**A Review of the Mechanism of Action, Metabolic Profile & Haemodynamic Effects of SGLT2 Inhibitors**

**Emily Brown, Surya Panicker Rajeev, Daniel J Cuthbertson, John PH Wilding**

**Obesity and Endocrinology Research**

**Institute of Ageing and Chronic Disease,**

**University of Liverpool, Liverpool, United Kingdom**

**Corresponding author & address for reprints:**

**Professor John Wilding**

**Obesity and Endocrinology Research**

**Clinical Sciences Centre,**

**University Hospital Aintree,**

**Longmoor Lane,**

**Liverpool, L9 7AL**

**E-mail: J.P.H.Wilding@liverpool.ac.uk**

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**Abstract**

Inhibition of glucose transport in the kidney, to produce glucosuria and thus directly lower blood glucose seems a remarkably simple way to treat diabetes (type 1 or type 2). The development of sodium-glucose co-transporter-2 (SGLT2) inhibitors and their subsequent clinical development has on one hand shown this to be true, but at another level has helped reveal a complex web of interacting effects starting in the kidney and modulating multiple metabolic pathways in a variety of other organs. These underlie the now clear benefits of this class of drugs in the management of type 2 diabetes from glucose lowering, weight loss and blood pressure reduction through to the reductions in cardiovascular and renal complications observed in long-term outcomes trials. They also explain some of the adverse effects that have emerged, including the risk of diabetic ketoacidosis. This review describes the effects of SGLT2 inhibition in relation to this complex physiology, and shows how this can favourably alter the pathophysiology of type 2 diabetes.

**Introduction**

Sodium Glucose Transporter 2 inhibitors (SGLT2i) are one of the newest classes of drugs available to lower glucose in people with type 2 diabetes, but their origins go back to the 19th Century, when phlorizin, extracted from the bark of apple trees was shown to induce glucosuria. Phlorizin was later used experimentally as a tool to help understand renal glucose transport and the effects of glucose toxicity, as it could be used to lower blood glucose without directly affecting insulin secretion or sensitivity [1]. However its therapeutic potential was limited, due to poor oral bioavailability, and effects on gut glucose absorption that resulted in diarrhoea; phlorizin also has an active metabolite (phloretin) that inhibits the GLUT1 glucose transporter that is important for normal glucose transport in many tissues [2]. Research conducted in the last 20 years has now identified the specific mechanisms by which phlorizin is able to induce glucosuria and lower blood glucose, and led to the development of drugs that are highly selective inhibitors of renal (and / or gut) glucose transport. These drugs work by inhibiting the facilitative sodium glucose co-transporters (SGLTs) that are responsible for renal glucose reabsorption (predominantly SGLT2 with some contribution from SGLT1, which also has a major role in gut glucose absorption)[3]. Despite early concerns about some adverse effects that occur as a result of glucosuria, the development of SGLT2 inhibitors (and potentially dual inhibitors of SGLT1 and SGLT2) has led to greater understanding of the fundamental physiological processes involved in glucose transport in the kidney and gastrointestinal (GI) tract. These medications have both predictable and surprising effects that underpin some of their observed therapeutic benefits and adverse effects. This review will focus on the underlying physiology and show how this is modified by pharmacological inhibition of SGLTs in the kidney.

**Role of SGLT2 and SGLT1 in renal and GI glucose transport and the effects of diabetes**

In the kidneys, glucose is freely filtered by the glomeruli, but there is not usually any glucosuria, as a result of the process of glucose reabsorption that occurs in the proximal tubule. This is an active transport mechanism whereby glucose is reabsorbed along with sodium via the sodium-dependent glucose co-transporter proteins 1 and 2 (SGLT1/2); approximately 90% by the high capacity, low affinity SGLT2 with the low capacity, high affinity SGLT1 transporter, in the distal segment, responsible for the remaining 10% [4]. Na+ /K+ ATP pumps on the basolateral membrane of the tubular cells provide the energy for this process; the reduction in intracellular sodium creates a concentration gradient that results in a conformation change in the transporter bringing sodium and glucose into the tubular cell. Glucose is subsequently returned to the blood via GLUT 2 transporters [2] (Figure 1).

When the blood glucose concentration rises above about 10mmol/l, filtered glucose load exceeds the tubular maximum reabsorptive capacity (TmG, approximately 375 mg/min [425 g/day] in healthy individuals) excess glucose is excreted in the urine. In the presence of chronic hyperglycaemia, there is paradoxically excessive glucose reabsorption [5, 6], due to compensatory upregulation of SGLT2[7] and/or SGLT1[8] expression in response to increased urinary glucose filtration, exacerbating hyperglycaemia. The mechanisms underlying this effect are thought to be mediated in part via induction of hepatic nuclear factor-1 (HNF1) alpha by the increased energy demands of increased glucose transport; experimental evidence suggests that the glucosuria seen in HNF1 alpha maturity onset diabetes of the young, is due to a failure of this mechanism, which in turn ameliorates the severity of hyperglycaemia in this condition [9, 10]. It is of note that genetic defects in the *SLC5A2* gene that codes for SGLT2 result in benign familial glucosuria which may result in up to 100g / day of glucosuria without known adverse effects [11] (12).

*Glucose transport in the GI tract and the role of SGLT1*

SGLT1 is the main glucose transporter mediating glucose transport in the GI tract. It is essential for normal absorption of both glucose and galactose. Genetic defects in SGLT1 result in the condition of glucose-galactose malabsorption which may be rapidly fatal due to severe diarrhoea, unless glucose and galactose are eliminated from the diet [12]. Some SGLT2 inhibitors may have modest effects to inhibit SGLT1 when tested in vitro, but the clinical relevance of this is uncertain; dual SGLT1/2 inhibitors have also been developed, but it is notable that these are relatively more selective for SGLT2 and do not seem to cause significant GI adverse effects at clinically relevant doses [13].

*The effects of SGLT inhibition*

SGLT2 inhibitors are highly selective inhibitors of renal glucose reabsorption, and result in development of substantial glucosuria, usually around 70-80g /day at therapeutic doses. SGLT1 is also present in the renal tubules, and in healthy people is probably responsible for about 10% of glucose transport (it has a higher affinity for glucose, but a lower transport capacity; it is also less selective and able to transport galactose). (Table 1)

**SGLT2 inhibitors and their clinical effects**

In the United States and Europe, three SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) are approved and in widespread clinical use. Ertugliflozin is approved and likely to be available soon, several other SGLT2 inhibitors are also approved in other countries (for example Japan where ipragliflozin, tofogliflozin and luseogliflozin are also available), but these will not be discussed further. Normal urinary glucose reabsorption is about 180 g /day, and is much higher in people with diabetes, In practice, SGLT2i inhibit much less of the filtered glucose load (<50%), so SGLT2 inhibition results in about 70-90g of urinary glucose excretion, with an associated energy loss of about 300 kcal/day [14, 15]. This is at odds with the widely quoted statement that SGLT2 is responsible for approximately 90% of renal glucose reabsorption [2]. This could be due to further upregulation of SGLT1 expression during SGLT2i treatment [8, 15] or incomplete blockade of SGLT2. Despite similar structures between the different SGLT2i, differences between the relative selectivity profiles of SGLT2 over SGLT1 exist, ranging from ~200:1 for canagliflozin and ~2500:1 for empagliflozin [16]; in contrast the dual SGLT1 / 2 inhibitor sotagliflozin is about 20:1 selective for SGLT1 (Table 2).

All of the currently available SGLT2i’s reduce blood glucose and hence HbA1c between 0.6 – 1% (6-11 mmol/mol), depending on the baseline HbA1c and the trial design; in general these drugs work independently of other glucose lowering drugs and can be combined with other treatments, including insulin. Effects to lower HbA1c are reduced in the context of significant renal impairment, and none are currently approved for use when the eGFR is below 45mls/min. Weight loss of around 2-3kg is also expected, as is a modest reduction in blood pressure (2-3mmHg of systolic BP). The main adverse effects include an increased risk of fungal urogenital infection, particularly in women, an increased risk of bacterial urinary tract infections, adverse effects related to blood pressure lowering such as dizziness and postural hypotension. Rarer adverse effects include diabetic ketoacidosis (especially in those with type 1 diabetes); concerns have also been raised about bladder cancer, lower limb amputations and Fournier’s gangrene, but recent data from the DECLARE trial suggests the risk for these may not be increased, at least for dapagliflozin [17]. Importantly the risk of hypoglycaemia is low with SGLT2 inhibition due to the elimination of urinary glucose excretion when the filtered glucose level falls below the transport capacity of SGLT1 [18], alongside the compensatory metabolic changes seen including increased hepatic glucose production [19, 20], and the fact that these drugs do not stimulate insulin secretion. Nevertheless hypoglycaemia may occur in the context of background therapy with insulin or sulfonylureas [21, 22].

*Dual inhibition of SGLT1/2*

The dual SGLT1/2 inhibitor sotagliflozin is currently under evaluation as an adjunctive treatment for type 1 diabetes; clinical trials show that there is an additional glucose lowering effect when added to optimised insulin treatment, together with modest weight loss (approx. 2kg) and blood pressure lowering [23-25].

Much of recent understanding of the effects of SGLT2i on underlying pathophysiology of diabetes has come from the CV and renal effects observed in long-term outcomes trials that were originally designed to test cardiovascular safety, so it is important to briefly describe those effects here. Three trials have now reported, the EMPA-REG outcomes trial [26], the CANVAS programme (in fact a combined analysis of two trials) [27] and DECLARE TIMI-58 [17]. All three trials showed a clear reduction in hospitalisation for heart failure in patients treated with SGLT2 inhibitors; this effect was seen in patients with and without pre-existing heart failure and in those with and without pre-existing cardiovascular disease. There were also reductions in overall and cardiovascular mortality, that was significant in EMPA-REG and CANVAS but not in DECLARE. A recent meta-analysis supports the overall conclusion that SGLT2 inhibitors are effective at reducing risk of heart failure hospitalisation in a broad population of people with type 2 diabetes, irrespective of a history of CVD, but that reductions in major cardiovascular events are only apparent in those with pre-existing cardiovascular disease [28]. This is also supported by large scale observational studies such as CVD-REAL [29].

Finally, although not a primary endpoint, all three trials showed improvements in renal function, with reduction in albuminuria and a reduction in composite renal outcomes that include significant reductions in GFR, end-stage renal disease and renal death.

**Extrarenal Effects**

SGLT2 primarily is expressed in the kidney but also is found in the pancreas (alpha-cells)[30]; in contrast, SGLT1 is predominantly found in the gut [31]. There is some evidence to support low levels of expression in skeletal muscle, liver, brain and heart, but the physiological relevance is uncertain [31].

***Acute changes in glucagon, glycogen and gluconeogenesis***

Two independent publications have shown that the increased urinary glucose excretion (UGE) following SGLT2 inhibition is associated with a paradoxical increase in endogenous (hepatic) glucose production[19, 20] caused by a compensatory release of glucagon from the alpha cells in the pancreatic islets.[30] This may partially negate the SGLT2i effect and is potentially problematic in a patient population with hyperglucagonaemia, raising questions about the mechanisms of action of SGLT2i beyond glucose reabsorption. The kidney also plays a key role in glucose metabolism by regulation of glucose reabsorption, glycolysis and gluconeogenesis. In patients with T2DM, both renal and hepatic glucose release are increased as a result of increased gluconeogenesis, with the relative increase substantially greater in the kidney than in the liver (300% vs 30%).[32] This is further modulated by SGLT2 inhibition affecting glucose control in the fasting (postabsorptive) state [33].

***Shifts in substrate utilisation and ketogenesis***

The significant increased glucosuria and energy loss associated with SGLT2 inhibition is associated with (mal)adaptive compensatory changes in glucoregulatory hormones. Further information is needed on the potential changes involving energy balance (intake, expenditure or both), substrate utilisation and ketogenesis.

**Metabolic effects of SGLT2 inhibition**

***Effects on energy balance***

The glucosuria and osmotic diuresis associated with SGLT2 inhibition is translated into clinically significant benefits in terms of reducing glycaemia and weight loss. SGLT2 inhibition causes significant glucosuria of 75 g glucose/day which is equivalent to energy loss of 300 kcal/day and osmotic diuresis of ~ 400 ml/day. Hence, the anticipated weight loss is in the range of 10 kg per year. However, clinical trial data with SGLT2 inhibitors has revealed that the observed weight loss is in the range of 2 to 3 kg. This difference between expected and actual weight loss could be explained due to the maintenance of homeostasis through a complex metabolic adaptive process including differences in energy intake, energy expenditure and substrate utilisation.

Unlike the effects of SGLT2 inhibition on glycaemia which is proportional to baseline glucose concentration [34] and glomerular filtration [35], its effects on energy balance, plasma volume and renal filtration are independent of glucosuria. SGLT2 inhibition can exert effects on body weight as early as 7 days and have been shown to persist in clinical trials of up to 4 years duration although weight loss reaches a plateau after about 6 months of treatment [36]. While the reduction in hepatic glycogen stores and osmotic diuresis contributes to early onset weight loss, the reduction in steatosis, visceral and subcutaneous adipose tissue accounts for the late effects on body weight [37].

Mathematical models were used to quantify the feedback control of human energy intake as a consequence of SGLT2 inhibition. In a study with empagliflozin, it was concluded that there is a 13% increase in calorie intake coupled with a 2% increase in daily energy expenditure due to diet induced thermogenesis which accounts for the attenuated weight loss seen as a result of SGLT2 inhibition [38]. Polidori et al used a validated mathematical method to calculate energy intake changes during a 52 week placebo-controlled trial in 153 patients treated with canagliflozin. Their data showed that weight loss led to increase in energy intake by ~ 100 kcal/ day per kilogram of lost weight which is threefold greater than the adaptations in energy expenditure [39]. If weight loss has been achieved as a result of dietary restriction, energy expenditure would have been decreased in contrast to the above findings. Animal data shed initial light on the theory of compensatory hyperphagia when Devenny et al demonstrated that dapagliflozin treated rats who were allowed ad libitum access to food had a 30% increase in food intake [40]. Other animal studies observed slight increases in energy intake (4%) [41, 42]. SGLT2 inhibition has been shown to cause preferential increase in hunger for sugar-rich foods similar to that seen with low carbohydrate diets [43]. However, we were unable to demonstrate an compensatory increase in energy intake in the ENERGIZE study, a prospective randomized, double blind, cross-over trial, in people with type 2 diabetes which compared the effects of dapagliflozin with placebo on food intake and energy expenditure over 12 weeks[44]. Dapagliflozin treatment was associated with reduction in body weight compared to placebo (-2.84 vs -0.87 kg), but with no significant increase in test meal food intake (2.63g, 95% CI-31.65, 36.91; p=0.659) measured by the Sussex Ingestion Pattern Monitor [45]. However, resetting of energy homeostasis due to a compensatory increase in intake which result in plateauing of body weight would need only a minor increment in food intake and such subtle changes can be difficult to capture with the typical appetite studies in research lab settings.

***Effects on pancreas, liver and adipose tissue metabolism***

The glucosuria associated with SGLT2 inhibition and the depletion of glucose in the extracellular space results in reduction of fasting and post prandial glucose concentrations. This decline in glucose level leads to consequent reduction in insulin secretion and increase in glucagon secretion [46]. It has been suggested that the hyperglucagonaemia is due to the paracrine effect of reduced inhibition of pancreatic alpha cells due to the decrease in insulin concentrations. However it has also been demonstrated that SGLT2 is expressed in the glucagon producing alpha cells of pancreatic islets. Furthermore, the expression of SLC5A2 which encodes SGLT2 was lower and glucagon gene expression was higher in patients with type 2 diabetes. Inhibition of SLC5A2 or SGLT2 (through dapagliflozin) triggered glucagon production in islet cells of mouse pancreas through KATP channel activation [30].

Due to the reduction in insulin-glucagon ratio, fasting endogenous glucose production is elevated. The suppressive effect of insulin on post meal endogenous glucose production is also attenuated [47, 48]. The increase in endogenous glucose production is mediated by hepatic glycogenolysis and gluconeogenesis. SGLT2 inhibition has also been elucidated to affect renal gluconeogenesis [49].

However, in the long term, other metabolic changes operate resulting in normalisation of glucagon, glycogen as well as hepatic glucose production [47]. Nevertheless, this increment in endogenous glucose production may attenuate the glucose lowering efficacy of SGLT2 inhibitors.

The reduction in insulin levels secondary to SGLT2 inhibition also results in lipolysis and an increase in circulating free fatty acids (FFA). This influx of FFA is directed into ketogenesis in the liver resulting in production of ketone bodies which is taken up by most tissues including heart through monocarboxylic acid transporters [50]. This has been postulated as one of the reasons for the cardio protective effect of SGLT2 inhibitors.

The reduction in insulin levels due to SGLT2 inhibition hampers tissue glucose uptake through both oxidative and non-oxidative pathways resulting in a metabolic switch to lipid oxidation [51] and increase in ß- hydroxybutyrate levels. This lipid oxidation and hyperketonaemia has been postulated to strengthen over time in spite of abatement of hyperglucagonaemia. Another interesting enigma is the improvement in insulin sensitivity with SGLT2 inhibition [47, 48] as the use of FFA by insulin sensitive tissues is expected to result in insulin resistance. The improvement in glucotoxicity with SGLT2 inhibition has been postulated as a reason for this beneficial response.

***Effects on uric acid, phosphate, PTH and Vitamin D levels***

SGLT2 inhibitors increase the renal clearance of uric acid in a dose dependent manner resulting in reduction of plasma uric acid levels [52]. The uricosuric effect of SGLT2 inhibition is due to the increased intraluminal concentration of glucose and is mediated by GLUT9 isoform 2 in the renal collecting ducts [53].

There are also other metabolic implications due to SGLT2 inhibition including a reduction in circulating lactate levels and branched chain amino acids. While the reduction in lactate levels may be due to increased hepatic uptake, decreased tissue glucose disposal and increased renal clearance [51], the alterations in amino acid levels could be due to urinary excretion or improvements in insulin sensitivity [54].

Early studies with SGLT2 inhibitors showed small increases in serum phosphate and decreases in calcium, accompanied by increases in parathyroid hormone, raising potential concerns about adverse effects on bone mineralisation and increased fracture risk. An excess of treatment-emergent bone fractures were subsequently observed in clinical trials of some SGLT2 inhibitors [55-57]. In one study, canagliflozin 300 mg resulted in decrease in bone mineral density of hip and lumbar spine with no changes at distal forearm or femoral neck [58]; which is in contrast to the increase in distal forearm fractures seen in the CANVAS study [27]. However a study with dapagliflozin showed no significant effect on bone mineral density [59], and no increase in fractures was seen in the long term EMPA-REG or DECLARE trials [17, 26]. In one study canagliflozin treatment increased biomarkers of osteogenesis (osteocalcin) and osteolysis (collagen type1 beta-carboxy-telopeptide). One short term study demonstrated that canagliflozin increased proximal tubular reabsorption of phosphate which activates the fibroblast growth factor 23 (FGF23)-1, 25-dihydroxyvitamin D (1, 25 (OH)2 D)-parathyroid hormone (PTH) axis [60]. Canagliflozin has been shown to increase the serum phosphate, FGF23 and PTH levels while decreasing the plasma 1,25 (OH)2  D levels at a dose of 300 mg/day in a single-blind randomised cross-over study in hospitalised healthy adults over a 5 day period. Low levels of 1,25 (OH)2 D levels decrease gastrointestinal calcium absorption, further triggering PTH secretion[58].

Though the triggering of FGF23-1,25 (OH)2- PTH axis might be a class effect of SGLT2 inhibitors, the magnitude of the potential effect on bone health may vary according to the differences in SGLT2/SGLT1 selectivity of the various SGLT2 inhibitors, and does not seem to result in a significant increase in fracture risk in long-term trials.

**Haemodynamic effects of SGLT2 inhibition**

SGLT2i were developed for the management of hyperglycaemia, but large randomised controlled trials have highlighted both renal and cardiovascular protection in people with type 2 diabetes beyond the benefits of improved glycaemic control, blood pressure and weight loss. Three SGLT2i have been evaluated in large cardiovascular outcome trials in individuals with T2DM: empagliflozin in the EMPA-REG OUTCOME trial[26], canagliflozin in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program [61] and most recently in the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial [17]. All three trials showed SGLT2i have their greatest and most consistent effect on reducing the relative risk of hospitalisation for heart failure (~31%) and progression of renal disease (~45%). The exact protective mechanisms behind this remain unclear but the diuretic and natriuretic effects of SGLT2i with direct haemodynamic and renovascular effects are likely to play a central role.

**Diuresis, Natriuresis and Blood Pressure Effects**

SGLT2i is associated with a sustained reduction in systolic and diastolic blood pressure of 3-6mmHg systolic and 1-2mmHg diastolic respectively, in patients with T2DM.[62] In addition to its glucosuric effects, SGLT2 inhibition also leads to inhibition of sodium reabsorption resulting in a diuresis (approximately 400mls/day) and potential modest intravascular volume depletion. It has been shown that dapagliflozin at doses of 5, 25, and 100mg caused a dose-dependent increase in 3 day sodium excretion ranging from 55 to 134 mmol after 24 hour [63, 64]. The natriuresis and associated diuresis that accompanies SGLT2 inhibition reduces plasma volume, measured at 7% in one study using dapagliflozin in subjects with T2DM and normal renal function, with a parallel increase in haematocrit [65]. Such reductions in plasma volume have been hypothesised to underlie reductions in blood pressure, however the natriuresis associated with SGLT2i is modest when compared with conventional diuretics [66] and similar changes in plasma volume are observed in subjects with reduced eGFR and minimal glucosuria [67]. Ongoing trials designed to examine the mechanisms of natriuretic-diuretic effects of SGLT2 inhibition in patients with normal and impaired renal function will provide some insight into this (NCT03152084).

It is generally accepted that abnormal renal sodium handling is one of the key mechanisms leading to hypertension and volume overload in individuals who are overweight or with T2DM. More recently, skin sodium content has been closely associated with left ventricular mass and systolic blood pressure [63, 68] with 23Na-magnetic resonance imaging studies suggest that the skin may act as a buffer for excessive sodium intake. [63] Treatment with dapagliflozin was shown to decrease the sodium content of the skin by 5.8% in one study [69]. The precise importance of the apparent association between skin sodium content and cardio-metabolic risk is unclear. It is possible that skin sodium content merely reflects sodium content within the extracellular space and renal sodium excretion without playing any direct role itself. It is also possible however, that skin sodium participates actively in cardio-metabolic risk through mechanisms that are currently unknown.

The diuretic effects of SGLT inhibition are also thought to improve arterial stiffness, which is a key risk marker for cardiovascular events, heart failure and mortality, particularly in diabetes [70, 71]. The typical abnormalities that are seen in individuals with diabetes such as hyperglycaemia, increased fatty acids and insulin resistance can lead to changes in nitric oxide, the renin-angiotensin-aldosterone system and sympathetic system activity leading to hypertension and arterial stiffness [72]. In patients with type 1 diabetes, empagliflozin reduced arterial stiffness measured by aortic pulse wave velocity, but the results could not be explained by any of the typical metabolic characteristics associated with arterial stiffness [72]. Postulated mechanisms explaining reduced arterial stiffness after treatment with a SGLT2i include improved glycaemic control, weight loss and the direct effects on vascular smooth muscle relaxation after induction of a negative sodium balance. This improvement in arterial stiffness, coupled with an overall reduction in plasma volume secondary to natriuretic and diuretic effects, currently represent two of the leading theories to explain the cardio-metabolic benefits of SGLT2i.

**Renoprotective Pathways**

In patients with T2DM, SGLT2 inhibition is consistently associated with an acute, dose-dependent reduction in estimated glomerular filtration rate by ~5 mL·min–1·1.73 m–2 and ~30% to 40% reduction in albuminuria [73]. Hyperfiltration and the intrarenal haemodynamic changes responsible for the hyperfiltration play a central role in the development of chronic kidney disease, particularly in diabetes and/or obesity [74]. Inhibition of sodium reabsorption, through SGLT2 inhibition, leads to increased delivery of sodium to the macula densa, which stimulates tubuloglomerular feedback and afferent arterial vasoconstriction and reduces glomerular hyperfiltration. This is in contrast to the efferent vasodilation observed with renin-angiotensin-aldosterone system (RAAS) inhibition. SGLT2 inhibition leads to haemodynamic changes clinically manifested as an acute reduction in estimated glomerular filtration rate (eGFR) and albuminuria, despite an increase in plasma aldosterone and angiotensin II [75]. Activation of the RAAS is highly supportive of a reduced plasma volume in response to SGLT2i. The eGFR decline with SGLT2i is completely reversible after drug discontinuation and independent of the changes seen with RAAS inhibition [76]. Some studies support the concept that a combination of SGLT2i and RAAS inhibitors may lead to synergistic effects on blood pressure and renoprotection [77, 78].

In contrast to the reversible reduction in eGFR, albuminuria in the EMPA-REG OUTCOME trial was only partially reversed on discontinuation of empagliflozin, suggestive of long-term structural changes in the kidney [79]. As chronic kidney disease progresses, increases in intraglomerular pressure are associated with glomerular fibrosis and inflammation. Glucose reabsorption occurs via both SGLTs and renal glucose transporters (GLUTs) [31, 80]. The energy for SGLT-mediated active transport of glucose (against its concentration gradient) across the cell membrane is derived from the sodium electrochemical potential gradient. This is maintained by the transport of intracellular sodium ions into the blood via sodium potassium adenosine triphosphatase (ATPase) pumps situated in the basolateral membrane [31, 80]. When SGLT2i are administered, excessive glucose reabsorption from the proximal tubular epithelial cells is inhibited, thereby reducing the oxygen-consuming workload of reabsorption, with possible improvements to tubulointerstitial cell structure and even function [81]. Elevation of haematocrit has generally been assumed to be related to haemoconcentration, in parallel with reduced plasma volumes, however transient increases in reticulocyte count and erythropoietin (EPO) secretion may provide an alternative explanation [65]. Since these changes are not observed in patients treated with hydrochlorthiazide, increased EPO may be a sign of tubulointerstitial recovery after treatment with SGLT2i [82].

**Summary**

Despite having their primary effect in a single organ, the kidney, SGLT2 inhibitors have pleiotropic effects that result in multiple and profound clinical benefits when used in the treatment of people with type 2 diabetes. SGLT2 inhibitors may yet be found to also be of use in other conditions, particularly heart failure and renal disease outside of the context of diabetes.

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**Table 1**

|  |  |  |
| --- | --- | --- |
|  | **SGLT1** | **SGLT2** |
| **Anatomical location** | Intestine/kidney  (segment 3) | Kidney  (segments 1/2) |
| **Specificity** | Glucose/galactose | Glucose |
| **Glucose affinity** | High (Km=0.4mM) | Low (Km=2mM) |
| **Glucose transport capacity** | Low | High (x5 fold higher) |
| **Physiological role** | Inhibition of intestinal  glucose uptake | Inhibition of renal  glucose uptake |
| **Clinical symptoms from mutation in transporter protein** | Diarrhoea | Glucosuria |

The differing clinical effects and side effect profile of the various SGLT2 inhibitors maybe explained by the relative specificity to the different SGLT receptors (Table 2)[83].

**Table 2**

|  |  |
| --- | --- |
| **Drug name** | **SGLT2:SGLT1 relative specificity** |
| Empagliflozin | 2500 |
| Ertugliflozin | 2235 |
| Dapagliflozin | 1200 |
| Canagliflozin | 200 |
| Sotagliflozin | 20 |

Empagliflozin has the highest selectivity for SGLT2 receptors (2500 fold). Dual SGLT1/2 inhibition (e.g. sotagliflozin) could potentially reduce hyperglycemia more than SGLT2-selective inhibition in patients with type 2 diabetes. SGLT2 inhibitors with low SGLT2/1 selectivity increase circulating GLP1 concentrations probably due to inhibition of intestinal SGLT1 (and thus inhibiting intestinal glucose uptake). This is particularly apparent when these specific SGLT2 inhibitors are co-administered with DPP-IV inhibitors[84]. However, altered gastrointestinal (GI) luminal glucose and tolerability maybe an issue.

**Legends to Figures**

**Figure 1 –** Mechanisms of renal glucose transport in the proximal tubule

**Figure 2 –** Effects of SGLT2 inhibition in multiple organ systems and metabolic pathways