

# Preservation of Urinary Podocyte Markers in Diabetic Kidney Disease by Sodium-Glucose Cotransporter 2 Inhibitor Therapy

Chuanlei Li<sup>a,b</sup> Jack Kit-Chung Ng<sup>a</sup> Gordon Chun-Kau Chan<sup>a</sup>  
Winston Wing-Shing Fung<sup>a</sup> Kai-Ming Chow<sup>a</sup> Cheuk-Chun Szeto<sup>a,b</sup>

<sup>a</sup>Carol and Richard Yu Peritoneal Dialysis Research Centre, Department of Medicine and Therapeutics, Prince of Wales Hospital, Hong Kong, Hong Kong SAR; <sup>b</sup>Li Ka Shing Institute of Health Sciences (LiHS), Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR

## Keywords

Chronic kidney disease · Podocyte · Proteinuria

## Abstract

**Introduction:** Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a standard treatment for kidney and cardiovascular protection in diabetic kidney disease (DKD). We investigated the effect of SGLT2i on the urinary podocyte-associated molecule levels in DKD. **Methods:** We studied 24 DKD patients who were started on SGLT2i treatment and 25 patients who were not treated (control group). Urinary levels of podocyte-associated molecules, their corresponding mRNA levels in urinary sediment, estimated glomerular filtration rate (eGFR), and urine albumin-creatinine ratio (UACR) were measured at baseline and 3 months later. **Results:** Urinary levels of podocin, podocalyxin, and synaptopodin increased significantly over 3 months in the control group, while the levels remained static in the treatment group. After 3 months of treatment, urinary podocin (2.95 [0.92–5.45] vs. 9.15 [1.88–24.80] ng/μmol-Cr,  $p < 0.01$ ), podocalyxin (367.3 [299.5–768.6] vs. 920.6 [369.3–2,060.4] ng/μmol-Cr,  $p < 0.01$ ), and synaptopodin levels (13.17 [9.86–47.02] vs. 35.56 [17.59–134.08] ng/μmol-Cr,  $p < 0.05$ ) were significantly lower in the treatment than the control group. Urinary sediment mRNA levels of po-

docin, podocalyxin, synaptopodin, and nephrin did not change in both groups. However, there was no significant correlation between urinary podocyte-associated marker levels and eGFR or UACR at baseline or after treatment.

**Conclusion:** SGLT2i prevents the progressive increase in the urinary excretion of podocyte-specific molecules in DKD patients, suggesting that SGLT2 inhibitors have a protective effect on the podocytes.

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## Introduction

Diabetic kidney disease (DKD) is the leading cause of dialysis-dependent chronic kidney disease, with albuminuria as a key symptom of nephropathy. DKD progresses due to glomerular filtration barrier (GFB) damage and the loss of podocytes [1, 2]. As type 2 diabetes advances, the glomerulus is often the first affected part of the kidney. Podocytes, specialized glomerular cells, form interconnected foot processes that regulate the GFB's permeability [3–5]. They work with endothelial and mesangial cells to coordinate signals that maintain glomerular function [6]. Under hyperglycemic conditions, podocyte detachment can accelerate, causing these cells to exhibit hypertrophy, foot process effacement, and

detachment during glomerular injury [7]. Of note, podocytes are critical for the GFB and have limited ability to proliferate. The irreversible loss of podocytes therefore results in proteinuria and glomerular disease [8–10]. Recent research highlights that podocyte excretion in urine, known as podocyturia, could serve as a marker for the progression of glomerular pathologies [11].

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) were initially developed for the treatment of diabetes [12, 13]. Recent clinical trials, however, showed that SGLT2is have benefits beyond glucose reduction, offering end-organ protection [14–16]. They have been found to lower the risk of kidney failure in individuals with or without diabetes. This renal protection cannot be solely attributed to glucose-lowering effects; it is believed to involve reduced intraglomerular pressure and the protection of glomerular cells [17, 18]. Notably, dapagliflozin, an SGLT2i, has been reported to reduce podocyte damage in proteinuria nephropathy by maintaining the actin cytoskeleton architecture [19]. However, there are few data on the effect of SGLT2i on urinary podocyte loss. In this study, we investigated the effects of SGLT2is on urinary podocyte markers in patients with DKD.

## Methods

### *Patient Selection and Follow-Up*

We recruited 25 patients with DKD in our clinic. All patients had type 2 diabetes, proteinuria over 0.5 g/day, and the absence of clinical or laboratory evidence of other kidney disease [20]. All patients were receiving maximally tolerate dose of renin-angiotensin-aldosterone system blocker therapy. After written informed consent, they were treated with an addition of SGLT2is (either dapagliflozin 10 mg daily or empagliflozin 25 mg daily) (the treatment group). We studied another 24 patients with DKD who were continued with renin-angiotensin-aldosterone system blocker therapy (control group). The treatment group assignment was decided by individual clinician and not randomized.

All patients were followed for 3 months. Preexisting comorbid conditions were recorded. Biochemical tests including serum creatinine, urea, electrolyte, albumin, liver enzymes, and urinary albumin-to-creatinine ratio were measured at 0 and 3 months. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [21]. All physicians were blinded from the results of urinary gene expression. Dosage of anti-hypertensive medication remained unchanged during the study period.

### *RNA Extraction*

The method of mRNA extraction and quantification in urinary sediment has been described previously [22, 23]. Briefly, urine samples were centrifuged immediately after collection at 4°C for 15 min, 3,200 g. The supernatant was removed, the pellet suspended in 1.5 mL diethyl pyrocarbonate-treated phosphate-buffered saline, and then centrifuged at 12,000 g for 5 min at 4°C. The washed pellet was resuspended in 0.6 mL lysis buffer (QIAGEN Sciences, Germantown, MD, USA) and then kept frozen at –80°C until analysis.

### *Real-Time Quantitative Polymerase Chain Reaction*

Total RNA was extracted from the urinary pellet using an RNeasy mini kit (QIAGEN Sciences), and cDNA was prepared with the SuperScript IV First-Strand Synthesis System and Master Mix (Thermo Fisher Scientific, Waltham, MA USA). Podocin, nephrin, synaptopodin, and podocalyxin mRNA expressions were measured by real-time quantitative polymerase chain reaction, using the Applied Biosystems Step One Plus System (Applied Biosystems, Foster City, CA, USA). Commercially available TaqMan primers and probes were used (all from Applied Biosystems). 18s RNA was used as the house-keeping gene. All samples were performed in triplicate. Step One software version 2.3 (Thermo Fisher Scientific) was used for detection of amplification, and relative quantification ( $\Delta\Delta C_t$  method) was applied for expression of targets. The ratio of podocin to nephrin mRNA was calculated as described in our previous study [24].

### *Urine Podocyte Marker Levels*

Urinary supernatant podocin, nephrin, synaptopodin, and podocalyxin levels were detected by commercially available ELISA kits (all from Biorbyt, Cambridge, UK) following the manufacturer's protocol. The enzymatic reaction was detected at 450 nm in an automatic microplate reader (Tecan SPECTRAFluor Plus Microplate Reader, Tecan Life Science, Switzerland) and adjusted to urinary creatinine level as measured by a commercially creatinine colorimetric assay kit (Abcam, Cambridge, MA, USA). Each sample was measured in duplicate, and all measured creatinine concentrations were within range of the standard curve.

### *Statistical Analysis*

Statistical analysis was performed using SPSS for Windows software version 26.0 (IBM Corporation, Armonk, NY, USA). The normality of data distribution was checked with the Shapiro-Wilk test. Descriptive data were presented as mean  $\pm$  standard deviation if normally distributed or

**Table 1.** Baseline demographic and clinical characteristics

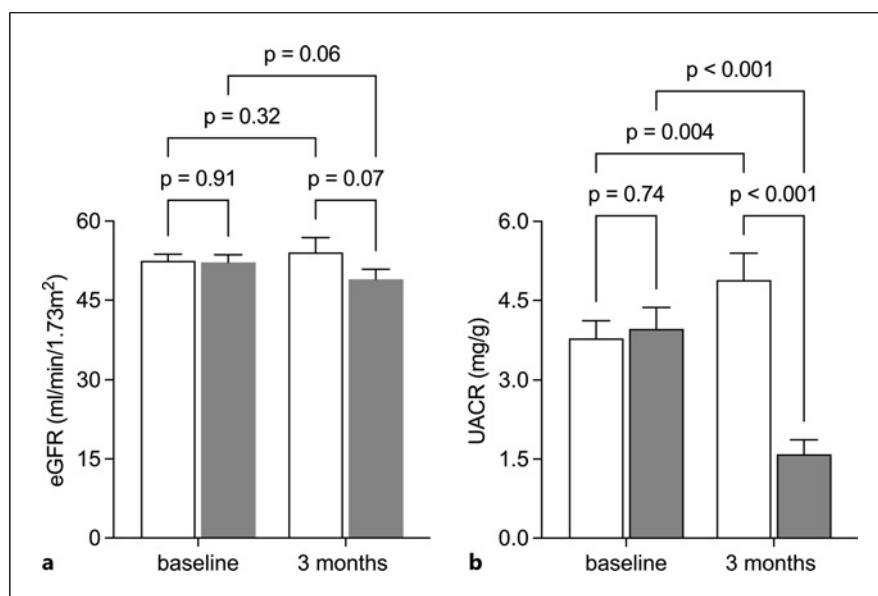
| Group                                           | Control group | Treatment group |
|-------------------------------------------------|---------------|-----------------|
| Patients, <i>n</i>                              | 25            | 24              |
| Age, years                                      | 68.09±7.31    | 68.80±7.29      |
| Male, <i>n</i> (%)                              | 10 (40.0)     | 10 (41.7)       |
| Duration of diabetes, years                     | 10.16±3.60    | 11.88±4.78      |
| Height, cm                                      | 162.68±7.13   | 162.13±8.83     |
| Target weight, kg                               | 56.21±10.63   | 57.17±8.72      |
| Body mass index, kg/m <sup>2</sup>              | 21.14±3.23    | 21.73±2.60      |
| Blood pressure, mm Hg                           |               |                 |
| Systolic                                        | 147.88±12.50  | 146.21±14.76    |
| Diastolic                                       | 79.44±7.40    | 81.38±9.42      |
| Renal function profile                          |               |                 |
| Serum creatinine, µmol/L                        | 112.08±16.06  | 112.92±21.90    |
| GFR, mL/min/1.73 m <sup>2</sup>                 | 52.48±6.28    | 52.16±7.24      |
| UACR, mg/g                                      | 3.79±1.70     | 3.97±1.94       |
| Serum lipid profile, mmol/L                     |               |                 |
| Total cholesterol                               | 4.64±1.06     | 4.81±0.94       |
| LDL cholesterol                                 | 2.71±0.96     | 2.83±0.86       |
| HDL cholesterol                                 | 1.17±0.31     | 1.25±0.28       |
| Triglycerides                                   | 1.73±1.43     | 1.77±1.10       |
| HbA1c, %                                        | 7.63±1.44     | 7.65±1.55       |
| Concomitant medication, cases, <i>n</i> (%)     |               |                 |
| Statin                                          | 6 (24.0)      | 10 (41.7)       |
| Aspirin                                         | 14 (56.0)     | 9 (37.5)        |
| RAAS blocker                                    | 21 (84.0)     | 20 (83.3)       |
| Diuretics                                       | 12 (48.0)     | 8 (33.3)        |
| Comorbid conditions, cases, <i>n</i> (%)        |               |                 |
| Retinopathy                                     | 13 (52.0)     | 8 (33.3)        |
| Coronary artery disease                         | 9 (36.0)      | 4 (16.7)        |
| Congestive heart failure                        | 6 (24.0)      | 4 (16.7)        |
| Cerebrovascular disease                         | 4 (16.0)      | 4 (16.7)        |
| Peripheral vascular disease                     | 2 (8.0)       | 0               |
| Peripheral neuropathy                           | 5 (20.0)      | 2 (8.3)         |
| Use of antidiabetic agents, cases, <i>n</i> (%) |               |                 |
| Metformin                                       | 19 (76.0)     | 20 (83.3)       |
| Sulfonylurea                                    | 13 (52.0)     | 16 (66.7)       |
| DPP4 inhibitor                                  | 10 (40.0)     | 5 (20.8)        |
| Insulin                                         | 8 (32.0)      | 4 (16.7)        |
| GLP1ra                                          | 0             | 1 (4.2)         |
| Thiazolidinedione                               | 0             | 4 (16.7)        |

SGLT2i, sodium-glucose cotransporter 2 inhibitor; GFR, glomerular filtration rate; UACR, urinary albumin-creatinine ratio; RAAS, renin-angiotensin-aldosterone system; DPP4 inhibitor, dipeptidyl peptidase-4 inhibitor; GLP1ra, glucagon-like peptide-1 receptor agonist; UACR, urine albumin-creatinine ratio.

median (interquartile range [IQR]) otherwise. Variables that were not normally distributed were log-transformed for subsequent analysis. Treatment outcome and data between groups were compared using unpaired Student's *t* test or

Mann-Whitney U test as appropriate. Paired data were compared by paired Student's *t* test or Wilcoxon rank-sum test as appropriate. A two-tailed *p* < 0.05 was regarded as statistically significant.

**Fig. 1.** Changes in eGFR (**a**) and UACR (**b**) from baseline to 3 months after SGLT2i treatment (gray) and the control group (white). Error bars denote SEM. Data were compared by Wilcoxon signed-rank test for paired data, and Mann-Whitney U test for unpaired data. eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; SEM, standard error of mean.



## Results

We studied 49 patients with DKD; 24 were started on SGLT2i (the treatment group), and 25 received other glucose-lowering treatment only (the control group). Their demographic, baseline clinical and biochemical characteristics are summarized in Table 1. There was no significant difference in any baseline clinical or biochemical characteristics between the groups.

The change in kidney function and proteinuria in over 3 months in the treatment and control groups is summarized in Figure 1 and online supplementary Table 1 (for all online suppl. material, see <https://doi.org/10.1159/000545225>). In essence, urine albumin-creatinine ratio reduced from 3.73 (IQR 2.34–5.44) to 1.22 (IQR 0.61–2.62) g:g-Cr in the treatment group ( $p < 0.001$ ) but increased from 3.47 (IQR 2.45–5.22) to 4.60 (IQR 3.10–6.48) g:g-Cr in the control group ( $p = 0.013$ ).

### Urinary Podocyte Marker Levels

The change in urinary podocyte marker levels in the treatment and control groups is summarized in Figure 2 and online supplementary Table 2. In short, urinary levels of podocin, podocalyxin, synaptopodin, and nephrin increased over 3 months in the control group, although the change in urinary nephrin level did not reach statistical significance. In contrast, urinary levels of podocin, podocalyxin, synaptopodin, and nephrin remained static in the treatment group. After 3 months of treatment,

urinary podocin, podocalyxin, and synaptopodin (but not nephrin) levels were significantly lower in the treatment than the control group.

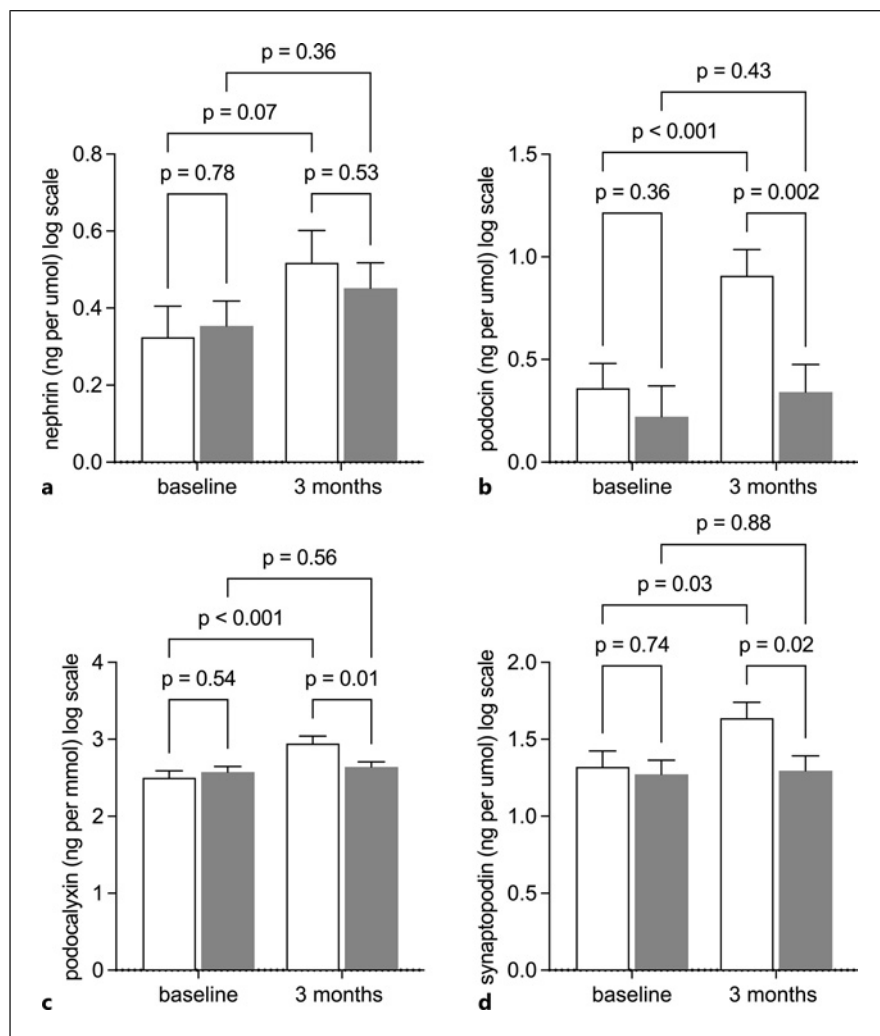
### Urinary Sediment mRNA Levels of Podocyte Marker

The change in urinary sediment mRNA levels of podocyte marker in the treatment and control groups are summarized in Figure 3 and online supplementary Table 2. In short, urinary sediment nephrin mRNA levels decreased over 3 months in the treatment group ( $p < 0.001$ ), and urinary podocin-to-nephrin mRNA ratio also decreased, while urinary sediment mRNA levels of podocin, podocalyxin, and synaptopodin remained static. During the same period, urinary sediment mRNA levels of nephrin, podocin, podocalyxin, and synaptopodin did not have significant change in the control group. After 3 months of treatment, urinary sediment mRNA level of nephrin was significantly lower in the treatment than the control group ( $p < 0.001$ ).

### Relation with Clinical Parameters

The relationship between urinary podocyte marker levels, urinary sediment podocyte-specific mRNA levels, and other clinical parameters during the study period is summarized in online supplementary Table 2. In essence, there was no significant correlation between the level of urinary podocyte-associated markers or and urinary sediment podocyte-specific mRNA levels with estimated glomerular filtration rate or urine albumin-creatinine ratio at baseline, after 3 months, or the magnitude of change during this period. The result remained the same

**Fig. 2.** Changes in urinary levels of nephrin (a); podocin (b); podocalyxin (c); and synaptopodin (d) from baseline to 3 months after SGLT2i treatment (gray) and the control group (white). Error bars denote SEM. Data were compared by Wilcoxon signed-rank test for paired data, and Mann-Whitney U test for unpaired data. SEM, standard error of mean.



when the treatment and control groups were analyzed separately. The result also remained similar when the usage of other diabetic medications (metformin, sulfonylurea, and dipeptidyl peptidase-4 inhibitor) was analyzed as subgroups (online suppl. Table 3).

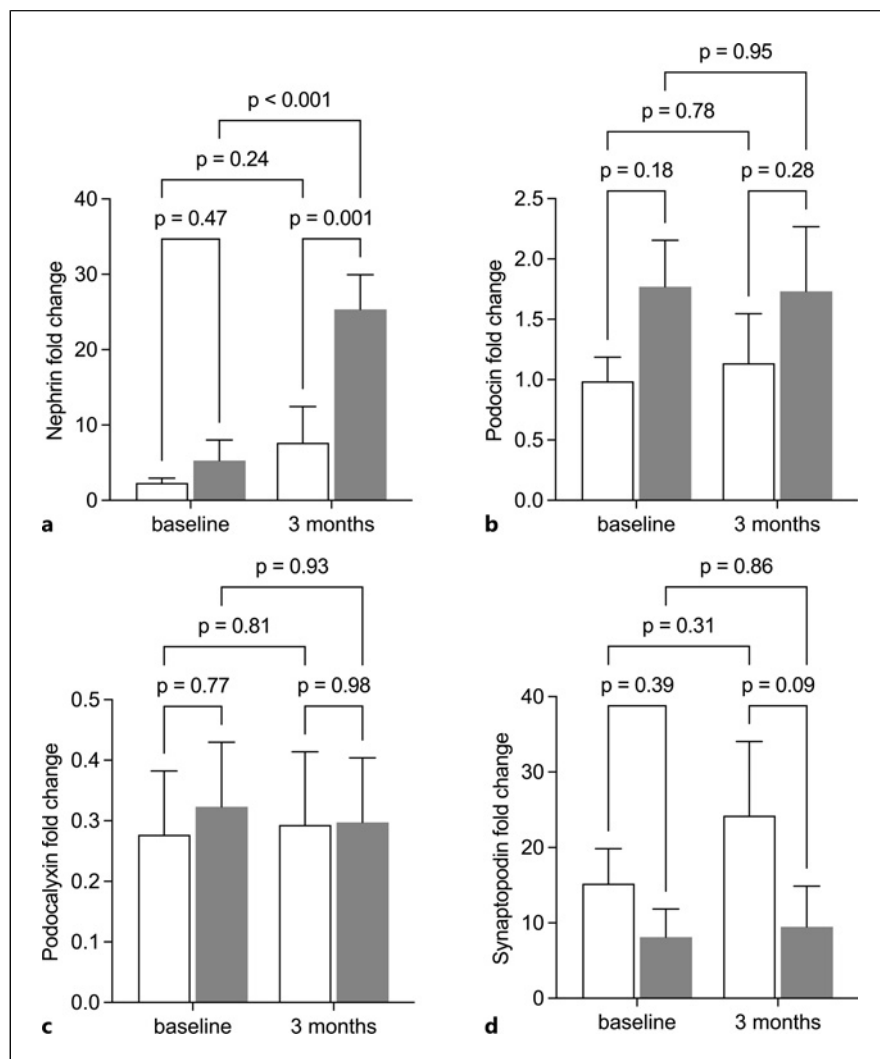
## Discussion

In this study, we found significant increases in the urinary excretion of podocyte-specific molecules in DKD patients over 3 months, and the trend of increase was abolished in the group treated with SGLT2i. By the end of 3 months, urinary levels of podocin, podocalyxin, and synaptopodin were significantly lower in the SGLT2i group than the control group. Although the SGLT2i group also had significantly lower albuminuria after

treatment, urinary level of podocyte-specific molecules did not correlate with kidney function at baseline or after SGLT2i treatment. Urinary sediment mRNA levels of podocyte-associated markers did not change from baseline to 3 months in either group.

Our results should be regarded as complementary to previous reports on the efficacy of SGLT2is on podocy-turia in patients with DKD. For example, Durcan et al. [25] showed that after 6 months of SGLT2i treatment, male patients with DKD had a significantly reduced excretion rate of synaptopodin and podocalyxin-positive cells, and better levels of DKD-related parameters and podocy-turia than those at baseline and in controls. Unlike the report of Durcan et al. [25], we used conventional ELISA to measure podocyte marker levels in urine supernatant, which may originate from cell leakage following sublethal podocyte injury. Theoretically, podocytes

**Fig. 3.** Changes in urinary sediment mRNA levels of nephrin (**a**); podocin (**b**); podocalyxin (**c**); and synaptopodin (**d**) from baseline to 3 months after SGLT2i treatment (gray) and the control group (white). Error bars denote SEM. Data were compared by Wilcoxon signed-rank test for paired data, and Mann-Whitney U test for unpaired data. SEM, standard error of mean.



can be detached from the glomerular basement membrane even under physiological conditions, and these proteins may be excreted into the urine. When exposed to hemodynamic or metabolic stress (e.g., hyperglycemia), shedding of podocytes or their fragments into the urine may be accelerated [7]. In this study, we did not determine the source of the podocyte-specific molecules in the urine. Our results should be regarded as preliminary, and the urinary level of other podocyte markers would be required to determine whether the change in podocyte marker level represents a change in the quantity of urinary podocyte loss or a reflection of qualitative change (i.e., dysfunction) of the podocytes.

In this study, proteinuria was significantly reduced by SGLT2i treatment, but urinary mRNA expression did not change. Moreover, we did not find any correlation between the urinary level or mRNA expression of podocyte-specific

molecules with any clinical parameters or the rate of kidney function decline. Our results are consistent with previous studies, but there are important differences. Podocyte-specific mRNA in urine particles may serve as a biomarker of glomerular disease [11, 26]. A study on IgA nephropathy showed that urinary podocyte mRNA correlated with disease activity, including segmental glomerulosclerosis and acute extra capillary proliferative lesions [27]. Previous studies also demonstrated that the expression of podocyte-related molecules in urinary sediment of DKD patients correlated with baseline kidney function [28], a result that is different from ours. However, urinary podocyte mRNA level is expected to reflect disease activity in a time-dependent manner [29]. Theoretically, podocyte depletion leads to proteinuria and glomerulosclerosis, and sustained podocyte loss is a major factor driving glomerular disease progression [11]. In the early stages of the disease,

the number of urinary podocytes may reflect ongoing glomerular injury and is expected to correlate negatively with renal function. In advanced DKD, however, podocytes are depleted, and the relationship between urinary podocyte marker level and kidney function should be different. Moreover, urine mRNA level may also vary according to the type of disease. For example, available data suggest that the correlation is high for minimal change nephropathy but low for membranous nephropathy [11].

Although we measured urinary podocyte markers in this study, the detection of intrarenal podocyte marker levels may be more valuable for the assessment of DKD prognosis. In a previous study, we found that intrarenal podocalyxin levels correlated with the severity of glomerulosclerosis, and intrarenal podocalyxin level (but not its urinary level) was an independent predictor of dialysis-free survival [30]. Nonetheless, given the invasive nature of assessing intrarenal podocyte marker levels, it has severe limitations for routine clinical use. In the present study, we did not perform serial monitoring of urinary mRNA or podocyte marker levels to determine whether their longitudinal changes reflect the treatment response or help monitor disease progression.

In addition, there are other limitations of the present study. First, this was a retrospective study of DKD patients who had undergone kidney biopsy. Since kidney biopsy is not routinely required for all DKD, there may have been selection bias in our cases. Second, it was a single-center study; the small sample size and relatively short follow-up period may not have been sufficient to observe significant changes in clinical or laboratory parameters, which may weaken the external validity of our study. In essence, our results must be interpreted with caution and further large-scale studies are required to confirm our findings.

In conclusion, our findings suggest that SGLT2is prevent the progressive increase in the urinary excretion of podocyte-specific molecules in DKD patients, suggesting that SGLT2is have a protective effect on the

podocytes. Further studies are required to determine the value of monitoring urinary podocyte-specific molecules as an indicator of treatment response.

### Statement of Ethics

The study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (Approval No. CRE-2018.582). All study procedures were in compliance with the Declaration of Helsinki. All patients provided written informed consent.

### Conflict of Interest Statement

Cheuk-Chun Szeto was a member of the journal's Editorial Board at the time of submission. The authors have no other conflicts of interest to declare.

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### Author Contributions

C.L. performed the laboratory assay, analyzed the data, and wrote the first draft of the manuscript. J.K.-C.N., G.C.-K.C., and W.W.-S.F. collected and validated the clinical data. K.-M.C. was responsible for database maintenance and project administration. C.-C.S. was responsible for the original idea, overall supervision, and writing the final version of the manuscript.

### Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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