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Do Sodium-glucose Cotransporter-2 Inhibitors Affect Renal Hemodynamics by Different Mechanisms in Type 1 and Type 2 Diabetes?

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Abstract

Cardiovascular and renal outcome trials demonstrate nephroprotection with sodium-glucose cotransporter-2 (SGLT2) inhibitors in people with type 2 diabetes (T2D). Attenuation of hyperfiltration is believed to be responsible for the nephroprotection, and studies in young adults with type 1 diabetes (T1D) suggest that afferent arteriolar vasoconstriction induced by a tubuloglomerular feedback mechanism may be responsible for this effect. The study by van Bommel *et al.* suggests that this mechanism may not hold true in older adults with T2D, who instead attenuate elevated GFR via post-glomerular vasodilation.

Commentary:

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have impeded progression of diabetic kidney disease (DKD) in several large trials of participants with type 2 diabetes (T2D) (1). The mechanisms of nephroprotection with SGLT2 inhibitors, however, are poorly understood and the salutary effects of this drug class are likely incompletely mediated by the modest improvements in blood pressure, glycemic control, body weight, and serum urate. Mechanistic trials and murine models demonstrate that SGLT2 inhibition also elicits renal hemodynamic changes that attenuate glomerular hyperfiltration and reduce urine albumin

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Commentary for van Bommel *et al.* “Renal hemodynamic effects of SGLT2 inhibitor dapagliflozin compared with sulfonylurea gliclazide in metformin-treated people with type 2 diabetes: A 12-week, randomized, double-blind trial (RED)”

Conflicts of interest

PB has acted as a consultant for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Novo Nordisk and Horizon Pharma. PB serves on the advisory board of XORTX. RGN and MEP report no conflicts of interest.

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excretion (2). Cherney et al. proposed that attenuation of glomerular hyperfiltration in response to 8 weeks of empagliflozin in young adults with type 1 diabetes (T1D) and glomerular hyperfiltration was mediated by tubular-glomerular feedback mechanisms that induced afferent arteriolar vasoconstriction and increased renal vascular resistance. This hypothesis was validated in a murine model of T1D using in vivo multiphoton microscopy imaging techniques (3). It remains unclear, however, whether these renal hemodynamic effects explain the nephroprotection observed in clinical trials.

To address this knowledge gap, van Bommel *et al.* sought to determine whether the renal hemodynamic effects of SGLT2 inhibitors observed in young adults with T1D and murine models of T1D held true in older adults with T2D, as this latter group were frequent participants in the cardiovascular and renal outcome trials. Accordingly, the study aimed to define the renal hemodynamic effects of dapagliflozin in older adults with T2D (mean age 63 ± 7 years), and their data suggest potential differences in the mechanisms affecting renal hemodynamic function in T1D vs. T2D. Their mechanistic trial (4) compared the renal and *intrarenal* hemodynamic effects of dapagliflozin vs. gliclazide over 12 weeks in 44 metformin treated adults with T2D, estimated GFR ~ 60 ml/min/1.73m² and urine albumin to creatinine ratio < 300 mg/g. The investigators used a randomized, double-blind trial design and measured renal hemodynamic function in the participants (e.g. glomerular filtration rate [GFR], effective renal plasma flow [ERPF], filtration fraction and renal vascular resistance) and parameters of calculated *intrarenal* hemodynamic function (e.g. afferent and efferent arteriolar resistance by Gomez equations). They found that dapagliflozin reduced GFR, filtration fraction and intraglomerular pressure without increasing renal vascular resistance by lowering efferent arteriolar resistance, findings which potentially implicate disparate effects of SGLT2 inhibition on renal hemodynamic function in T2D vs. T1D. Data in young adults with T1D suggest that SGLT2 inhibition attenuates hyperfiltration and intraglomerular pressure by afferent arteriolar vasoconstriction, whereas van Bommel's study in older adults with T2D instead implicate efferent arteriolar vasodilation as the mediator of the decrease in GFR and intraglomerular pressure. These are profoundly different hemodynamic effects of SGLT2 inhibitors in two different groups of individuals with diabetes and the explanation for these differences is not clear. First, there are important differences between van Bommel's T2D cohort and Cherney's T1D cohort beyond diabetes type, including age, glycemic control, blood pressure and renal function, which could all contribute to the observed differences in mechanisms underlying the renal hemodynamics observed in response to SGLT2 inhibition. Second, nephron numbers decline with age. In healthy kidney donors, for example, nephron numbers decrease by 50% between 20 and 70 years of age (5). Therefore, the differences observed in the two studies may also reflect variability in nephron number among the participants. Third, studies involving research kidney biopsies demonstrate greater structural heterogeneity of DKD in older persons with T2D than in T1D (6–8), suggesting that co-morbid conditions and structural heterogeneity could also be affecting renal hemodynamics.

Several strengths of the elegant mechanistic trial by Bommel *et al.* are worth highlighting, including gold standard measures of GFR and ERPF by inulin (or iohexol) and *p*-aminohippurate clearance techniques during fasting, clamped euglycemic and hyperglycemic conditions. These methods are technically challenging, expensive and

cumbersome, and the authors are to be commended for such comprehensive work. The authors also sought to define potential mediators of the renal hemodynamic effects of SGLT2 inhibition by measuring several biomarkers of the renin-angiotensin aldosterone system and other vasoactive substances, including endothelin-1, thromboxane β_2 , 8-oxoGuo, adenosine, 6kPGF $_{1\alpha}$, and PGE2. They found that dapagliflozin increased renin, and augmented the ratios of urinary adenosine, 6kPGF $_{1\alpha}$, and PGE2 to urinary creatinine. Notably, increased urinary adenosine in response to SGLT2 inhibition has been linked with afferent arteriolar vasoconstriction via adenosine A1 receptor activity in T1D models (3), but this did not hold true in older adults with T2D.

The question remains whether the nephroprotection demonstrated in participants with T2D in cardiovascular and renal outcome trials can be extrapolated to people with T1D or youth with T2D? At present, we are unable to answer this question due to the lack of dedicated outcome trials in these patient populations, although certain kidney biomarkers in non-dedicated renal studies suggest that SGLT2 inhibition may also offer nephroprotection in people with T1D. Dedicated renal trials investigating the effects of SGLT2 inhibitors in people with T1D and youth with T2D are needed. Although, the obvious take-home message from van Bommel's important study is the possibility that SGLT2 inhibition affects renal hemodynamics by different mechanisms in T1D and T2D, perhaps more importantly, the disparate findings also help us recognize how little we still know about the mechanisms underlying SGLT2 inhibition in DKD. Indeed, two rigorously conducted mechanistic trials with SGLT2 inhibition in young adults with T1D (2) and older adults with T2D (4) demonstrated remarkably different reasons for the modest decrease in intraglomerular pressure observed in both trials. This begs the question whether a modest decline in intraglomerular pressure is truly contributing to the nephroprotection afforded by SGLT2 inhibition? Therefore, this study emphasizes the need to comprehensively establish the mechanisms underlying the nephroprotection afforded by SGLT2 inhibition. To achieve this goal will likely require an integrated biological approach (9) (Figure). Substantial advances and maturation of transcriptomic and metabolomic technologies offer a platform to identify key genes and metabolic pathways involved in DKD and how they respond to therapy. Crucial components of this mechanistic approach are the integration of deep clinical phenotyping by renal clearance studies and perhaps functional imaging to quantify whole-kidney structure and function with histopathological and molecular phenotyping from kidney tissue. Identifying the mechanisms of benefit of SGLT2 inhibition and their role in different disease subtypes will provide an important foundation for future drug development, inform strategies for combination therapy and target the patients who will most likely respond to these therapies.

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References:

1. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380(24):2295–306. [PubMed: 30990260]
2. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129(5):587–97. [PubMed: 24334175]
3. Kidokoro K, Cherney DZI, Bozovic A, Nagasu H, Satoh M, Kanda E, et al. Evaluation of Glomerular Hemodynamic Function by Empagliflozin in Diabetic Mice Using In Vivo Imaging. *Circulation*. 2019;140(4):303–15. [PubMed: 30773020]
4. van Bommel E, Muskiet MH, van Baar MJB, Tonneijck L, Smits M, Emanuel AL, et al. Renal hemodynamic effects of SGLT2 inhibitor dapagliflozin compared with sulfonylurea gliclazide in metformin-treated people with type 2 diabetes: A 12-week, randomized, double-blind trial (RED). *Kidney Int*. 2019.
5. Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med*. 2017;376(24):2349–57. [PubMed: 28614683]
6. Mauer M, Caramori ML, Fioretto P, Najafian B. Glomerular structural-functional relationship models of diabetic nephropathy are robust in type 1 diabetic patients. *Nephrol Dial Transplant*. 2015;30(6):918–23. [PubMed: 25183630]
7. Najafian B, Mauer M. Morphologic features of declining renal function in type 1 diabetes. *Semin Nephrol*. 2012;32(5):415–22. [PubMed: 23062981]
8. Fioretto P, Mauer M, Brocco E, Velussi M, Frigato F, Muollo B, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia*. 1996;39(12):1569–76. [PubMed: 8960844]
9. Mulder S, Hamidi H, Kretzler M, Ju W. An integrative systems biology approach for precision medicine in diabetic kidney disease. *Diabetes Obes Metab*. 2018;20 Suppl 3:6–13. [PubMed: 30294956]

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Integrated Biological Approach to Diabetic Kidney Disease