# Sodium–glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering?

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**The proximal tubule's sodium–glucose linked transporter-2 (SGLT2) accounts for the vast majority of glucose reabsorption by the kidney. Its selective inhibition, accordingly, leads to substantial glycosuria, lowering blood glucose, and facilitating weight loss in individuals with diabetes. During the past year, two SGLT2 inhibitors, canagliflozin and dapagliflozin, have been approved for the treatment of type 2 diabetes. Beyond their anti-hyperglycemic properties, however, this new class of drugs has several other attributes that provide a theoretical basis for kidney protection. Like agents that block the renin–angiotensin system, SGLT2 inhibitors also reduce single-nephron glomerular filtration rate (SNGFR) in the chronically diseased kidney, though by quite different mechanisms. Additional potentially beneficial effects of SGLT2 inhibition include modest reductions in blood pressure and plasma uric acid. Finally, cell culture studies indicate that glucose uptake from the tubular lumen, as well as from the basolateral compartment, can contribute to proximal tubular production of extracellular matrix proteins. Whether such attributes will translate into reducing the progression of chronic kidney disease will require the undertaking of long-term, dedicated studies.**

*Kidney International* (2014) **86,** 693–700; doi:10.1038/ki.2013.451; published online 20 November 2013

KEYWORDS: blood pressure; glomerular filtration rate; proximal tubule; sodium–glucose linked cotransporter-2; tubuloglomerular feedback; uric acid

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**Received 19 July 2013; revised 9 September 2013; accepted 12 September 2013; published online 20 November 2013**

Pharmacovigilance is a necessary part of medical practice. Serious adverse effects, discovered largely only after many years of prescribing abound in the recent past with drugs, such as rofecoxib, rosiglitazone, and rimonobant, either withdrawn from the market or receiving a warning label. Accordingly, even after a drug has passed the rigorous review of regulatory authorities, it behoves us to continue a high level of scrutiny. However, physicians have also become accustomed to the converse scenario whereby unexpected benefits surface when drugs are used for conditions other than their primary indication. Aspirin, for instance, is used as an antiplatelet agent as well as an antipyretic and analgesic, the phosphodiesterase type 5 inhibitors attenuate pulmonary hypertension in addition to improving erectile function and angiotensin-converting enzyme (ACE) inhibitors slow the decline in kidney function, beyond their ability to lower blood pressure. With these more positive considerations of drug effects in mind, here, relying on both published articles and submissions to the Food and Drug Administration and European Medicines Agency, we explore the theoretical basis for renoprotection as a possible, unintended consequence of the sodium–glucose liked transporter 2 (SGLT2) inhibitors. Indeed, in some respects, this latest class of anti-hyperglycemic therapy exerts additional effects that are somewhat reminiscent of those associated with blockade of the renin–angiotensin system (RAS).

To date, two SGLT2 inhibitors, dapagliflozin and canagliflozin, have been approved for patient use. These compounds are highly selective for SGLT2 versus SGLT1 with ratios of $>1200$ and $>250$ for dapagliflozin and canagliflozin, respectively.[1] Although some earlier low stringency northern blot and PCR-based studies had suggested that SGLT2 expression was widespread, these findings have not been replicated by others or not seen under high stringency conditions.[2–5] Indeed, most recent studies indicate that SGLT2 is expressed almost exclusively in the kidney cortex at levels that are several 100-fold higher than the next most abundant sites, the renal medulla and ileum.[4,5] Although not addressed here, those interested in these and more general aspects of SGLT2 physiology, pharmacology and the balance between safety and efficacy of SGLT2 inhibitors in diabetes are referred to the many excellent reviews on such subjects.[6–8]

## GLOMERULAR HEMODYNAMICS: BACK TO THE FUTURE

### Intraglomerular hypertension

Three decades ago, the hyperfiltration theory revolutionized our understanding of progressive kidney disease. On the basis of their experimental findings in rodents in conjunction with observational studies in humans, Brenner[9] explained that regardless of the initiating insult, the compensatory increase in glomerular filtration rate (GFR) among remaining nephrons was ultimately maladaptive. This notion was grounded, in part, on studies in the remnant kidney model where an increase in single-nephron GFR (↑SNGFR) arose from a proportionally greater decrease in afferent versus efferent arteriolar resistance. The increase in intraglomerular pressure ($P_{GC}$) engendered by these hemodynamic changes, led in turn, to ongoing barotrauma with glomerular hyalinosis, sclerosis, proteinuria, and eventually reduction in filtration. Akin to the remnant kidney model, rats with streptozotocin-induced diabetes were noted to also display relative afferent arteriolar dilatation and glomerular hyperfiltration.[10]

The hemodynamic theory not only provided a pathophysiological basis for the progressive nature of renal dysfunction associated with disease and ageing but also offered insight into therapeutic strategies whereby reduction in $P_{GC}$, either by reducing tone in the efferent arteriole or increasing it in the afferent arteriole, should slow the inexorable decline in GFR.

### Reducing efferent arteriolar tone: renoprotection by RAS blockade

As angiotensin II preferentially constricts the efferent arteriole,[11] reducing its production with an ACE inhibitor or blocking its receptor with an angiotensin receptor blocker should lower $P_{GC}$ and attenuate disease progression. Following proof-of-concept studies in experimental studies,[12,13] pivotal clinical trials in both diabetic[14–16] and non-diabetic kidney disease[17] subsequently placed blockade of the RAS at the cornerstone of renal medicine.

Despite the robust evidence base for the renoprotective effects of ACE inhibition, initial usage was less than expected, reflecting in part, concern over the acute elevation in serum creatinine that followed the commencement of therapy.[18] Consistent with the attendant reductions in intraglomerular pressure and blood pressure, variable increases in serum creatinine were noted following the initiation of ACE inhibitor therapy, affecting those with pre-existing renal disease to a greater extent than those with normal kidney function. For instance, although subjects with normal kidney function might expect a 10% increase, those with a baseline creatinine of ~130 μmol/l could experience an increase of up to 25% in the first month following initiation of therapy. These early rises in serum creatinine were not only reversible but associated with long-term renal protection.[18] Indeed, a greater initial rise in serum creatinine, seemed to portend a slower subsequent decline in kidney function.[19] As such, an early fall in GFR that is followed subsequently by a slowing in its rate of decline is an expected finding in a chronic kidney disease (CKD) patient started on an ACE inhibitor or angiotensin receptor blocker.

### Increasing afferent arteriolar tone: SGLT2 and tubuloglomerular feedback

Glomerular filtration and electrolyte reabsorption are finely coordinated within individual nephrons whereby minute-to-minute changes in the flow and composition of urine are sensed by the macula densa through the action of the $Na^+/K^+/2Cl^-$ cotransporter, located on its luminal surface.[20] This region of specialized epithelium, located between the distal loop of Henle and the early distal convoluted tubule, lies in close proximity to the afferent and efferent arterioles of the same nephron. This conjunction of nephron components, constituting the juxtaglomerular apparatus, responds to increased delivery of NaCl with afferent arteriolar constriction and relative efferent arteriolar relaxation, thereby reducing both SNGFR and $P_{GC}$.[21] In diabetes, the reverse applies. Here, increased proximal tubular glucose reabsorption is accompanied by augmented SGLT1/2-mediated $Na^+$ reabsorption, reducing the NaCl concentration at the macula densa, and increasing GFR via tubuloglomerular feedback, as shown in Figure 1. Meticulously conducted, micropuncture studies by Vallon *et al*[22] have recently provided proof-of-principle for this phenomenon in diabetic $SGLT2^{-/-}$ mice. Similar findings have also been reported in diabetic rats where administration of the SGLT2 inhibitor, dapagliflozin led to an acute, threefold increase in Na excretion. Notably, this natriuresis did not persist with chronic SGLT2 blockade, suggesting that an adaptive increase in Na reabsorption distal to the juxtaglomerular apparatus occurs in the long-term setting.

Without affecting systolic blood pressure, acute SGLT2 blockade leads to an approximate 20% fall in GFR. Unlike the situation for Na excretion, however, the reduction in GFR (~15%) persists with chronic SGLT2 blockade.[23] These changes are reflected at the single-nephron level with micropuncture studies revealing parallel reductions in SNGFR following both acute (33%) and chronic (16%) SGLT2 inhibition.[23] Finally, consistent with a role for tubuloglomerular feedback in mediating these changes, at least in part, SGLT2 administration was found to increase the chloride concentration in the early distal tubule by 70% and 35% in the acute and chronic settings, respectively.[23]

### GFR in human studies

Evaluating the impact of intervention on kidney function, particularly in the CKD setting has been an integral part of the safety studies for SGLT2 blockers. Although changes in estimated GFR (eGFR) between baseline and study end are routinely examined, closer scrutiny of the time course suggests that the data can be resolved into acute and chronic components.

In a 6-month study of 269 patients with type 2 diabetes and eGFR between 30 and 50 ml/min per 1.73 $m^2$, administration of canagliflozin 100 mg and 300 mg was associated