Nephrol Dial Transplant (2020) 35: i1–i2
doi: 10.1093/ndt/gfz282

ndt
Nephrology Dialysis Transplantation

EDITORIAL

Editorial: The role of sodium-glucose cotransporter 2 inhibitors in the management of chronic kidney disease

Hiddo J. L. Heerspink[1,2], Denis Fouque[3] and Christoph Wanner[4]

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, The Netherlands, [2]George Institute for Global Health, Sydney, Australia, [3]Department of Nephrology, Université de Lyon, Carmen, Centre Hospitalier Lyon-Sud, Pierre Bénite, France and [4]Department of Medicine, Division of Nephrology, University Hospital Würzburg, Würzburg, Germany

Correspondence to: Hiddo J. L. Heerspink; E-mail: h.j.lambers.heerspink@umcg.nl; Twitter handles: @denisfouque1, @ChristophWanne4

The kidneys play an important role in maintaining glucose homoeostasis through the production of glucose via gluconeogenesis. They not only filter and reabsorb plasma glucose, but also use glucose as a metabolic fuel. These physiologic processes have been studied for a long time but have become an area of renewed and intense research interest in recent years as a result of the benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors in reducing cardiovascular outcomes and delaying the progression of chronic kidney disease (CKD) in patients with type 2 diabetes.

The kinetics of glucose reabsorption was first studied in the early 1930s [1]. These early studies demonstrated that renal glucose transport in the tubules can reach a maximum beyond which glucose is excreted in the urine. Wright *et al.* [2] demonstrated in the 1990s that the SGLT1 and SGLT2 transporters are responsible for the glucose reabsorption in the proximal tubule.

Phlorizin was the first inhibitor of the SGLT transporters, but it never entered clinical practice due to its gastrointestinal side effects and metabolism to phloretin, which inhibits glucose transporters. Phlorizin's poor tolerability and the molecular characterization of the SGLT transporters in the 1990s stimulated further development of small molecules that selectively inhibit the SGLT2 transporter. Interestingly, in hindsight, early studies demonstrated the potential of first-generation SGLT2 inhibitors to slow CKD progression. The first selective SGLT2 inhibitor, T-1095, showed profound reductions in urinary albumin excretion in experimental studies, suggesting that SGLT2 inhibitors could indeed protect the kidney [3]. Further early evidence for possible kidney protective effects came in the early 1990s from elegant micropuncture studies using phlorizin. Pollock *et al.* [4] demonstrated that single nephron hyperfiltration, which has been associated in experimental and clinical studies with CKD progression, is associated with SGLT2-mediated tubular sodium reabsorption and tubuloglomerular feedback (TGF) in experimental models of type 1 diabetes. Intriguingly, Pollock *et al.* demonstrated that the hyperfiltering state could be reversed with phlorizin, supporting a potential role for SGLT2 inhibition in the treatment of CKD.

These initial signals of potential kidney protective effects are now confirmed in large cardiovascular and kidney outcome trials. Since 2015, three cardiovascular outcome trials in patients with type 2 diabetes at high-cardiovascular risk demonstrated that SGLT2 inhibition causes a profound reduction in the rate of kidney function decline [5–7]. The Canagliflozin and Renal Events in Diabetes and Nephropathy Clinical Evaluation trial, which was specifically designed to test the kidney protective effects of the SGLT2 inhibitor canagliflozin, demonstrated that in patients with type 2 diabetes and established CKD, canagliflozin substantially reduces the risk of major kidney outcomes [8].

This supplement of *Nephrology Dialysis and Transplantation* (*NDT*) aims to provide a series of comprehensive and up-to-date reviews on recent advances in the field of SGLT2 inhibition. Cherney *et al.* [9] summarize recent studies that have shown that the kidney-specific benefits of SGLT2 inhibitors are unlikely mediated by improving glycaemic control but are most likely a result of multiple non-glycaemic effects directly or indirectly related to increased natriuresis. Specifically, they review recent clinical and experimental studies that used *in vivo* intrarenal imaging to show that the restoration of TGF during SGLT2 inhibition is dependent on adenosine signalling.

Given the multiple mechanisms of action, it is important to address the position of SGLT2 inhibitors in the pharmacotherapeutic management of patients with type 1 diabetes or patients without type 2 diabetes [10, 11]. In this *NDT* supplement, Bjornstad and van Raalte [12] review the pathophysiology and treatment of CKD in patients with type 1 diabetes. They review the results of three large clinical trial programmes on the effects of SGLT2 inhibitors in patients with type 1 diabetes that reported haemoglobin A1c (HbA1c) reductions of ∼0.4% with

SGLT2 inhibition compared with control treatment. Unfortunately, long-term clinical trials in this patient population have not been performed and thus the effects on important patient outcomes are unknown. However, in a pooled analysis of two clinical trials it was shown that sotagliflozin reduces albuminuria and blood pressure and causes an acute decline in estimated glomerular filtration rate, suggesting that renoprotective mechanisms in patients with type 1 diabetes are similar as those observed in type 2 diabetes [13].

One of the alleged pathways by which SGLT2 inhibitors slow progression of CKD is correction of hyperfiltration. Since the long-term benefits of SGLT2 inhibitors are unlikely mediated by reductions in HbA1c and various types of kidney diseases are characterized by hyperfiltration, it is tempting to speculate on the role of SGLT2 inhibitors in patients with CKD without type 2 diabetes, as reviewed by Dekkers and Gansevoort [14]. Previous studies have indeed suggested that the pharmacodynamic activity persists in non-diabetic conditions. For example, in nearly 400 obese individuals, canagliflozin reduced body weight, blood pressure and uric acid [15]. Moreover, in 10 patients with focal segmental glomerular sclerosis, reductions in both numerical and measured proteinuria were noted, although these did not reach statistical significance [16]. Further mechanistic and clinical outcome trials are ongoing in patients with CKD. The Dapagliflozin and Prevention of Adverse Outcomes in CKD trial assesses the effect of the SGLT2 inhibitor dapagliflozin on kidney and cardiovascular events in patients with CKD with and without diabetes. The rationale and the design of the trial are described in this month's issue of *NDT* [17]. The Empagliflozin Kidney (EMPA-KIDNEY) trial is another large clinical trial to assess the efficacy of empagliflozin on major kidney outcomes. The results will increase our understanding about the position of SGLT2 inhibitors in patients with CKD without diabetes.

Should SGLT2 inhibitors be prescribed to any patients with type 2 diabetes and CKD? It is possible that some patients do not tolerate these drugs or use concomitant medications, such as renin-angiotensin-aldosterone system inhibitors or loop diuretics that may impact the efficacy or safety of SGLT2 inhibitors. These questions are discussed by Neuen *et al.* [18] in this *NDT* supplement.

After more than a century of research into the physiology of tubular glucose reabsorption, we are now entering a new era of kidney protection with proven effective therapeutic approaches that prevent clinically important outcomes in patients with type 2 diabetes. It is now up to the nephrology community to implement these treatments in clinical practice.

CONFLICT OF INTEREST STATEMENT

H.J.L.H. is consultant for AbbVie, AstraZeneca, Boehringer Ingelheim, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe and Retrophin. He received research support from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen. C.W. reports honoraria from AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly and Company, and Mundipharma.

REFERENCES

1. Shannon JA, Fisher S. The renal tubular reabsorption of glucose in the normal dog. *Am J Physiol* 1938; 122: 765–774
2. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. *Physiol Rev* 2011; 91: 733–794
3. Oku A, Ueta K, Arakawa K *et al.* T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes. *Diabetes* 1999; 48: 1794–1800
4. Pollock CA, Lawrence JR, Field MJ. Tubular sodium handling and tubuloglomerular feedback in experimental diabetes mellitus. *Am J Physiol* 1991; 260: F946–F952
5. Wanner C, Inzucchi SE, Lachin JM *et al.* Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334
6. Perkovic V, de Zeeuw D, Mahaffey KW *et al.* Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018; 6: 691–704
7. Mosenzon O, Wiviott SD, Cahn A *et al.* Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol* 2019; 7: 606–617
8. 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
9. Cherney DZ, Kanbay M, Lovshin JA. Renal physiology of glucose handling and therapeutic implications. *Nephrol Dial Transplant* 2020; 35 (Suppl 1): i3–i12
10. Górriz JL, Navarro-González JF, Ortiz A *et al.* Sodium-glucose cotransporter 2 inhibition: towards an indication to treat diabetic kidney disease. *Nephrol Dial Transplant* 2020; 35 (Suppl 1): i13–i23
11. Shivakumar O, Sattar N, Wheeler DC. Sodium-glucose cotransporter 2 inhibitor effects on cardiovascular outcomes in chronic kidney disease. *Nephrol Dial Transplant* 2020; 35 (Suppl 1): i43–i47
12. van Raalte DH, Bjornstad P. Role of sodium-glucose cotransporter 2 inhibition to mitigate diabetic kidney disease risk in type 1 diabetes. *Nephrol Dial Transplant* 2020; 35 (Suppl 1): i24–i32
13. van Raalte DH, Bjornstad P, Persson F *et al.* The impact of sotagliflozin on renal function, albuminuria, blood pressure, and hematocrit in adults with type 1 diabetes. *Diabetes Care* 2019; 42: 1921–1929
14. Dekkers CCJ, Gansevoort RT. Sodium-glucose cotransporter 2 inhibitors: extending the indication to non-diabetic kidney disease? *Nephrol Dial Transplant* 2020; 35 (Suppl 1): i33–i42
15. Bays HE, Weinstein R, Law G *et al.* Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. *Obesity (Silver Spring)* 2014; 22: 1042–1049
16. Rajasekeran H, Reich HN, Hladunewich MA *et al.* Dapagliflozin in focal segmental glomerulosclerosis: a combined human-rodent pilot study. *Am J Physiol Renal Physiol* 2018; 314: F412–F422
17. Heerspink HJL, Stefansson BV, Chertow GM *et al.* Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. *Nephrol Dial Transplant* 2020; 35: 274–282
18. Neuen BL, Jardine MJ, Perkovic V. Sodium-glucose cotransporter 2 inhibition: which patient with chronic kidney disease should be treated in the future? *Nephrol Dial Transplant* 2020; 35 (Suppl 1): i48–i55

Received: 4.12.2019; Editorial decision: 3.1.2020