Uric acid and the cardio-renal effects of SGLT2 inhibitors

Clifford J Bailey

Correspondence to:
Clifford J. Bailey,
School of Life and Health Sciences,
Aston University,
Birmingham B4 7ET, UK
c.j.bailey@aston.ac.uk
Tel +44 121 204 3898
Fax +44 121 204 4187

ABSTRACT

Sodium/glucose co-transporter-2 (SGLT2) inhibitors, which lower blood glucose by increasing renal glucose elimination have been shown to reduce the risk of adverse cardiovascular (CV) and renal
events in type 2 diabetes. This has been ascribed in part to haemodynamic changes, body weight reduction and several possible effects on myocardial, endothelial and tubulo-glomerular functions as well as reduced glucotoxicity. This review evaluates evidence that an effect of SGLT2 inhibitors to lower uric acid may also contribute to reduced cardio-renal risk.

Chronically raised circulating uric acid concentrations are associated with increased risk of hypertension, CV disease and chronic kidney disease (CKD). The extent to which uric acid contributes to these conditions either as a cause or aggravating factor remains unclear, but interventions that reduce urate production or increase urate excretion in hyperuricaemic patients have consistently improved cardio-renal prognoses. Uric acid concentrations are often raised in type 2 diabetes, contributing to the ‘metabolic syndrome’ of CV risk. Treating type 2 diabetes with an SGLT2 inhibitor increases uric acid excretion, reduces circulating uric acid and improves parameters of CV and renal function. This raises the possibility that the lowering of uric acid by SGLT2 inhibition may assist in reducing adverse CV events and slowing progression of CKD in type 2 diabetes. SGLT2 inhibition might also be useful in the treatment of gout and gouty arthritis, especially when co-existent with diabetes.

Introduction

Sodium/glucose co-transporter-2 (SGLT2) inhibitors lower blood glucose in an insulin-independent manner by reducing the reclamation of glucose from the renal filtrate [1]. The resulting glucosuria causes caloric loss which assists weight control and generates an osmotic diuresis that may contribute to a lowering of blood pressure [2]. Studies in type 2 diabetes indicate that treatment with an SGLT2 inhibitor can reduce the risk of some major adverse cardiovascular events (MACE) and slow or reverse aspects of deteriorating renal function: and these effects are at least partly independent of glucose-lowering efficacy [3]. How SGLT2 inhibitors exert these cardiovascular (CV) and renal effects is not entirely clear, and several potential mechanisms have been proposed. One possible contributing factor may be a reduction in the circulating concentration of uric acid. This review considers how SGLT2 inhibitors affect uric acid, and the implications for CV and renal function in type 2 diabetes and in hyperuricaemia.

Cardio-renal effects of SGLT2 inhibitors

Several recent large prospective randomised studies in type 2 diabetes have observed reduced CV risk and improved renal function during treatment with an SGLT2 inhibitor [3]. In the EMPA-REG OUTCOME trial treatment with empagliflozin was associated with a reduced composite 3-point MACE of CV death, nonfatal myocardial infarction (MI) and stroke by 14%: CV mortality was reduced by 38%, overall mortality by 32% and hospitalisation for heart failure by 35% [4]. Empagliflozin also reduced by 39% the deterioration in nephropathy (measured as a composite of progression to macroalbuminuria, doubling of serum creatinine, initiation of renal-replacement therapy or death from renal disease) [5].

In the CANVAS Program, canagliflozin also reduced the 3-point MACE of CV death, nonfatal MI and stroke by 14%, but did not significantly alter CV deaths or overall mortality, although hospitalisation for heart failure was reduced by 33%. Canagliflozin also reduced (by 40%) a composite of decreased glomerular filtration rate, need for renal replacement therapy or death from renal causes, alongside a nominal 27% reduction in the progression of albuminuria [6]. In the DECLARE trial, dapagliflozin reduced hospitalisation for heart failure by 27% and reduced a renal composite of decreased glomerular filtration rate, end stage renal disease or death from renal or CV causes by 24% [7].
Several large database studies have noted reductions in CV deaths and hospitalisation for heart failure amongst type 2 diabetes patients treated with an SGLT2 inhibitor [8] and there is emerging evidence that the occurrence of acute kidney injury is reduced [9].

While reduced glucotoxicity may contribute to the cardio-renal benefits of SGLT2 inhibitors, the correlation with glucose-lowering is modest [3, 10-12]. The CV effects emerge too quickly to be explained by decreased body weight, improved insulin sensitivity or reduced atherosclerosis [13]. Haemodynamic effects consequent to the osmotic diuresis, such as lowered blood pressure and decreased intra-vascular volume are anticipated to play a role in the CV and renal effects [14], and increased delivery of sodium to the macular densa during SGLT2 inhibition will increase the release of adenosine which mediates tubulo-glomerular feedback to constrict afferent glomerular vessels and protect glomeruli through reduced intra-glomerular pressure [15, 16].

There are several possible mechanisms through which SGLT2 inhibition could assist myocardial function in ischaemia. Lowering blood glucose together with reduced insulin concentrations will promote lipolysis and increase diversion of fatty acids into ketones: availability of ketones will provide a rapidly usable energy source to facilitate contraction by cardiac muscle [17, 18]. Decreased catabolism of branched-chain amino acids (BCAAs) in heart failure disrupts myocardial pyruvate utilization and increases susceptibility to ischaemia-reperfusion injury. Improved myocardial metabolism with use of an SGLT2 inhibitor can partially overcome this effect [19, 20]. SGLT2 inhibition has also been shown to reduce activity of the sarcolemmal Na⁺/H⁺ exchanger in the myocardium, which favours a lowering of intracellular sodium and a rise in mitochondrial calcium [21]. Another potential inotropic influence of SGLT2 inhibition might involve the small increase in plasma glucagon observed with use of an SGLT2 inhibitor [22].

A further potential mechanism through which SGLT2 inhibitors might influence CV risk is via a reduction in the circulating concentration of uric acid, considered below.

**SGLT2 inhibitors and uric acid**

Uric acid is mostly produced from the breakdown of dietary and endogenous purines, and about two thirds of uric acid is excreted in the urine. At near neutral physiological pH, uric acid exists almost entirely as the urate anion, but in high concentration at low pH uric acid is prone to form the characteristic crystals of nephrolithiasis and gout [23, 24]. Raised serum uric acid concentrations are associated with increased CV risk, and are recognised as part of the collection of CV risk factors that typically accompanies insulin resistance [25-27]. Raised uric acid concentrations are also associated with renal tubulo-interstitial fibrosis and chronic kidney disease (CKD) [28-30]. Many different pathways of increased production and/or reduced elimination of uric acid can account for raised serum uric acid as reviewed elsewhere [23, 24], but it is relevant to note in the context of type 2 diabetes that uric acid production is increased by a diet high in fructose (corn syrup). This is because excess uncontrolled phosphorylation of fructose by fructokinase in the liver depletes ATP to ADP and AMP and the adenosine is converted to uric acid [23]. High uric acid concentrations promote insulin resistance by inhibition of postreceptor insulin signalling pathways [31, 32].

Uric acid concentrations are generally higher in type 2 diabetes patients than in non-diabetic individuals, and although uric acid concentrations are usually still within the normal physiological range, they are independently associated with an additional risk of CV and renal disease [33-35]. Although type 2 diabetes is associated with an increased risk of gout this appears to be mostly attributable to the co-morbidities linked to the diabetes [36].
In a meta-analysis of 62 clinical trials with a total of 34,941 type 2 diabetes patients, treatment with an SGLT2 inhibitor consistently reduced circulating uric acid concentrations [37]. When baseline uric acid values were within a normal range [eg ~200-400 umol/L (~3.3-6.7 mg/dL)], SGLT2 inhibitors available in Europe and North America (canagliflozin, dapagliflozin and empagliflozin) usually reduced serum/plasma uric acid concentrations by 35-45 umol/L (0.60-0.75 mg/dL) in trials of 6-12 months. The effect was rapidly generated (within days) and persisted throughout trials of 2 years duration [37]. Reductions of uric acid are generally greater if the HbA1c value is higher, consistent with greater uricosuria accompanying greater glucosuria (discussed below), but there was no clear difference in the extent of uric acid-lowering across the range of ‘low-to-high’ normal uric acid values. At therapeutic doses of SGLT2 inhibitors, mean reductions in plasma/serum uric acid with use of empagliflozin (~45 umol/L at 10mg and 25mg) were typically marginally (not significantly) greater than with canagliflozin (~42 umol/L at 100mg and 300mg) and dapagliflozin (~38 umol/L at 10mg), but there were no consistent dose-related effects or correlations with differences in the IC50 values for inhibition of the SGLT transporters [37]. More detailed comparisons between agents are limited by many confounding variables and incomplete information, such as uncertainties regarding the history or presence of CV disease and kidney disease, and the use of potentially interfering medications. Thus the similar lowering of uric acid observed with each of the SGLT2 inhibitors indicates a class effect with no substantive differences between agents or doses used routinely in the treatment of type 2 diabetes.

The uric acid-lowering effect of SGLT2 inhibitors raises questions regarding the mechanism, whether the effect is relevant to the reduced cardio-renal risk associated with SGLT2 inhibitors, and whether there are implications for the treatment of hyperuricaemia?

Renal handling of uric acid with SGLT2 inhibitors

SGLT2 inhibitors lower urate concentrations by increasing renal urate elimination [38, 39]. Urate is freely filtered by the kidney and also reabsorbed and secreted along the proximal convoluted tubule (PCT) [40]. Almost all of the filtered urate is reabsorbed in the first segment (S1) of the PCT: uptake across the apical membrane is mostly via the urate transporter URAT1 (SLC22A12) and the facilitative hexose/urate transporter GLUT9b (SLC2A9 isoform b) with minor contributions of the organic anion transporters OAT4 and OAT10. Transfer of urate out of the proximal cells across the basolateral membrane is via GLUT9a (SLC2A9 isoform a) (Fig 1). The near total reuptake of filtered urate indicates that tubular secretion must be important for the overall elimination of urate. Secretion is mostly in the second segment (S2) of the PCT and more distal regions of the nephron where urate is transferred from the interstitium across the basolateral membrane via OAT1 and OAT3. The uric acid is then transferred across the apical membrane into the lumen of the nephron mostly via multidrug resistance-associated protein-4 (MRP4) and ATP-binding cassette transporter G2 (ABCG2). The sodium/phosphate cotransporters NPT1 and NPT4 may also transport urate across the apical membrane into the lumen [40-44].

URAT1 is inhibited by uricosuric agents that lower serum urate such as probenecid, losartan and lesinurad [45]. Also, mutations that reduce the function of URAT1 increase uricosuria and reduce serum urate [46], and URAT1 knockout mice show increased uricosuria [42]. However SGLT2 inhibitors do not appear to affect URAT1 [38]. The more likely mechanism through which SGLT2 inhibitors increase uricosuria and lower circulating uric acid is by suppression of the activity of GLUT9b. When the transport function of SGLT2 is reduced there is an increased concentration of glucose within the lumen of the PCT which competes with urate for GLUT9b [39]. Indeed, the reduction in serum urate in type 2 diabetes patients receiving an SGLT2 inhibitor declines at low eGFR (<60 mL/min/1.73 m²) as does the glucosuria, consistent with reduced filtration of both urate...
and glucose, and thence reduced competition for the hexose/urate transporter [37]. Also, uricosuria was increased and plasma uric acid was reduced in a study of type 1 diabetes patients in whom euglycaemia was clamped while glucosuria was induced with an SGLT2 inhibitor [39].

**Uric acid, hypertension and adverse CV events**

A persistently raised uric acid concentration has been implicated as a risk factor for hypertension and for several types of MACE.

**Hypertension**

Many epidemiological analyses have concluded that hyperuricaemia is an independent risk factor for hypertension [47-50]. The association of raised uric acid and raised blood pressure is evident within the normal range of uric acid concentrations, and interventions that lower uric acid concentrations (such as the xanthine oxidase inhibitors allopurinol and febuxostat which reduce uric acid production) modestly reduce blood pressure in hypertensive patients independently of antihypertensive therapies [51-55]. This suggests a possible pathogenic role of raised uric acid in the development of raised blood pressure. Elevated uric acid concentrations have been reported to alter several parameters of vascular function indicative of arterial stiffness, notably higher carotid-femoral and carotid-radial pulse wave velocities and impaired flow-mediated vasodilation [56-57]. Hyperuricaemic hypertension is also typically associated with increased activity of the renin-angiotensin-aldosterone system (RAAS) including increased plasma renin activity and increased aldosterone secretion, and hyperuricaemia has been linked with increased salt-sensitivity in some individuals [58-62]. However, the extent to which excess uric acid might contribute to these effects is unclear [63].

**Major adverse cardiovascular events**

Observational and cohort studies have noted an association of hyperuricaemia with CV death, non-fatal MI and stroke, atrial fibrillation and heart failure [64-69], and modestly raised uric acid concentrations within the normal concentration range represent a risk for adverse CV events [70-73]. For example, a meta-analysis of 29 prospective cohort studies totalling 958,410 participants found a 13% increased relative risk of CV mortality for each 1 mg/dL (59.5 umol/L) increase in uric acid [73]. Indeed, raised uric acid may be associated with a greater increase in CV mortality in people with type 2 diabetes than the general population [74]. Assessing whether uric acid is an independent risk factor for CV events is confounded by the co-existence of other CV risk factors [75-77]. A meta-analysis of 11 studies with 172,123 participants indicated uric acid was an independent predictor of CV mortality [78], whereas another meta-analysis involving 16 studies and 164,342 participants was inconclusive [79].

Lowering uric acid concentrations with xanthine oxidase inhibitors (allopurinol or febuxostat) or a uricosuric agent (probenecid) reduces CV events and improves the CV prognosis of patients with gout. Many prospective and observational studies have confirmed reduced risk of fatal and non-fatal stroke and MI amongst patients receiving allopurinol and this has been linked to reduced uric acid concentrations, although it is recognised that allopurinol exerts relevant anti-oxidant effects independently of uric acid [80-85]. In a propensity score-matched cohort study there was an 11% reduction in a composite outcome of MI, stroke and CV death and a 32% reduction in all-cause mortality amongst 7,127 patients receiving allopurinol [86]. A case-control analysis of a cohort of 25,090 patients with heart failure found that use of allopurinol for those with gout was associated
with a 31% reduction of heart failure readmission or death, and a 26% reduction of all-cause mortality [87]. Prospective studies with febuxostat and probenecid have also reduced adverse CV events together with reduced uric acid concentrations in patients with gout. This suggests that the anti-oxidant effects of allopurinol are unlikely to fully explain the improved CV prognosis with this agent, supporting the possibility that reduced uric acid itself contributes to improved CV prognosis [88-90].

Several mechanisms could account for the epidemiological link between hyperuricaemia and CV risk. Although circulating uric acid has potentially beneficial antioxidant properties, intracellular uric acid stimulates nicotinamide adenine dinucleotide phosphate (NADPH) oxidases which generate reactive oxygen species (ROS) [91-93]. ROS cause endoplasmic stress which in turn accentuates ROS production by mitochondria and interfere with several key cellular signalling pathways. Increased uric acid promotes pro-inflammatory responses and fibrosis within the vascular wall and increases turnover of vascular smooth muscle [94-99]. Hyperuricaemia is also associated with an increased rate of apoptosis of endothelial cells [100] and depleted nitric oxide (NO) levels due to reduced NO production and to increased conversion of NO to 6-aminouracil [101, 102].

Uric acid and CKD

Mounting evidence implicates chronic hyperuricaemia as a risk for development and progression of CKD, especially in diabetes. A 5-year prospective study of 1,449 type 2 diabetes patients with normal kidney function found the incidence of CKD (eGFR <60 mL/min/1.73 m²) more than doubled (29% versus 11%) with raised uric acid concentrations (>7.0 or 6.5 mg/dL for men or women respectively, or allopurinol treatment) after adjusting for other variables [103]. A 4-year cohort study of 13,964 type 2 diabetes patients noted that raised uric acid concentrations are strongly associated with increased risk of CKD [104], and faster progression of CKD was independently linked to higher uric acid concentrations in a 4.6 year cohort study of 2,367 type 2 diabetes patients [105]. A raised uric acid:creatinine ratio predicted development of CKD in a 4 year study of 1,339 type 2 diabetes patients [106], and raised uric acid concentrations independently predicted the rate of progression of CKD in a retrospective analysis of 270 type 2 diabetes patients with CKD [107]. An independent association of raised uric acid concentrations with the development and progression of CKD has been noted in prospective and retrospective studies with non-diabetic populations and in prospective studies with type 1 diabetes patients [108-111].

Several studies have implicated uric acid as a modifiable risk factor for progression of CKD in type 2 diabetes. A post-hoc analysis of 1,342 type 2 diabetes patients with nephropathy in the RENAAL (Reduction of End Points in Non–Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan) trial found a 6% decrease in adverse renal outcomes for each 0.5 mg/dL (30 umol/L) decrease in uric acid concentrations during 6 months of treatment with losartan (URAT1 inhibitor) [112]. Interventions to reduce uric acid concentrations reduced CKD progression in individuals with and without type 2 diabetes [105, 113], and lowering uric acid with allopurinol in diabetic (db/db) mice reduced albuminuria and ameliorated tubule-interstitial injury, but did not prevent mesangial expansion [114].

Although urate crystal formation in the renal tubules and interstitium contributes to kidney damage in individuals with severe hyperuricaemia, other mechanisms are undoubtedly important, particularly in people with lesser degrees of hyperuricaemia [115, 116]. Hypertension, afferent glomerular hypertension and afferent vessel thickening associated with raised uric acid concentrations in animal studies are anticipated to contribute to glomerular disease in humans [117, 118]. Activation of NADPH oxidases, generation of ROS and endoplasmic stress have also been
linked to increased production of extracellular matrix, inflammation and interstitial fibrosis with reduced tubular cell viability [119, 120]: uric acid decreased viability and increased apoptosis of cultured human proximal tubule (HK-2) cells, and this was prevented by inhibition of NADPH oxidases and inhibition of urate transport into the cells [96]. Epithelial-to-mesenchymal transition (EMT) was increased by uric acid in cultured rat tubular (NRK) cells, and the interstitial fibrosis in rats with experimental hyperuricaemia was reduced by allopurinol [121]. Raised uric acid concentrations promote inflammatory responses of renal tubular cells by increasing production of nuclear factor-κB (NF-κB), tumour necrosis factor-alpha (TNFα), monocyte chemoattractant protein-1 (MCP-1) and ‘regulated upon activation normal T-cell expressed and presumably secreted’ (RANTES) protein [122]. The inflammatory effect of raised uric acid concentrations in mice is associated with increased infiltration of T-cells and macrophages in the renal interstitial spaces, and this is relieved by the uricosuric probenecid [122]. In cultured glomerular mesangial cells endoplasmic stress induced by raised uric acid increased production of biomarkers of fibrogenesis such as α-smooth muscle actin (α-SMA), transforming growth factor-β1 (TGF-β1) and fibronectin [123].

Thus accumulating evidence suggests that raised uric acid concentrations have a detrimental effect on glomerular and tubule-interstitial integrity independently of hypertension, and these effects are ameliorated by therapies that lower uric acid concentrations.

Treatment of gout

The increased uric acid elimination with use of SGLT2 inhibitors usually lowers circulating uric acid concentrations by about 35-45 μmol/L (0.60-0.75 mg/dL) in individuals with a baseline uric acid value in the normal concentration range of ~200-400 μmol/L (~3.3-6.7 mg/dL). Comparing the uric acid-lowering efficacy of SGLT2 inhibitors with that of allopurinol or febuxostat is not straightforward as the latter agents are mostly used in gouty patients with much higher baseline uric acid concentrations than in studies with SGLT2 inhibitors, and doses of the xanthine oxidase inhibitors are customarily titrated aiming to reduce uric acid values to <6 mg/dL (<360 μmol/L) [124-127]. In hyperuricaemic patients, up-titration of allopurinol and febuxostat achieves reductions of serum/plasma uric acid concentrations by 30-40% [~1-4 mg/dL (60-240 μmol/L)] from a typical baseline of 8-12 mg/dL (~475-710 μmol/L). Where modest doses of allopurinol have been used in individuals with uric acid concentrations at the upper end of the normal serum/plasma range, reductions of circulating uric acid are more commonly around 1-1.5 mg/dL (60-90 μmol/L).

Although SGLT2 inhibitors lower uric acid concentrations [typically 0.60-0.75 mg/dL (35-45 μmol/L)] within the normal range with lesser potency than xanthine oxidase inhibitors, their mode of action is different and potentially complementary, offering the possibility of an additive effect if used with a xanthine oxidase inhibitor. The renal mechanism of action of SGLT2 inhibitors to increase uric acid elimination is also different to the URAT1 inhibiting uricosuric agents such as probenecid, suggesting potential for additive efficacy. Whether SGLT2 inhibitors might be useful in the management of hyperuricaemia is now being investigated, for example in a small (n=36) randomised clinical study comparing dapagliflozin and febuxostat over 7 days in hyperuricaemic patients [128]. There are also examples of derivatives of current SGLT2 inhibitors that are particularly potent uricosuric agents, such as 3-oxy dapagliflozin [129]. It is appreciated that increased uric acid elimination in the urine with use of an SGLT2 inhibitor could aggravate the risk of renal calculi, but studies to date have not observed this possible long-term risk [130].

This article is protected by copyright. All rights reserved.
Conclusions

Raised uric acid concentrations are associated with increased adverse cardiovascular and renal events in diabetic and non-diabetic individuals. Although there are isolated reports that metformin and pioglitazone reduced symptoms in some patients with gout, there is no consistent evidence that glucose-lowering agents can reduce uric acid concentrations in type 2 diabetes, except for SGLT2 inhibitors [131-133]. The uric acid-lowering effect of SGLT2 inhibitors may contribute to the cardio-renal benefits associated with this class of glucose-lowering agent (Fig 2), and it is possible that SGLT2 inhibitors may assist the management of hyperuricaemia in diabetes.

REFERENCES


36. Wijnands JM, van Durme CM, Driessen JH, Boonen A et al. Individuals With Type 2 Diabetes Mellitus Are at an Increased Risk of Gout But This Is Not Due to Diabetes. A Population-Based Cohort Study. Medicine 2015; 94: e1358.


57. Tsai WC1, Huang YY, Lin CC, Li WT, Lee CH, Chen JY, Chen JH. Uric acid is an independent predictor of arterial stiffness in hypertensive patients Heart Vessels. 2009; 24: 371-5.


This article is protected by copyright. All rights reserved.


78. Zhao G, Huang L, Song M, Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: A meta-analysis of prospective studies. DOI: https://doi.org/10.1016/j.atherosclerosis.2013.08.023


This article is protected by copyright. All rights reserved.


This article is protected by copyright. All rights reserved.


SGLT2 inhibitors Increase renal urate elimination. This involves filtration of urate, most of which is reabsorbed in segment S1 of the proximal tubule, while urate is also secreted into the nephron lumen mostly in segment S2 and more distally. SGLT2 inhibitors increase the concentration of glucose in the proximal tubules, and current evidence indicates that the glucose competes with urate for the facilitative hexose/urate transporter GLUT9b, reducing urate reabsorption.

ABCG2, ATP-binding cassette transporter G2; GLUT9a/b, glucose transporter SLC2A9 isoform a or b; MRP-4, multidrug resistance-associated protein-4; NPT, sodium/phosphate co-transporter; OAT, organic anion transporter; SGLT, sodium/glucose co-transporter; URAT1, urate transporter SLC22A12.

SGLT2 inhibitors increase urate elimination in the urine which reduces plasma urate concentration. Lower plasma urate concentrations contribute to the cardiovascular and renal protective effects of SGLT2 inhibitors.

GLUT, glucose transporter; NADPH, nicotinamide adenine dinucleotide phosphate; PCT, proximal convoluted tubule; S1, S2, segments 1 and 2 of proximal convoluted tubule; SGLT, sodium/glucose co-transporter.
Bailey. Figure 1.

Bailey. Figure 2.