Renal effects of dapagliflozin in patients with type 2 diabetes

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Abstract: Diabetes mellitus was originally conceived as a renal disorder. In the last decade, however, there has been renewed interest in role of the kidney in the development and maintenance of high glucose levels. This has led to the development of novel agents to inhibit sodium glucose transporter-2 ($SGLT_2$) as a means to better control glucose levels and at the same time augment calorie wasting and lower insulin, blood pressure and uric acid levels. Such actions, indirectly, may also have benefits for the prevention of diabetic complications including renal disease. However, there are also data to support the potential for direct renoprotective actions arising from inhibition of $SGLT_2$, including actions to attenuate diabetes-associated hyperfiltration and tubular hypertrophy, as well as reduce the tubular toxicity of glucose. Some studies have demonstrated significant reductions in albumin excretion in various experimental models, independent of its effects on blood pressure or glucose control. Although promising, such actions remain to be established by comprehensive clinical trials with a renal focus, many of which are currently in progress. This article reviews the clinical and experimental data pertaining to the renal effects of $SGLT_2$ inhibition with a particular focus on dapaglifozin.

Keywords: dapagliflozin, diabetes, diabetic nephropathy, hyperfiltration, $SGLT_2$, $SGLT_2$ inhibition

Background

Diabetes mellitus was originally conceived as a renal disorder, as the 'wasting of flesh into urine'. The discovery of insulin changed the focus of diabetes management to the pancreas. In the last decade, however, there has been renewed interest in role of the kidney in the development and maintenance of high glucose levels [Gerich and Bastien, 2011; Tahrani and Barnett, 2012]. In healthy adults, approximately 180 litres of plasma containing 5.5 mM glucose is filtered every day through the kidneys. This means that approximately 180 grams of glucose are filtered daily through the glomeruli and lost into the primary urine. Almost of this filtered load (~ 99.9%) is then actively reabsorbed by sodium-coupled transport across the brush border membrane of the proximal tubule and then returned to the circulation by glucose transporters [Gerich and Bastien, 2011; Tahrani and Barnett, 2012]. More than 90% of the glucose that is initially filtered is reabsorbed by a low affinity, high capacity system controlled by sodium glucose transporter-2 ($SGLT_2$) in the early convoluted segment of the proximal tubule (s1) [Gerich and Bastien, 2011]. Reabsorption of almost all remaining filtered glucose is performed by sodium glucose transporter-1 ($SGLT_1$), a low affinity, high capacity transporter further down in the straight segment of the descending proximal tubule (s3) [Gerich and Bastien, 2011; Tahrani and Barnett, 2012]. So efficient is this glucose reabsorption pathway that, under normal circumstances, less than 0.1 g will ever find its way into the urine of nondiabetic individuals [Gerich and Bastien, 2011; Kim and Babu, 2012; Tahrani and Barnett, 2012; Whaley *et al.* 2012].

Yet, however efficient the renal reabsorption of glucose is, its capacity is limited. If plasma glucose levels rise, as in patients with diabetes, the filtered load may exceed the capacity for glucose

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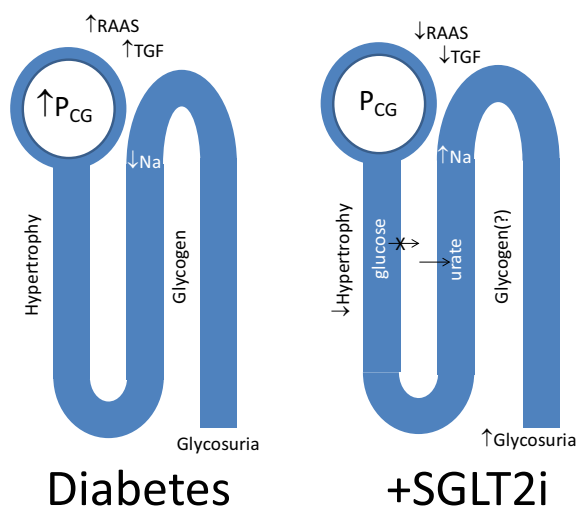**merlin.thomas@bakeridi. edu.au**

Figure 1. Direct effects of sodium glucose transporter-2 ($SGLT_2$) inhibition in the kidney. P_{CG}, intraglomerular capillary pressure; RAAS, renin–angiotensin aldosterone system; SGLT2i, sodium glucose transporter-2 inhibitor; TGF, tubuloglomerular feedback.

reabsorption. At which time, glucose (and the water held with it) will spill over into the urine. This produces the classical symptoms of polyuria, frequency and polydipsia that characterizes uncontrolled hyperglycaemia. The threshold at which elevated blood glucose levels results in glycosuria is 10–11 mM on average, but this can vary significantly from person to person. In some people, blood glucose levels greater than 7 mM may produce glycosuria, especially in children and pregnant women. In others, spillover of glucose into the urine may not occur until much higher plasma glucose levels up to 15 mM. This is more often the case in individuals with diabetes where, perhaps as a way to conserve energy, the glucose reabsorption capacity from the proximal tubule is upregulated. This is partly due to tubular hypertrophy and increased of Na/K/ATPase activity in the diabetic kidney. In addition, the expression and activity of apical $SGLT_2$ and basolateral glucose transporter proteins are also increased.

These changes act to increase the threshold for glycosuria and retain extra glucose, paradoxically at a time when glucose levels are already elevated. Moreover, all the extra glucose retained by the kidneys means extra insulin needs to made (or given) to keep the plasma glucose levels under control. And instead of losing the calories attributable to glucose into the urine, (glucose) energy is retained, chiefly as body fat. These changes in renal glucose reabsorption are considered to

significantly contribute to the maintenance of hyperglycaemia in patients with diabetes [Defronzo *et al.* 2012] and provide a strong rationale for inhibition of $SGLT_2$ as a means to better control glucose levels, and at the same time augment calorie wasting and lower blood pressure. Such actions may also have benefits for the prevention of diabetic complications including renal disease. But in addition, there are data to support the potential for direct renoprotective actions arising from inhibition of $SGLT_2$ (Figure 1) [Gilbert, 2013]. This article reviews the clinical and experimental data pertaining to the renal effects of $SGLT_2$ inhibition with a particular focus on dapagliflozin.

What does dapagliflozin do to the kidney?

The molecular actions of dapagliflozin

Dapagliflozin is a potent selective reversible inhibitor of $SGLT_2$ in the kidney. The selectivity of dapagliflozin for $SGLT_2$ is at least 1200-fold greater than that for $SGLT_1$ [Riser Taylor and Harris, 2013]. $SGLT_2$ is exclusively expressed in the proximal tubule of the kidney [Chen *et al.* 2010]. In contrast, $SGLT_1$, with which $SGLT_2$ shares 59% identity, is also expressed in the brain, the heart, and in the intestinal epithelium, where it is involved in water and glucose uptake. Indeed, it has been estimated that almost half the daily uptake of water from the small intestine occurs *via* $SGLT_1$ dependent pathways [Meinild *et al.* 1998]. Moreover, $SGLT_1$ also serves as the intestinal glucose sensor for glucose-induced incretin secretion [Moriya *et al.* 2009], a key component in glycaemic control. These characteristics potentially make $SGLT_1$ a less acceptable clinical target, and selectivity for $SGLT_2$ a desirable property.

Inhibition of $SGLT_2$ following treatment with dapagliflozin reduces the capacity for tubular glucose reabsorption by approximately 30–50%. Why a greater level of inhibition is not achieved *in vivo*, despite being a potent and comprehensive inhibitor *in vitro* is unclear. It may be that pharmacokinetics at the proximal tubule, including shuttling of transporters, means that at any one time most $SGLT_2$ are not occupied [Abdul-Ghani *et al.* 2013]. In addition the upregulation of $SGLT_1$ expression and activity also acts to reduce the excretion of filtered glucose following inhibition of $SGLT_2$ [Rieg *et al.* 2014]. Nonetheless, this level of inhibition is sufficient to lower the

threshold for spillover and result in urinary glucose wasting in both healthy volunteers and patients with diabetes. However, total urinary glucose losses are proportional to the ambient plasma glucose level, so that absolute losses are greater in patients with diabetes and especially those with poor control. In the short term, on average, a 10 mg daily dose of dapagliflozin will increase the amount of glucose excreted in the urine of a patients with type 2 diabetes by 50–80 g per day. However, in the long term it may be less, as improvements in glycaemic control leading to reduction in plasma glucose act to attenuate glycosuria.

There are no clear data that dapagliflozin has actions beyond inhibition of $SGLT_2$ and the induction of glycosuria. Its parent compound, the plant-derived dihydrochalcone phlorizin has been associated with actions on other targets including histone deacetylase, the sodium iodide symporter, as well as antioxidant activities [Ehrenkranz, 2009]. However, these may reflect its other actions on $SGLT_1$ or other receptors.

The renal phenotype of benign familial glycosuria

To obtain some understanding of the long-term renal effects of inhibition of $SGLT_2$, it is possible to extrapolate from the experience of patients with familial glycosuria. The most common genetic forms involve a mutation in the *SLCA2* gene that reduces the expression and/or activity of $SGLT_2$. In type O glycosuria, the reabsorption of glucose is severely reduced or absent, meaning that otherwise normoglycaemic individuals can waste over a 100 g of glucose every day. Despite this, familial glycosuria is a generally benign condition, although dehydration and ketosis may sometimes develop during starvation or pregnancy. Such data suggest that long-term inhibition of $SGLT_2$ by selective pharmacological, at the very least, may represent a safe strategy for the management of patients with type 2 diabetes.

The renal effects of glycosuria

The presence of glucose in the urine beyond the straight segment of the descending proximal tubule has a number of effects on the kidney function. The most obvious is that urine flow is increased as water is held in the tubular lumen due to osmotic effects of unabsorbed glucose. This ultimately results in an increased urine output of about 300–400 ml/day. Glycosuria also results in the rapid accumulation of intracellular glycogen granules in the distal tubules, including the thick ascending limbs in the cortex and the outer stripe of the outer medulla (so-called Armanni–Ebstein lesion [Holck and Rasch, 1993]). But while glycogen accumulation may be associated with tubular apoptosis, the pathological significance of intracellular glycogen accumulation remains to be established. Certainly, the Fanconi–Bickel syndrome, a primary tubular disorder due to mutation of the GLUT-2 transporter, is associated with tubular glycogen accumulation as well as progressive diabetic-like changes in the kidney [Berry *et al.* 1995]. Hyperglycaemia also results in the rapid induction of tubular hypertrophy. Interestingly, in the absence of hyperglycaemia, the lack of $SGLT_2$ in mice is associated with a modest increase in kidney weight [Vallon *et al.* 2013]. This possibly reflects the impact of increased distal sodium and glucose delivery and storage as glycogen. Interestingly, although hyperglycaemia is associated with a compensatory increase in glomerular filtration rate (GFR) (discussed below), GFR is not affected genetic deletion or inhibition of $SGLT_2$ in nondiabetic mice [Vallon *et al.* 2013].

Indirect actions of $SGLT_2$ inhibitors on the kidney

Improving glucose control

By reducing the capacity for tubular glucose reabsorption and augmenting urinary glucose wasting, inhibition of $SGLT_2$ results in improved glycaemic control (including improvement in HbA_{1c}, fasting plasma glucose and postprandial glucose levels) in patients with type 2 diabetes [Wilding et al. 2009, 2010; List *et al.* 2009; Bailey *et al.* 2010; Ferrannini *et al.* 2010; Strojek *et al.* 2011]. There is consistent evidence across many trials that simply improving control, regardless of how it is achieved, is associated with a lower risk of new onset microalbuminuria and a lower rate of progression to overt nephropathy [Boussageon *et al.* 2011; Coca *et al.* 2012]. Moreover, these benefits appear to be sustained even if optimal glycaemic control is subsequently lost. In addition, both the United Kingdom Prospective Diabetes Study (UKPDS) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study reported a significant reduction in patients requiring renal replacement

therapy following intensification of glycaemic control. However, progressive declines in GFR and doubling of serum creatinine are not modified following improvement in glycaemic control [Boussageon *et al.* 2011].

Reduced insulin levels and improved insulin sensitivity

By promoting glycosuria and lowering the plasma glucose concentration in individuals with diabetes, insulin-stimulated tissue glucose disposal in skeletal muscle is substantially enhanced [Merovci *et al.* 2014]. This is probably due to the amelioration of glucotoxicity and reduction in body fat. In addition, reduction in glucose levels also leads to a compensatory fall in insulin secretion. Both result in a significant decline in insulin levels in patients with type 2 diabetes. This reduction may contribute to beneficial effects in many organs subject to the ravages of hyperinsulinism, including the kidneys [Han and Susztak, 2014]. It is now clear that insulin has direct actions in the microvasculature that influence the development and progression of microvascular disease. In type 2 diabetes, selective resistance to insulin mediated activation of the phosphatidylinositol-3-kinase signalling pathway leads to reduced synthesis of nitric oxide, impaired metabolic control and compensatory hyperinsulinemia. By contrast, insulin signalling *via* extracellular signal-regulated kinase dependent pathways is relatively unaffected in diabetes, tipping the balance of insulin's actions so that they favour abnormal vasoreactivity, angiogenesis, fibrogenesis and other pathways implicated in progressive renal disease [Groop *et al.* 2005].

Improving blood pressure control

In several studies, a mild naturetic effect has been observed following treatment with dapagliflozin associated with a reduction in systolic blood pressure of ~4 mmHg [Musso *et al.* 2012], although greater reductions may be observed in hypertensive patients. Although modest, these effects on blood pressure may contribute to the potential renoprotective actions of $SGLT_2$ inhibition. It is well established that improvements in blood pressure control in hypertensive patients are associated with improved renal outcomes. For example, in the UKPDS study of patients with type 2 diabetes, a reduction of blood pressure from 154 to 144 mm Hg was associated with a 30% reduction in microalbuminuria [UK Prospective Diabetes Study Group, 1998]. In the large ADVANCE study, treatment with the angiotensin-converting-enzyme (ACE) inhibitor, perindopril and the naturetic, indapamide (4 mg/1.25 mg daily) lowered the systolic blood pressure by ~7 mmHg and reduced new onset microalbuminuria by 26% compared with conventional antihypertensive treatment [Patel, 2007].

Worsening renal perfusion

Diabetic nephropathy is associated with impaired autoregulation of renal blood flow, meaning that drops in blood pressure will be more likely to be associated with reduction in renal perfusion in the diabetic kidney. This is particularly the case in patients with established renal impairment. In some cases, volume depletion and blood pressure lowering with dapagliflozin as well as other $SGLT_2$ inhibitors having been associated with acute-on-chronic renal impairment [Scheen, 2014]. For this reason, as well as the lack of glucose lowering efficacy in this setting, $SGLT_2$ inhibitors are not used in patients with moderate to severe renal impairment. Interestingly, effects on blood pressure and weight remain preserved in the setting of renal impairment [Kohan *et al.* 2014]. What may happen in patients with undiagnosed bilateral renal artery stenosis or very vulnerable renal perfusion at lesser degrees of renal impairment is unclear. Monitoring of renal function is currently justified when using renin–angiotensin system (RAS) blockers in patients with diabetes. Similar considerations may also be appropriate in selected (volume sensitive) patients receiving $SGLT_2$ inhibitors.

Improving weight control

In most clinical trials, dapagliflozin has been associated with modest reductions in body weight (approximately 2–3 kg over 12–24 weeks of therapy). This appears to be attributable to the loss of glucose energy, lower insulin levels and increased oxidative metabolism of fat [Cefalu, 2014]. Obesity is recognized as a risk factor for the development of kidney disease and may directly contribute to glomerulopathy [Kambham *et al.* 2001]. However, it is less clear whether weight loss prevents or attenuates the development of chronic kidney disease (CKD). In a meta-analysis of 5 controlled and 8 uncontrolled trials in which urinary protein was examined among obese or overweight adults, weight loss interventions including dietary restriction, exercise, anti-obesity medications and bariatric surgery

decreased urinary albumin excretion, such that each 1 kg weight loss was associated with 110 mg decrease in proteinuria and 1.1 mg decrease in microalbuminuria [Afshinnia *et al.* 2010]. The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study also reported that weight loss was associated with a reduction in urinary albumin excretion independent of blood pressure, albeit in the general population [Bello *et al.* 2007].

Lowering uric acid levels

Uric acid levels are elevated in many people with diabetes, in whom their levels are highly correlated with the risk of renal damage in diabetes [Hovind *et al.* 2011]. More than being a marker, it has been argued that uric acid and its metabolic effects may contribute to microvascular injury, especially in the kidney [Kang *et al.* 2002]. Consequently, recent attention has turned to whether lowering uric acid levels may have direct renoprotective effects in diabetes. In two small clinical studies, inhibition of xanthine oxidase with achieved a modest reduction in albuminuria [Goicoechea *et al.* 2010; Momeni *et al.* 2010]. Whether this is due to the antioxidant effects of inhibition of xanthine oxidase or secondary to lowering uric acid is unclear. A nonpurine alternative to allopurinol, febuxostat, is currently recruiting for a specific clinical trial in diabetic CKD [ClinicalTrials.gov identifier: NCT01350388]. Inhibition of $SGLT_2$ with dapagliflozin also has modest but significant effects on uric acid elimination and lowers plasma uric acid levels [Musso *et al.* 2012], which may contribute to its renal effects. Uricosuria following $SGLT_2$ inhibition is thought to be due to the actions of SLC2A9b which secretes urate back into the urine in exchange for luminal glucose [Cheeseman, 2009].

Potential direct renoprotective actions of $SGLT_2$ inhibitors?

Glomerular hyperfiltration

Uncontrolled hyperglycaemia is associated with an increase in GFR, driven by increases in glomerular capillary pressure and single-nephron GFR (SNGFR). According to the 'tubulocentric' hypothesis, this glomerular hyperfiltration is caused by increased proximal sodium reabsorption associated with tubular hypertrophy and augmented sodium glucose cotransport which leads to reduced distal sodium delivery and subsequent activation of tubuloglomerular feedback and a proportionally greater decrease in afferent *versus* efferent arteriolar resistance. Intraglomerular hypertension has been strongly implicated in the development and progression of diabetic kidney disease, and has been used to explain the role of nephron endowment in determining the predisposition for diabetic nephropathy as well as the renoprotective effects following from blockade of RAS. Similar arguments are now being used to explain the potential renoprotective actions of $SGLT_2$ inhibition. Certainly, genetic deletion or inhibition of $SGLT_2$ is able to attenuate hyperfiltration association with experimental diabetes [Vallon *et al.* 2013]. This is thought to be mediated by the reduction is proximal sodium absorption when $SGLT_2$ is inhibited, leading to increased distal sodium delivery to the macula densa, suppression of tubuloglomerular feedback pathways and a compensatory and persistent reduction in intraglomerular pressure [Thomson *et al.* 2012; Vallon *et al.* 2013].

Activation of RAS

One of the key pathways suppressed by increasing the distal delivery of sodium is the renin–angiotensin–aldosterone system (RAAS). RAAS activation is, at its most basic, a system for vascular homeostasis that promotes salt and water reabsorption in states of volume depletion. The less sodium that is delivered to the macula densa, which provides the signal of salt/volume depletion, the greater the activation of RAAS to retain salt. Equally, the more sodium that is delivered to the *macula densa*, the greater the suppression of RAAS to facilitate natriuresis. Consequently, natriuresis induced following inhibition of $SGLT_2$ should effectively inhibit the intrarenal RAAS. At the same time, volume depletion associated with osmotic diuresis will activate the systemic RAAS. In a recent study in patients with type 1 diabetes, aldosterone levels were increased following treatment with empagliflozin both in the presence and absence of hyperglycaemia [Cherney *et al.* 2014]. What the net effect is and how this may impact the RAAS dependent lesion of diabetic nephropathy is unclear. Certainly, RAAS activation is critical for diabetes associated hyperfiltration, tubular hypertrophy, fibrogenesis and many other pathogenic features of diabetic nephropathy. Indeed it is widely believed that the most potent means currently to inhibit kidney damage is inhibition of RAAS. Such changes may suggest that

a combination of RAAS blockade and $SGLT_2$ inhibition, as is the inadvertent norm in patients with type 2 diabetes, may have advantages for the diabetic kidney. Indeed in one experimental study, the combination of RAAS blockade with $SGLT_2$ inhibition was associated with additive renoprotective effects compared to either drug alone [Kojima *et al.* 2013].

Tubular hypertrophy

One of the earliest structural changes in the diabetic kidney is the hypertrophy and hyperplasia of the cortical tubuli and concomitant renal enlargement. Early studies have demonstrated that diabetic rats exhibit a 15% increase in whole kidney weight within 72 hours of exposure to hyperglycaemia [Osterby and Gundersen, 1975]. Although there are increases in glomerular and, in particular glomerular capillary volume, most of the increase in cortical mass may be accounted for by hypertrophy of the proximal tubule. Tubular epithelial cells in experimental diabetes undergo both proliferation and an increase in cellular size leading to overall increase in tubular length [Rasch and Dorup, 1997]. These abnormalities appear to be largely confined to the cortex and the outer stripe of the outer medulla, with little initial change in the inner stripe of the outer medulla or in the collecting ducts. It had been thought that tubular glucose reabsorption associated with hyperglycaemia is a dominant driving force, leading to increased expression of growth factors like transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF). In support, studies with the nonspecific SGLT inhibitor, phlorizin, and more recently with selective $SGLT_2$ inhibitor, empaglifozin, have shown that inhibition of glucose reabsorption was able to attenuate renal hypertrophy associated with experimental diabetes [Malatiali *et al.* 2008; Vallon *et al.* 2014]. In contrast, gene-targeted knockout of $SGLT_2$ did not prevent renal hypertrophy [Vallon *et al.* 2013]. However, this may be explained by the fact that knockout of $SGLT_2$ did not increase glycosuria in streptozotocin diabetes, as the profound reduction in plasma glucose in knockout mice completely offset their reduced threshold for urinary glucose retention [Vallon *et al.* 2013], meaning that the glucose load reaching the tubule was identical in wildtype and $SGLT_2$ knockout mice with diabetes. Whether hypertrophy is a mediator of long-term dysfunction, for example through accelerating the senescence of tubular cells, or is a

marker of the induction of pathogenic mediators like TGF-β, VEGF and IGF remains to be established. At least in experimental models, inhibition of tubular hypertrophy appears to have renoprotective effects [Thomson *et al.* 2001].

Tubulotoxicity of glucose

Exposure of proximal tubular cells to increased levels of glucose results in functional changes, including increased expression of pro-inflammatory cytokines, growth factors and profibrotic mediators, as well as increased formation of advanced glycation endproducts and reactive oxygen species. Each of these has been implicated in the development and progression of diabetic nephropathy. In so far as the induction of these pathways is mediated by glucose entry into the tubular cell and the major mechanism of entry is mediated by $SGLT_2$, inhibition of $SGLT_2$ would appear a useful way of reducing intracellular exposure to glucose in the proximal tubule and consequently its adverse actions in it. Indeed, in cell culture, inhibition of $SGLT_2$ may antagonize many of the deleterious actions of high glucose exposure [Panchapakesan *et al.* 2013]. Whether this is also the case *in vivo*, where effective $SGLT_2$ inhibition is far less complete, is unclear.

Nephrolithiasis

Renal stones occur in at least 1 in every 10 patients with diabetes. They remain a major cause of morbidity and can only be modestly reduced by lifestyle interventions. Although inhibition of $SGLT_2$ increases the excretion of uric acid (detailed above), the osmotic effect of glucose considerably dilutes the urine and increases urine flow rate making nidus formation less likely. Clinical studies with $SGLT_2$ inhibitors have not shown an increase in nephrolithiasis. Interestingly AstraZeneca holds a patent for preventing and treating kidney stones by inhibiting $SGLT_2$, although no data validating this strategy are currently available.

Summary

$SGLT_2$ inhibitors offer a complementary approach to reduce glucose levels by promoting urinary glucose wasting. This approach has the added advantage of losing calories that may be otherwise be deposited as fat and sodium that may otherwise support blood pressure elevation. This will have particular advantages in obese

Table 1. Actions of dapagliflozin with potential to directly or indirectly protect the kidney in diabetes.

Indirect effects	Direct effects
Improved glycaemic control	Prevent hyperfiltration
Reduced insulin levels	Renin angiotensin system (?)
Improved insulin sensitivity	Prevent tubular hypertrophy
Weight loss	Reduced tubular toxicity of glucose
Reduced blood pressure	Reduced nephrolithiasis?
Reduced uric acid	

and/or hypertensive patients. Beyond these actions, there are sound physiological reasons why inhibition of $SGLT_2$ may have beneficial effects in the kidney (Table 1), in particular by reducing hyperfiltration and renal hypertrophy in patients with incipient nephropathy. But while actions on hyperfiltration are clear, any direct effects of $SGLT_2$ inhibition on actual renal injury has been harder to detect. Gene-targeted knockout of $SGLT_2$, though it prevents hyperfiltration associated with diabetes, does not alter markers of renal injury, inflammation or fibrosis in streptozotocin diabetes [Vallon et al. 2013]. However, studies with $SGLT_2$ inhibitors have demonstrated significant reductions in albumin excretion in various experimental models independent of its effects on blood pressure or blood glucose control. Moreover, a recent clinical trial suggests the regression of albuminuria may be more common in patients treated with dapagliflozin than placebo, despite having little or no effect on glycaemic control [Kohan et al. 2014]. Although promising, such actions remain to be established by comprehensive clinical trials with a renal focus, many of which are currently in progress.

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Conflict of interest statement

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