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Mechanisms of action of the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin on tubular inflammation and damage: A *post hoc mediation* analysis of the CANVAS trial

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Abstract

Aims: To test the hypothesis that the reduction in urinary kidney injury molecule-1 (KIM-1) observed with the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin is mediated through its effects on urine albumin to creatinine ratio (UACR) and monocyte chemoattractant protein-1 (MCP-1) by assessing the proportion of the effect of canagliflozin on KIM-1 that is mediated through its effects on MCP-1 and UACR in patients with type 2 diabetes and albuminuric kidney disease.

Material and methods: We measured KIM-1 and MCP-1 levels in urine samples from the CANVAS trial at baseline and Week 52 with the Mesoscale QuickPlex SQ 120 platform. KIM-1 and MCP-1 were standardized by urinary creatinine (Cr). The proportion of the effect of canagliflozin that is mediated through UACR and MCP-1/Cr on KIM-1/Cr was estimated with G-computation.

Results: In total, 763 patients with micro- or macroalbuminuria (17.6% of the total cohort) were included. Baseline characteristics were well balanced between the canagliflozin and placebo group. At Year 1, canagliflozin compared to placebo reduced UACR, MCP-1/Cr and KIM-1/Cr by 40.4% (95% CI 31.0, 48.4), 18.1% (95% CI 8.9, 26.4) and 30.9% (95% CI 23.0, 38.0), respectively. The proportion of the effect of canagliflozin on KIM-1/Cr mediated by its effect on UACR and in turn on MCP-1/Cr was 15.2% (95% CI 9.4, 24.5).

Conclusion: Canagliflozin reduces urinary KIM-1, suggesting decreased tubular damage. This effect was partly mediated through a reduction in MCP-1, indicative of reduced tubular inflammation, which was in turn mediated by a reduction in UACR. This post hoc analysis suggests that urinary albumin leakage may lead to tubular inflammation and induction of injury, and provide mechanistic insight for how canagliflozin may ameliorate tubular damage, but further research is required to confirm these findings.

Taha Sen and Akihiko Koshino contributed equally to this study.

1 | INTRODUCTION

Clinical outcome trials have proven that sodium-glucose cotransporter type 2 (SGLT2) inhibitors have beneficial effects on kidney and heart failure outcomes in patients with and without diabetes and at varying stages of chronic kidney disease.[1,2] Although the mechanisms for kidney protection with SGLT2 inhibition are not completely understood, reductions in urinary albumin to creatinine ratio (UACR) contribute to the kidney-protective effects, as reported previously.[3,4] Some studies hypothesize that the reduction in intraglomerular pressure, which may precede a reduction in UACR, is a plausible pathway for the kidney-protective effect of SGLT2 inhibitors.[5]

Patients with micro- or macroalbuminuria show higher degrees of tubular inflammation which may be attributable to increased exposure of tubular cells to albumin.[6-8] This stimulates proinflammatory cytokines, such as monocyte chemoattractant protein-1 (MCP-1), a key inflammatory regulator in the kidney, which may result in interstitial fibrosis and tubular damage, reflected in an increased urinary kidney injury molecule-1 (KIM-1). Experimental studies have reported time- and concentration-dependent increases in MCP-1 as a result of increased exposure to albumin.[9,10] Moreover, inhibition of MCP-1 reduces recruitment of monocytes in the tubules and thereby reduces tubular inflammation.[11] KIM-1, a well-established marker of tubular cell injury, shows similar time- and concentration-dependent relations to albumin as MCP-1.[12,13] KIM-1 is released in the setting of inflammation and inhibition of KIM-1 with specific pharmacological inhibitors ameliorates tubular fibrosis.[14] Previous studies have shown decreased urinary MCP-1 and KIM-1 in response to treatment with SGLT2 inhibitors.[15-17]

In this post hoc analysis of the CANagliflozin cardioVascular Assessment Study (CANVAS) trial we hypothesized that the reduction in KIM-1 observed with SGLT2 inhibitors may be mediated, entirely or in part, through their effect on UACR and MCP-1. To test this hypothesis, we assessed the proportion of the effect of canagliflozin on KIM-1 that is explained by its effects on UACR and MCP-1 in participants with type 2 diabetes and micro- or macroalbuminuria.

2 | METHODS

2.1 | Patients and study design

This study was a post hoc analysis of the CANVAS trial, which was a prospective, multicentre, double-blind, placebo-controlled, randomized trial to assess the efficacy primarily on cardiovascular outcomes and secondarily on kidney outcomes as well as the safety of the SGLT2 inhibitor canagliflozin. The trial was conducted in participants with type 2 diabetes at high risk for cardiovascular disease or who had a history of cardiovascular disease. The study design and main results of the CANVAS trial have been published previously.[1] In brief, a total of 4330 participants were enrolled and were randomly assigned using a web-based response system in a 1:1:1 ratio to canagliflozin 300 mg, canagliflozin 100 mg or matching placebo. The median follow-up duration during the trial was 6.1 years. During the study, all participants, care providers, trial staff and outcome assessors were blinded to treatment randomization. The trial was approved by an ethics committee at each site and was conducted according to the principles of the Declaration of Helsinki. The trial is registered with clinicaltrials.gov (NCT01032629). All participants were given the opportunity to also provide informed consent for the collection of blood and urine samples for future exploratory biomarker research. This was optional and separate from the informed consent provided for the main trial.

Participants eligible for randomization were diagnosed with type 2 diabetes with a glycated haemoglobin (HbA1c) level of ≥53 mmol/mol and ≤91 mmol/mol, had an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m^2 and were either aged ≥30 years with a history of symptomatic atherosclerotic cardiovascular disease, or aged ≥50 years with ≥2 risk factors for cardiovascular disease. The risk factors were defined as a diabetes duration of at least 10 years, a systolic blood pressure >140 mm Hg, receiving >1 antihypertensive agent, current smoking, micro- or macroalbuminuria, or an HDL cholesterol level of <1 mmol/L. Participants also needed to meet other criteria for inclusion as described previously.[1]

For this post hoc exploratory biomarker study we included only patients in whom urine samples were collected (N = 3475) and further excluded patients with normoalbuminuria at baseline (UACR <30 mg/g; N = 2712) because canagliflozin does not decrease albuminuria in patients with normoalbuminuria, precluding assessment of potential mediating effects in these patients.

2.2 | Biomarker assessment

Urine samples for exploratory biomarker research obtained at baseline and 52 weeks after randomization were stored at −80°C. Urinary MCP-1 and KIM-1 at baseline and Week 52 were measured as markers of inflammation and tubular cell injury, respectively. Urine biomarkers were measured using the Mesoscale QuickPlex SQ 120 platform (Meso Scale Diagnostics [MSD], Rockville, Maryland), which is a high-performance electrochemiluminescence immunoassay. Samples were measured between April 2019 and February 2020. A random sample of 381 were measured in duplicate. The mean (SD) coefficient of variation of these samples was 9 (11)% and 6 (5)% for urinary MCP-1 and KIM-1, respectively.

2.3 | Statistical analysis

Baseline characteristics with normal distributions are reported as means with SD values and skewed distributions are reported as median with interquartile ranges (IQRs) and were logarithmic transformed before analysis. Categorical baseline characteristics are reported as percentages.

Each urine biomarker was indexed to urine creatinine (Cr) concentrations to adjust for hydration status. The effects of canagliflozin on MCP-1, UACR and KIM-1 were assessed using analysis of covariance adjusted for the change in biomarker (MCP-1, UACR and KIM-1, each indexed to urine Cr) from baseline to Week 52. The 1-year change in biomarker from baseline and the effect of canagliflozin on the biomarker adjusted for placebo are reported as percentages with 95% confidence interval (CI). The effect of canagliflozin on these biomarkers was also assessed in subgroups of UACR (micro- or macroalbuminuria) and eGFR (<60 or ≥60 mL/min/1.73 m^2).

We estimated the effect of canagliflozin on KIM-1/Cr explained by MCP-1/Cr and UACR using g-computation. This consisted of first specifying linear models for the main effects of: i) canagliflozin on UACR; ii) canagliflozin and UACR on MCP-1/Cr; and iii) canagliflozin, UACR and MCP-1/Cr on KIM-1/Cr. These models enabled us to produce counterfactual scenarios in the g-formula to estimate, firstly, the percentage of the effect of canagliflozin on KIM-1/Cr not explained by its effect on MCP-1/Cr and UACR; secondly, the percentage of the effect of canagliflozin on KIM-1/Cr which was explained by MCP-1/Cr or UACR alone; and thirdly, the percentage of the effect of canagliflozin on KIM-1 explained by its effect on MCP-1/Cr that was in turn explained by its effect on UACR. Standard errors were calculated using a nonparametric bootstrap. Additional details about the g-computation are provided in Appendix S1. All biomarkers were logarithmic transformed before being entered into the analyses.

All analysis were performed in Stata/SE Version 17.0 (StataCorp LCC, College Station, Texas) or R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). P values <0.05 were considered statistically significant for all analyses.

3 | RESULTS

3.1 | Study population

Out of the 4330 participants in the CANVAS trial, 763 (17.6%) had micro- or macroalbuminuria and available urine samples at both baseline and Week 52 to measure MCP-1 and KIM-1. Baseline characteristics of these 763 subjects generally were similar to the overall CANVAS population with the exception that systolic blood pressure was slightly higher and a history of heart failure was more frequently present (Table S1). The baseline characteristics of the 763 included participants were well balanced between the canagliflozin and placebo groups. The mean (SD) age of the participants was 62.9 (7.7) years, 560 (73.4%) were male, the mean (SD) duration of type 2 diabetes was 14.5 (7.4) years, HbA1c was 8.4 (0.9)% and eGFR was 77.2 (17.7)

mL/min/1.73 m^2, and the median (IQR) UACR was 8.9 (4.8, 25.6) mg/mmol. The median (IQR) MCP-1/Cr and KIM-1/Cr values were 26.3 (17.8, 42.0) ng/mmol and 110.5 (61.8, 186.0) ng/mmol, respectively (Table 1).

3.2 | Effect of canagliflozin on urinary MCP-1/Cr and urinary KIM-1/Cr

Canagliflozin reduced UACR by 40.4% (95% CI 31.0, 48.4) compared to placebo in this study sample, similar to observations reported in the entire CANVAS trial.[18] Canagliflozin significantly reduced both MCP-1/Cr and KIM-1/Cr compared to placebo by 18.1% (95% CI 8.9, 26.4) and 30.9% (95% CI 23.0, 38.0), respectively (Figure 1). The reduction in MCP-1/Cr and KIM-1/Cr with canagliflozin compared to placebo was also observed in subgroups by UACR (≥3, <30 and ≥30 mg/mmol) and eGFR (<60 and ≥60 mL/min/1.73 m^2), although the proportional effect of canagliflozin on MCP-1/Cr was more pronounced in patients with baseline UACR ≥30 mg/mmol (P for interaction 0.02) or eGFR <60 mL/min/1.73 m^2 (P for interaction 0.01; Table 2).

3.3 | Effect of canagliflozin on KIM-1 mediated through effect on MCP-1/Cr and UACR

For each biomarker (UACR, MCP-1/Cr and KIM-1/Cr) we calculated the 1-year change from baseline and modelled these to estimate the direct and indirect effects of canagliflozin on UACR, MCP-1/Cr and KIM-1/Cr. The direct effect of canagliflozin compared to placebo on KIM-1/Cr was 53.4% (95% CI 39.2, 68.4; Figure 2). The effect of canagliflozin on KIM-1/Cr explained by its effect on UACR or MCP-1/Cr alone was 8.2% (95% CI 3.1, 15.3) and 23.2% (95% CI 5.6, 37.1), respectively (Figure 2). The percentage of the effect of canagliflozin on KIM-1/Cr explained by its effect through UACR and subsequently MCP-1/Cr was 15.2% (95% CI 9.4, 24.5; Figure 2).

4 | DISCUSSION

The underlying mechanisms for how SGLT2 inhibitors exert kidney protection is not completely understood; however, there are many theories proposed regarding the mechanistic effects including a reduction in intraglomerular pressure and intrarenal inflammation.[19] In this study we aimed to connect some of these pathways and demonstrated that the reduction in KIM-1/Cr, indicative of kidney damage, is to some extent explained by a reduction in MCP-1/Cr, indicative of intrarenal inflammation, which in turn was partly explained by the reduction in UACR.

Several small clinical studies have previously demonstrated that SGLT2 inhibitors decrease urinary MCP-1 and KIM-1 levels. Dapagliflozin reduced KIM-1/Cr in patients with type 2 diabetes after 6 weeks of treatment by approximately 23% relative to placebo.[17] Similar findings were observed in two other small placebo-

TABLE 1 Baseline characteristics of the total, placebo-treated and canagliflozin-treated group

Characteristic	Total N = 763	Placebo N = 239	Canagliflozin N = 524
Age, years	62.9 (7.7)	62.9 (7.7)	62.9 (7.7)
Male sex, n (%)	560 (73.4)	171 (71.6)	389 (74.2)
Current smoker, n (%)	142 (18.6)	53 (22.2)	89 (17.0)
Race, n (%)			
White	618 (81.0)	193 (80.8)	425 (81.1)
Asian	92 (12.1)	27 (11.3)	65 (12.4)
Other	53 (6.9)	19 (7.9)	34 (6.5)
History of HF, n (%)	114 (15.0)	37 (15.5)	77 (14.7)
Duration of diabetes, years	14.5 (7.4)	13.9 (7.8)	14.7 (7.2)
History of CVD, n (%)	435 (57.0)	128 (53.6)	307 (58.6)
BMI, kg/m^2	32.6 (6.0)	32.4 (5.4)	32.7 (6.3)
Systolic BP, mm Hg	141.2 (16.2)	142.1 (16.0)	140.8 (16.2)
Diastolic BP, mm Hg	78.3 (9.9)	79.3 (9.7)	77.9 (10.0)
HbA1c			
mmol/mol	67.9 (9.9)	67.4 (9.6)	68.2 (10.0)
%	8.4 (0.9)	8.3 (0.9)	8.4 (0.9)
eGFR, mL/min/1.73 m^2	77.2 (17.7)	78.8 (16.0)	76.5 (18.3)
eGFR <60, n (%)	130 (17.0)	30 (12.6)	100 (19.1)
eGFR ≥60, n (%)	633 (83.0)	209 (87.4)	424 (80.9)
UACR, mg/mmol (IQR)	8.9 (4.8, 25.6)	9.0 (5.0, 29.9)	8.8 (4.8, 23.6)
Microalbuminuria, n (%)	603 (79.0)	180 (75.3)	423 (80.7)
Macroalbuminuria, n (%)	160 (21.0)	59 (24.7)	101 (19.3)
Urinary MCP-1, pg/mL (IQR)	210 (123, 348)	224 (123, 371)	206 (123, 335)
Urinary KIM-1, pg/mL (IQR)	805 (423, 1505)	790 (390, 1492)	817 (437, 1526)
MCP-1/Cr, ng/mmol (IQR)	26.3 (17.8, 42.0)	27.4 (18.6, 44.6)	25.7 (17.3, 41.8)
KIM-1/Cr, ng/mmol (IQR)	110.5 (61.8, 186.0)	105.3 (62.1, 188.4)	111.6 (61.2, 183.8)

Abbreviations: BMI, body mass index; BP, blood pressure; Cr, creatinine; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1.
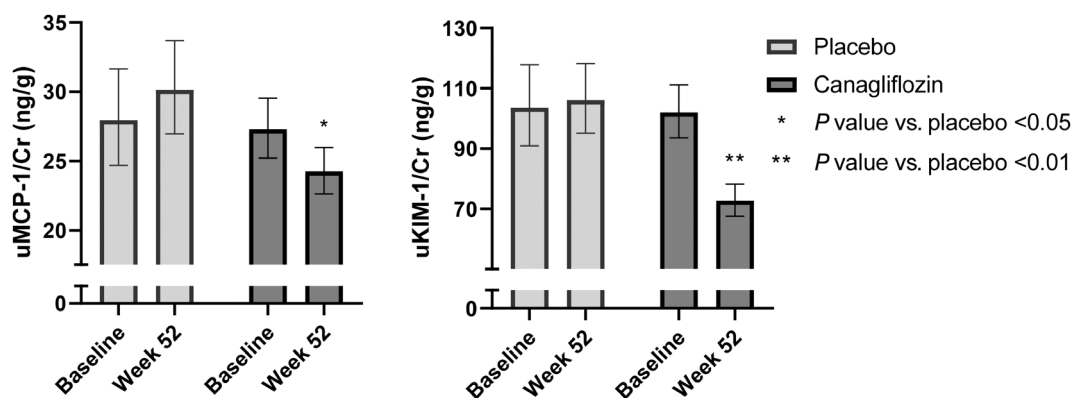

FIGURE 1 Geometric means (95% CI) of monocyte chemoattractant protein-1 (MCP-1)/creatinine (Cr) and kidney injury molecule-1 (KIM-1)/Cr at baseline and Week 52 in the placebo and canagliflozin group. The median (IQR) MCP-1/Cr at Week 52 was 28.1 (17.8, 50.8) ng/g and 22.9 (15.4, 35.1) ng/g for the placebo- and canagliflozin-treated group, respectively. The median (IQR) KIM-1/Cr at Week 52 was 107.5 (62.5, 176.3) ng/g and 75.0 (45.3, 125.1) ng/g for the placebo- and canagliflozin-treated group, respectively

TABLE 2 Changes in urine albumin to creatinine ratio (UACR), monocyte chemoattractant protein-1/creatinine (Cr) and kidney injury molecule-1/Cr in the canagliflozin and placebo group from baseline to Week 52, overall and in participant subgroups defined by baseline UACR and estimated glomerular filtration rate

Biomarker	Baseline biomarker in canagliflozin	Baseline biomarker in placebo	Canagliflozin change, % (95% CI)	Placebo change, % (95% CI)	Placebo corrected effect canagliflozin, % (95% CI)	P interaction
UACR, mg/mmol	2.2	2.2	−43.4 (−47.8, −38.5)	−5.0 (−15.8, 7.1)	−40.4 (−48.4, −31.0)	
UACR						0.01
≥3, <30 mg/mmol	1.9	2.0	−39.7 (−45.0, −34.0)	−9.8 (−21.4, 3.6)	−33.2 (−43.4, −21.2)	
≥30 mg/mmol	4.2	4.3	−55.0 (−62.3, −46.3)	6.1 (−16.0, 33.9)	−57.6 (−68.4, −43.1)	
eGFR						0.83
<60 mL/min/1.73 m²	2.6	2.4	−38.9 (−50.6, −24.2)	8.2 (−26.4, 59.9)	−43.5 (−63.6, −12.2)	
≥60 mL/min/1.73 m²	2.1	2.2	−44.5 (−49.2, −39.4)	−6.3 (−17.3, 6.2)	−40.8 (−49.2, −31.0)	
MCP-1/Cr, ng/mmol	25.7	27.4	−11.8 (−16.9, −6.3)	7.7 (−1.4, 17.6)	−18.1 (−26.4, −8.9)	
UACR						0.02
≥3, <30 mg/mmol	24.7	24.8	−7.7 (−13.9, −1.2)	5.0 (−5.4, 16.6)	−12.1 (−22.5, −0.4)	
≥30 mg/mmol	31.0	36.3	−25.3 (−33.4, −16.3)	12.2 (−3.4, 30.4)	−33.5 (−44.9, −19.6)	
eGFR						0.01
<60 mL/min/1.73 m²	22.9	34.8	−7.7 (−20.7, 7.4)	63.1 (24.0, 114.5)	−43.4 (−58.7, −22.5)	
≥60 mL/min/1.73 m²	26.8	27.0	−12.7 (−18.2, −6.9)	1.4 (−7.5, 11.2)	−14.0 (−23.1, −3.7)	
KIM-1/Cr, ng/mmol	111.6	105.3	−28.9 (−33.0, −24.4)	3.0 (−5.8, 12.7)	−30.9 (−38.0, −23.0)	
UACR						0.20
≥3, <30 mg/mmol	109.4	96.5	−26.6 (−31.5, −21.3)	1.5 (−8.7, 12.9)	−27.7 (−36.3, −17.9)	
≥30 mg/mmol	129.8	145.9	−36.0 (−43.2, −27.8)	2.8 (−12.2, 20.4)	−37.7 (−48.9, −24.0)	
eGFR						0.18
<60 mL/min/1.73 m²	90.2	97.7	−5.5 (−18.3, 9.3)	15.2 (−11.7, 50.3)	−18.0 (−39.4, 11.1)	
≥60 mL/min/1.73 m²	115.1	105.3	−33.2 (−37.5, −28.6)	0.7 (−8.5, 10.7)	−33.7 (−40.9, −25.5)	

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; KIM-1, kidney injury molecule-1; MCP-1, monocyte chemoattractant protein-1; UACR, urine albumin to creatinine ratio.

controlled studies with dapagliflozin in patients with type 2 diabetes.[15,16] However, previous studies included only a small number of participants and were of short duration. In the present study, we extend the previous findings to a large cohort of patients with type 2 diabetes and provide robust evidence that, in this setting, canagliflozin compared to placebo reduces markers of kidney inflammation and injury over at least 52 weeks. These effects appeared particularly pronounced in patients with macroalbuminuria compared to microalbuminuria.

How canagliflozin reduces urinary KIM-1, a well-established marker of tubule cell injury, is not completely understood. Based on a previous study which demonstrated that the degree of albuminuria reduction was associated with the degree of urinary KIM-1 reduction during treatment with dapagliflozin,[17] and because experimental studies have demonstrated that enhanced exposure of tubular cells to albumin stimulates proinflammatory responses, including the release of MCP-1, NFK-β and endothelin-1,[20] we hypothesized that the reduction in urinary KIM-1 is explained by reduced intrarenal inflammation and albuminuria. Our results support our hypothesis, suggesting that at least a portion of the effect of canagliflozin on tubular cell injury was partly mediated by a reduction in intrarenal inflammation, which in turn was mediated by a reduction in albuminuria. In this respect, it is of interest to note that early reduction in albuminuria has been associated with the acute decline in eGFR on initiation of SGLT2 inhibition.[5] The acute decline in eGFR is a clinical manifestation of the reduction in intraglomerular pressure and glomerular hyperfiltration observed with all SGLT2 inhibitors. We therefore speculate that, by reducing glomerular hyperfiltration, albumin leakage across the glomerular membrane decreases, which results in decreased tubular exposure, inflammation and damage.

Previous studies have shown that KIM-1 is associated with fibrosis in tubular tissues. Experimental and clinical studies have suggested that SGLT2 inhibitors exert antifibrotic effects which may have contributed to the observed reduction in urinary KIM-1 in our study.[13] Further clinical studies are needed that collect preferably kidney tissue biopsies to delineate the potential antifibrotic effects of SGLT2 inhibitors.

Key strengths of this study are its sample size relative to prior studies evaluating changes in biomarkers in response to SGLT2 inhibitors, the randomized controlled trial setting, and the 52-week study
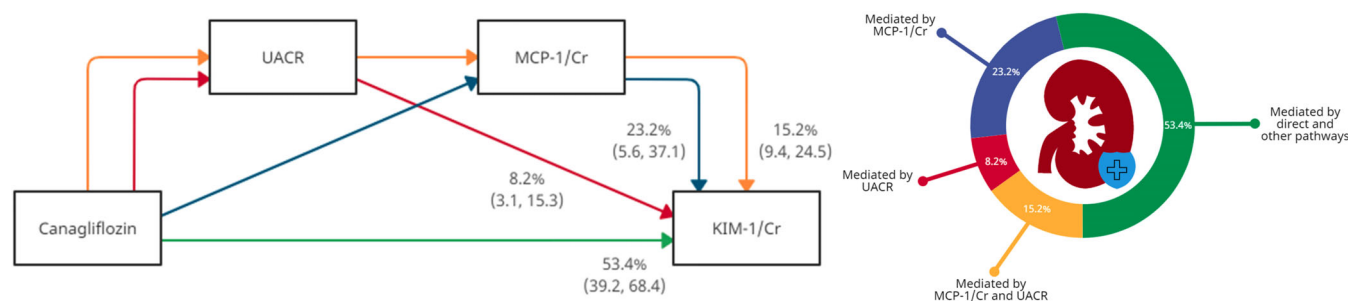
FIGURE 2   Mediation of canagliflozin through direct and other pathways (green), urine albumin to creatinine ratio (UACR; red), monocyte chemoattractant protein-1 (MCP-1)/creatinine (Cr; marker of inflammation; blue) and both MCP-1/Cr and UACR (yellow) on kidney injury molecule-1 (KIM-1)/Cr (marker of tubular damage)

observation period. The study also has some limitations. Firstly, an inherent limitation to any mediation analyses is that we cannot be certain that the identified mediators are truly on the causal pathway and therefore our results are at best viewed as hypothesis-generating and the proportion of the total effect of canagliflozin on KIM-1 explained by MCP-1 and in turn UACR may be overestimated. Second, there may have been other proinflammatory substances involved which we did not measure. Third, UACR and MCP-1 were measured concurrently, which makes it impossible to be sure that effects on MCP-1 were attributable to reductions in UACR rather than the reverse, that effects on UACR were mediated by MCP-1. Each biomarker evaluated here was measured only once at baseline and after 52 weeks, and there is inherent measurement error with any biomarker. Thus, the measurements may not fully capture the biology of albuminuria, inflammation and damage, which would underestimate the degree of mediation observed here. Moreover, SGLT2 inhibitors increase urinary glucose excretion, which may reduce inflammation independent of reductions in albuminuria. This, or other as-yet unexplored pathways, may be the reason why the proportion of the total effect explained was only 15%, when a higher proportion might have been anticipated based on our broader knowledge of the pathophysiology. Finally, our mediation analyses were limited by their capacity to control for interaction between variables.

In summary, we demonstrate that, compared to placebo, canagliflozin reduces KIM-1/Cr, indicative of decreased tubule cell injury, in a large cohort of participants with type 2 diabetes, established cardiovascular disease or multiple cardiovascular risk factors and micro- or macroalbuminuria. This effect was partly mediated through a reduction in MCP-1/Cr, indicative of reduced tubular inflammation, which was in turn mediated by a reduction in UACR. These data suggest that urinary albumin leakage may lead to tubular inflammation and induction of tubule cell injury, and provide new mechanistic insight for how canagliflozin may ameliorate tubular damage.

AUTHOR CONTRIBUTIONS

T. Sen, A. Koshino and B. Neal contributed to collection of the data. T. Sen and M.J. Bijlsma performed statistical analysis. All authors contributed to the interpretation of the data. T. Sen and H.J.L. Heerspink wrote the first draft of the manuscript. B. Neal, C. Arnott,

M.K. Hansen and H.J.L. Heerspink were involved in the design. All authors provided critical revision for important intellectual content and approved the final version of the manuscript for submission. The corresponding author (H.J.L. Heerspink) takes full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

CONFLICTS OF INTEREST

T. Sen, A. Koshino, M.J. Bijlsma and J. Li have nothing to disclose. B. Neal is an employee of the George Institute for Global Health and is supported by a National Health and Medical Research Council Investigator Grant. His institution has received fees for his roles in advisory boards, steering committees or scientific presentations from AstraZeneca, Janssen, Merck and Mundipharma. C. Arnott is an employee of the George Institute for Global Health and is supported by an NSW Health Early- and Mid-Career Researcher Grant and a Medical Research Future Fund Investigator Grant. M.K. Hansen is an employee of Janssen Research & Development, LLC. J.H. Ix is serving on the National Academy of Medicine panel "Review of the Dietary Reference Intakes for Sodium and Potassium" and is receiving research grant support from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Heart, Lung, and Blood Institute, and the American Heart Association. H.J.L. Heerspink has served as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly, Gilead, Goldfinch, Janssen, Merck, Novo Nordisk and Travere Pharmaceuticals, and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Deidentified participant data will be made available on reasonable request 2 years after the date of publication. Requests should be directed to the senior author (Hiddo JL Heerspink). Requestors will be required to send a protocol, statistical analysis plan and sign a data access agreement to ensure the appropriate use of the study data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.