SGLT-2 inhibition in patients with kidney disease

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Abstract

Accustomed to managing diabetes with agents that mostly act by modulating the secretion and actions of insulin, with the advent of sodium-glucose linked transporter-2 (SGLT-2) inhibitors, physicians are now aware that the kidney also needs to be considered in the spectrum of action of anti-hyperglycaemic agents. Though familiar with the need for dose adjustment when prescribing many of our current anti-hyperglycaemic drugs in the setting of kidney dysfunction, with the SGLT-2 inhibitors pharmacodynamic as well as pharmacokinetic aspects also need to be considered. Finally, through their ability to reduce intraglomerular pressure, systemic blood pressure and plasma uric acid concentration, the SGLT-2 inhibitors offers the possibility of kidney protection. An hypothesis that will need to be tested with long term studies that address changes in the kidney beyond albuminuria, assessing the rate of decline in glomerular filtration rate and 'hard' kidney-related endpoints such as the need for renal replacement therapy (dialysis, transplantation) will be important in this setting.

Keywords: SGLT-2 inhibitors; Kidney; Renal failure; Diabetes; Kidney disease

1. Physiological basis of SGLT-2-mediated glucose lowering in CKD

Glucose in plasma is filtered freely at the glomerulus but is subsequently completely reabsorbed in the proximal tubule until its maximal reabsorptive capacity (Tm\text{G}) is exceeded. Accordingly, urine glucose excretion and therefore plasma glucose lowering, may be viewed as a function of three variables: plasma glucose (PG), glomerular filtration rate (GFR) and Tm\text{G}, that can be expressed mathematically as [1]:

$$\text{UGEx} \propto (\text{PG} \times \text{GFR}) – \text{Tm}_\text{G}$$

1.1. Plasma glucose

The above relationship explains why glucosuria only develops when the plasma glucose exceeds 10-12 mmol/l (renal threshold for glucose excretion, RT\text{G}) and the proportionality between urinary glucose excretion and plasma glucose. Though both fasting and two-hour postprandial glucose concentrations are well below this threshold in healthy subjects, glucose concentrations may transiently rise above it shortly after a meal such that a small amount of glucose (3.4 mmol/day, 0.50-0.65 mmol/l) can be detected in 24-hour urinary collections [1]. Indeed, once RT\text{G} has been exceeded, the relationship between plasma glucose and urinary glucose excretion allows the approximation of plasma glucose by the measurement of urinary glucose concentration. Indeed, this relationship provided the basis for the home assessment of glycaemic control, a generation ago.

1.2. Maximal reabsorptive capacity for glucose (Tm\text{G})

The Tm\text{G} in a healthy subject is around 3000 mmol/day with a reabsorptive capacity of approximately 2 mmol/min [1]. In individuals with diabetes, however, Tm\text{G} is increased by approximately 18%, presumably as a consequence of evolutionary conserved mechanisms for avoiding insensible nutrient loss [2,3].

Patients with familial renal glucosuria that mostly arise from mutation in the SLC5A2 gene that codes for SGLT-2, on the other hand, generally have a reduced Tm\text{G} and lowered RT\text{G} with glucosuria that ranges from <1 to >150g/1.73m²/day [4].
Pharmacological inhibition of SGLT-2 similarly lowers RT\textsubscript{\text{G}} and increases urinary glucose excretion. For instance, in a study of 28 subjects with type 2 diabetes, canagliflozin 100 mg shifted the RT\textsubscript{\text{G}} from 12.0±1.3 mmol/l down to 2.7±1.1 mmol/l with urinary glucose excretion that was commensurate with plasma glucose concentrations [5].

1.3. Glomerular filtration rate

The relationship between plasma glucose, Tm\textsubscript{\text{G}} and GFR also explains why patients who hyperfilter, as during pregnancy, may have glucosuria, despite normoglycaemia and an unchanged Tm\textsubscript{\text{G}}. The magnitude of glucosuria in this setting is usually quite modest. However, the development of pregnancy-induced hyperfiltration on a background of familial renal glucosuria can lead to massive increases in urinary glucose excretion with osmotic diuresis and volume depletion despite normoglycaemia [6]. Conversely, when GFR is reduced, less glucose enters the proximal tubule so that the effects of inhibiting its reabsorption pharmacologically will be proportionally reduced.

Notably, patients who have undergone uninephrectomy may also develop normoglycaemic glucosuria [1]. While GFR is not elevated in such individuals, the compensatory hypertrophy of remaining nephrons that occurs in the setting of a single kidney. This leads to an increase in GFR in individual nephrons (single nephron GFR, SNGFR) so that Tm\textsubscript{\text{G}} is exceeded.

2. SGLT-2 inhibitor efficacy in CKD

Given the interplay between (plasma glucose \times GFR) and Tm\textsubscript{\text{G}}, one would expect that the greatest glucose excretion and thus reduction in HbA1c to occur in patients whose GFR and plasma glucose are both high. Accordingly, given the age-dependent decline in GFR, young patients with diabetes would be anticipated to respond well to an SGLT-2 inhibitor. This may be particularly so, the need for insulin notwithstanding, in the setting of recently diagnosed type 1 diabetes where a supranormal GFR (glomerular hyperfiltration) is frequently seen. Conversely, the older patient or those with chronic kidney disease (CKD) would be expected to respond less favourably, especially if glycaemic control is already reasonably good.

Studies examining the efficacy of SGLT-2 inhibition in patients with diabetes have been reported for a number of SGLT-2 inhibitors including canagliflozin [7] dapagliflozin [8], empagliflozin [9] and ipragliflozin [10]. Among patients with type 2 diabetes and moderate renal impairment (CKD Stage 3, eGFR: 30-60ml/min/1.73m\textsuperscript{2}), SGLT-2 inhibition led, in general, to a 0.3 to 0.45% fall in HbA1c when compared with baseline measurements. Though modest, these reductions in HbA1c reached statistical significance when compared with placebo for both canagliflozin and empagliflozin but not for dapagliflozin where the placebo group experienced an uncustomarily large, 0.32% reduction in HbA1c. In addition to CKD Stage 3 patients, the empagliflozin study also examined those with Stage 2 (eGFR: 60-90ml/min/1.73m\textsuperscript{2}) and Stage 4 (eGFR: 15-30ml/min/1.73m\textsuperscript{2}) disease, reporting the expected greater reduction in HbA1c in Stage 2 when compared with Stage 3 disease while also noting the absence of any reduction in HbA1c in Stage 4 [9].

While comparatively smaller and with different objectives, the study of ipragliflozin in patients with CKD provides us with some important insights. This study quantified the magnitude of glucosuria in subjects with normal kidney function as well as those with CKD Stages 2, 3 and 4, providing numerical substance to the relationship between urinary glucose excretion, GFR and plasma glucose. Here, the investigators noted that not only was ipragliflozin-induced glucosuria directly related to eGFR and plasma glucose, as anticipated by the relationship UGEx = (PG \times GFR) – Tm\textsubscript{\text{G}}, but that its quantity could also be predicted. For each 20ml/min/1.73m\textsuperscript{2} decrement in GFR, the study reported a 15g/day fall in glucosuria while a 0.5mmol/L increment in plasma glucose led to a 7g/day increase [10].

3. Intraglomerular pressure, tubuloglomerular feedback and the potential for renoprotection

Changes in distal tubule delivery of Na, K and Cl are sensed by the specialised cells of the macula densa that, in turn, affect SNGFR by modulating vascular resistance, primarily in the preglomerular vessels. Through this mechanism, increased Na delivery, as occurs in the setting of SGLT-2 inhibition, leads to increased efferent arteriolar resistance, reducing intraglomerular pressure and thereby GFR. These effects, reflecting tubuloglomerular feedback (TGF), are thought to underlie the acute reduction in GFR seen with the initiation of SGLT-2 inhibitors (Fig. 1). Since intraglomerular hypertension is thought to be a key factor in the pathogenesis of many forms of CKD, including diabetic nephropathy, strategies that reduce intraglomerular pressure may be renoprotective. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers, for instance, decrease intraglomerular pressure by reducing efferent arteriolar tone and while this might not explain the entirety of their beneficial effects in kidney disease, it is viewed as a fundamental aspect of it. Since, SGLT-2 inhibitors will also lower intraglomerular pressure, though instead by increasing efferent arteriolar resistance, a similar renoprotective effect might be anticipated. Indeed, following the acute decline in GFR that follows initiation of an SGLT-2 inhibitor in patients with CKD, one gets the impression from some studies, that the rate of fall of GFR stabilises in contrast to a progressive fall among placebo-treated patients (Fig. 2). This observation raises the tantalising possibility that this new class of anti-hyperglycaemic agent might also be renoprotective, as detailed in a recent review [11]. Notably, however, trials that address this issue specifically will need to be conducted. Furthermore, the fact that blockers of the renin-angiotensin system and SGLT-2 inhibitors both lower intraglomerular pressure and thereby acutely reduce early GFR, means that caution should be exercised when adding one or the other and that it would seem imprudent to initiate both simultaneously [12].
3.1. Albuminuria

Based mostly on observational data and on drugs that block the renin-angiotensin system when used as single agents in standard doses, the impact of a reduction in albuminuria on kidney and cardiovascular outcomes in other settings is highly controversial. Moreover, while the effects of SGLT-2 inhibition on albuminuria has been examined in several studies [8,9,13], it is important to remember that the conducted studies do not directly compare the different SGLT-2 inhibitors and have different designs, study populations and placebo effects. Accordingly, no inferences of comparative efficacy should be drawn. With these caveats in mind, changes in albuminuria category (normo-, micro- and macroalbuminuria) with SGLT-2 inhibitors, a so-called ‘shift analysis’ show, in general, a trend to reduced progression (normo- to micro-, micro to macro- or normo- to macroalbuminuria) and greater regression (micro- to normo- or macro- to normoalbuminuria) when these agents are used in CKD Stage 3 patients. Table 1. Of far greater importance, from a kidney perspective, is whether SGLT-2 inhibition may prevent GFR loss.

3.2. The CREDENCE Trial

The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE, clinicaltrials.gov identifier: NCT02065791), sponsored by Janssen Research & Development and conducted in collaboration with the George Institute began in February 2014. As described on the ClinicalTrials.gov website, CREDENCE is a double blind, placebo controlled, parallel group, multicentre study examining the renal and vascular effects of canagliflozin 100 mg. The study will recruit type 2 diabetic individuals...
with CKD Stage 2-3 (eGFR: 30-90ml/min/1.73m²) and macroalbuminuria (urinary albumin: creatinine >300 mg/g) on maximal recommended doses of an ACE inhibitor or ARB. Following a pretreatment phase of several weeks, participants will enter a double-blind treatment phase of up to 66 months. Expected to be completed in early 2019, the study’s primary endpoint will be a cardio-renal composite of end-stage kidney disease, doubling of serum creatinine and cardiovascular death. Subjects randomised to receive canagliflozin would be expected to not only have better glycaemic control but also lower blood pressures and reductions in serum uric acid [11]. Since each of these has been associated with better kidney prognoses their impact vis à vis changes in intraglomerular pressure my be difficult to unravel [14-16]. Regardless of the precise mechanism of action, however, any new agent that slows the rate of GFR decline will be a most welcome addition to the renoprotective armamentarium.

### 3.3. EMPA-REG Outcome

The EMPA-REG Outcome trial (clinicaltrials.gov identifier: NCT01131676) is recruiting ~7000 patients with type 2 diabetes and a history of cardiovascular disease in a multicentre, randomised trial that compares empagliflozin (10 and 25 mg) with placebo [17]. Although its primary outcome is the time to first occurrence of a major adverse cardiovascular events (MACE) of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, EMPA-REG Outcome will also examine microvascular events as a pre-defined secondary outcome that in addition to retinal and albuminuria-related events will include doubling of serum creatinine with eGFR <45ml/min/1.73m², initiation of renal replacement therapy (dialysis or transplantation) or death due to kidney disease.

### 4. Dosage, administration and adverse events in CKD

In individuals with normal or mildly impaired kidney function (>60ml/min/1.73 m²), the dose of canagliflozin may be increased from the starting dose of 100 mg up to the maximal recommended dose of 300 mg, providing the drug is being well-tolerated and additional glycaemic control is required. In patients with CKD Stage 3a (45-60ml/min/1.73m²), however, the daily dose of canagliflozin should not exceed 100 mg and in those whose eGFR is <45ml/min/1.73 m², the drug should not be initiated. For dapagliflozin, the 5 mg starting dose may be doubled in patients with >60ml/min/1.73 m² but should not be initiated if eGFR is lower and for empagliflozin, the 10 mg starting dose may be increased to 25 mg if eGFR is >45ml/min/1.73 m² but should not be started if lower than this.

### 4.1. Volume depletion

Owing to their ability to initiate an osmotic diuresis, SGLT-2 inhibitors lead to intravascular volume contraction, the consequence of which will include an increase in the frequency of adverse events such as orthostatic and symptomatic hypotension, dehydration and syncope [18-20]. The attendant reduction in kidney perfusion may, accordingly, accentuate the acute reduction in eGFR that result from changes in TGF. As detailed in the prescribing information, kidney function should be assessed prior to starting patients on an SGLT-2 inhibitor and measured periodically thereafter. Those particularly prone to develop hypotension or worsening kidney function with an SGLT-2 inhibitor include the elderly, patients with <60ml/min/1.73 m², those with low starting blood pressures and patients who are receiving concomitant therapy with a diuretic (particularly a loop diuretic) and/or an agent that blocks the renin-angiotensin system (RAS) [18]. Notably, the reduction in eGFR with SGLT-2 inhibitor is mostly an acute phenomenon. Among study subjects with baseline eGFR 30-50ml/min/1.73 m², 6.9%, 18% and 22.5% experienced a significant, ≥30% reduction in GFR compared with baseline, after treatment with placebo, 100 mg and 300 mg canagliflozin, respectively [18]. By the end of the treatment period, however, the proportions with significant eGFR declines had diminished substantially to 4.6% for placebo, 3.4% for canagliflozin 100 mg and 3.4% for canagliflozin 300 mg [18]. Notably, the combination of RAS blockade and reduction in eGFR may render patients with moderate renal impairment more susceptible to hyperkalaemia so that periodic monitoring of potassium is indicated for predisposed patients treated with canagliflozin [18].

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