphrectomie. Des études prospectives de plus grande envergure sont nécessaires pour examiner l'efficacité et l'innocuité des stratégies d'inhibition du SGLT2 visant la protection rénale des patients post-néphrectomie.

Keywords

diabetes, chronic kidney disease (CKD)

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Introduction

Nephrectomy is a mainstay of treatment for many kidney cancers, but is associated with a higher risk of acute kidney injury and chronic kidney disease (CKD) progression. Individuals with renal cell carcinoma (RCC) have a significant risk of CKD progression after partial or radical nephrectomy.¹ Despite this high risk, the optimal medical approach to safely prevent CKD progression is unclear.

Historically, the pharmacologic management of CKD post-nephrectomy is based on attenuation of hyperfiltration and proteinuria using renin-angiotensin system (RAS) inhibition strategies.² Unfortunately, there are limited data specific to the population post-nephrectomy, despite elevated risks of CKD progression and predisposition to develop hyperfiltration. More recently, sodium-glucose cotransporter-2 (SGLT2) inhibition has been shown to decrease the risk of end-stage kidney disease, cardiovascular disease, and

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mortality in people with CKD, including those with type 2 diabetes mellitus (T2D).^{3,4} However, it is not yet known whether these benefits of SGLT2 inhibition extend to individuals with T2D post-nephrectomy, where reducing glomerular hypertension has the potential to translate into declines in proteinuria and CKD progression. Accordingly, in this report, we characterize the use of SGLT2 inhibition in a series of patients with T2D who previously underwent nephrectomy as a treatment for RCC. We describe the trends in kidney function, albuminuria and report on general safety and tolerability.

Methods

Patients post-nephrectomy who were initiated on an SGLT2 inhibitor were identified from an existing registry of patients followed in the University Health Network Onco-Nephrology Clinic from May 2019 to March 2021. Start dates for SGLT2 inhibitor therapies were determined from the outpatient medical records. One patient had 6 months of follow-up as the start date of SGLT2 inhibitor occurred in October 2020. Clinical data such as demographics, medication use, time since nephrectomy, and cancer diagnosis are described in Figure 1A. These details together with serum creatinine and urine albumin to creatinine (ACR) ratio measurements were extracted from electronic medical records. Time 0 was considered 1 to 4 weeks before SGLT2 inhibitor therapy was initiated and included the pre-ambulatory clinic serum and urine biochemistries. The study was approved by the Research Ethics Board at the University Health Network.

Results

After retrospective review, 5 patients were identified who had initiated SGLT2 inhibition post-nephrectomy. All patients were male, had T2D and a prior history of hypertension (Figure 1A). Renal cell carcinoma was the clinical indication for nephrectomy in all patients. None of patients were prescribed diuretics, and all were receiving RAS inhibition therapies. One of the 5 patients reviewed was receiving insulin therapy in addition to oral hypoglycemic agents. The time from nephrectomy to SGLT2 inhibitor initiation ranged from 5 to 74 months. Baseline mean eGFR values were 49 mL/min/1.73 m² (95% confidence interval [CI]: 31.5-66.5), and mean urine ACR was 8.7 mg/mmol (95% CI: 0.6-16.9) (Figure 1B). After 6 months of SGLT2 inhibitor treatment,

the mean eGFR and ACR values were 58 mL/min/1.73 m² (95% CI: 29.7-86.2) and 23.8 mg/mmol (95% CI: 0-60), respectively (Figure 1). After 16 to 18 months of follow-up (4 patients), the mean eGFR was 56 mL/min/1.73 m² (95% CI: 37.3-74.7), and ACR was 10.5 mg/mmol (95% CI: 0-30.5), similar to baseline values before SGLT2 inhibition.

At baseline, mean systolic blood pressure was 129.6 mm Hg (95% CI: 118.3-140.9) and remained similar after 12 months of treatment (mean 131.0 mm Hg [95% CI: 112.3-149.7]) (Figure 1C). There were no adverse events documented in the medical records related to acute kidney injury, electrolyte disturbances, ketoacidosis, or genitourinary infections during the 18-month follow-up period.

Discussion

SGLT2 inhibition is becoming a standard component of nephrology care to reduce kidney function decline, cardiovascular risk, and mortality. Kidney outcome trials with canagliflozin and dapagliflozin have not explicitly excluded patients with a solitary kidney or previous nephrectomy.³ However, the 5 patients in this series would have been excluded because of their history of malignancy. To our knowledge, our report is the first to provide longitudinal data on SGLT2 inhibitor usage in patients with T2D post-nephrectomy.

Glomerular hyperfiltration is a characteristic pathway leading to kidney injury in the setting of T2D.⁵ Mechanistic studies in people with type 1 diabetes have demonstrated an attenuation of hyperfiltration with SGLT2 inhibition—an effect that mirrors observations in experimental models of early type 1 diabetes.⁶ Similarly, we postulate that SGLT2 inhibition may yield analogous changes in glomerular hemodynamics in patients with T2D post-nephrectomy. Importantly, while we did not observe any specific issues related to safety, we also recognize that this analysis was limited by the small sample size, the lack of a comparison group, and the lack of uniform collection of clinical data, including eGFR levels soon after initiation of SGLT2 inhibition.

Conclusions

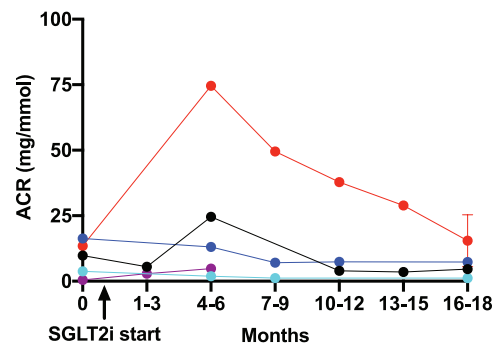
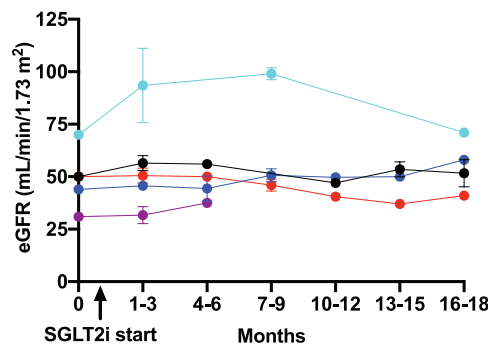
Larger prospective studies are needed to determine the efficacy and safety of SGLT2 inhibition strategies for kidney protection in patients post-nephrectomy.

A

Patient	1	2	3	4	5
Age	64	59	37	63	64
Gender	Male	Male	Male	Male	Male
Cancer diagnosis	RCC	RCC	RCC	RCC	RCC
Post-nephrectomy (months)	96	91	21	58	35
Medical conditions					
Diabetes mellitus	+	+	+	+	+
Hypertension	+	+	+	+	+
Coronary artery disease	-	-	-	-	+
Arrhythmia	-	-	-	-	-
Medication usage					
SGLT2 inhibitor	Canagliflozin	Canagliflozin	Canagliflozin	Canagliflozin	Empagliflozin
SGLT2i duration (months)	20	17	16	13	6
RAS inhibition	+	+	+	+	+
Insulin	-	+	-	-	+
Beta blocker	-	-	-	-	-
Calcium channel blocker	-	+	-	+	-
Diuretic	-	-	-	-	-
Creatinine (umol/L)	131	148	115	131	191
eGFR (mL/min/1.73m ²)	50	44	70	50	31
ACR (mg/mmol)	9.8	16.3	3.8	13.5	0.5
Hemoglobin (g/L)	108	115	140	135	149
Hematocrit	0.335	0.370	0.429	0.390	0.440
Hemoglobin A1c (%)	6.9	11.2	8.4	6.4	6.7

Abbreviations: ACR, albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; RCC, renal cell carcinoma

B



C

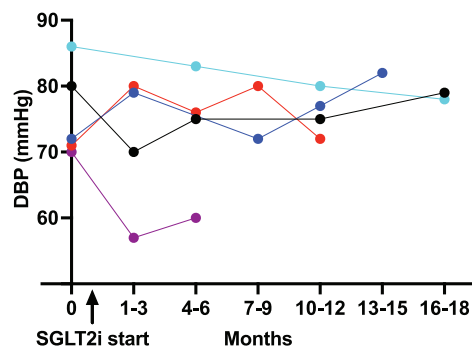
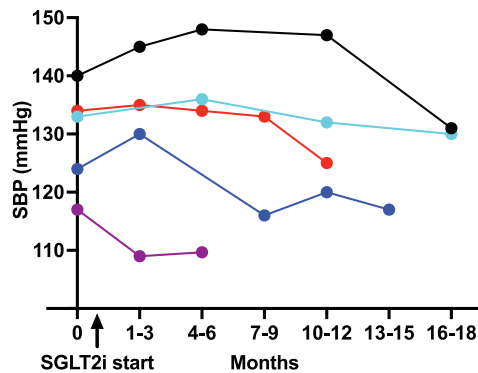


Figure 1. (A) Baseline characteristics of patients pre-SGLT2 inhibitor treatment. (B, C) eGFR, albumin to creatinine ratios and systolic (SBP) and diastolic blood pressures (DBP) of post-nephrectomy patients at baseline (0) and after initiation of SGLT2 inhibitors. Error bars represent standard deviation.

Note. SGLT2 = sodium-glucose cotransporter-2; eGFR = estimated glomerular filtration rate.

Ethics Approval and Consent to Participate

This study was approved by the Research ethics board of the University Health Network.

Consent for Publication

All authors read and approved the final version of this manuscript.

Availability of Data and Materials

The data in this study cannot be shared due to restrictions on confidential patient-level data. Questions about the data can be directed to the corresponding author.

Declaration of Conflicting Interests


The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: David Z.I. Cherney has received consulting fees or speaking honorarium, or both, from Bristol Myers Squibb, Novo Nordisk, Mitsubishi-Tanabe, MAZE, Janssen, Bayer, Boehringer Ingelheim-Eli Lilly, AstraZeneca, Merck & Co., Inc., Prometic, and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli Lilly, Sanofi, AstraZeneca, Novo Nordisk, and Merck & Co., Inc. Marko Škrtić is supported by un-restricted support from Amgen for Onco-Nephrology fellowship.


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References

1. Leppert JT, Lamberts RW, Thomas IC, et al. Incident CKD after radical or partial nephrectomy. *J Am Soc Nephrol.* 2018;29:207-216.
2. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med.* 2008;148:30-48.
3. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380:2295-2306.
4. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *New Engl J Med.* 2020;383(15):1436-1446.
5. Nelson RG, Bennett PH, Beck GJ, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. *N Engl J Med.* 1996;335:1636-1642.
6. Škrtić M, Yang GK, Perkins BA, et al. Characterization of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. *Diabetologia.* 2014;57:2599-2602.