



# The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure

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## Abstract

Inhibition of the sodium–glucose cotransporter (SGLT) 2 in the proximal tubule of the kidney has a broad range of effects on renal function and plasma volume homeostasis, as well as on adiposity and energy metabolism across the entire body. SGLT2 inhibitors are chiefly used in type 2 diabetes for glucose control, achieving reductions in HbA<sub>1c</sub> of 7–10 mmol/mol (0.6–0.9%) when compared with placebo. This glucose-lowering activity is proportional to the ambient glucose concentration and glomerular filtration of this glucose, so may be greater in those with poor glycaemic control and/or hyperfiltration at baseline. Equally, the glucose-lowering effects of SGLT2 inhibitors are attenuated in individuals without diabetes and those with a reduced eGFR. However, unlike the glucose-lowering effects of SGLT2 inhibitors, the spill-over of sodium and glucose beyond the proximal nephron following SGLT2 inhibition triggers dynamic and reversible realignment of energy metabolism, renal filtration and plasma volume without relying on losses into the urine. In addition, these processes are observed in the absence of significant glucosuria or ongoing natriuresis. In the long term, the resetting of energy/salt/water physiology following SGLT2 inhibition has an impact, not only on adiposity, renal function and blood pressure control, but also on the health and survival of patients with type 2 diabetes. A better understanding of the precise biology underlying the acute actions of SGLT2 inhibitors in the kidney and how they are communicated to the rest of the body will likely lead to improved therapeutics that augment similar pathways in individuals with, or even without, diabetes to achieve additional benefits.

**Keywords** Diabetes · Glucose-lowering · Review · SGLT2 · SGLT2 inhibitor · Sodium–glucose cotransporter 2 · Type 2 diabetes

## Abbreviations

AKI	Acute kidney injury
CANVAS	Canagliflozin Cardiovascular Assessment Study
CKD	Chronic kidney disease
EMPA-REG	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
FPG	Fasting plasma glucose

HGP	Hepatic glucose production
NHE3	Na <sup>+</sup> /H <sup>+</sup> exchanger-3
P <sub>Bow</sub>	Hydrostatic pressure in Bowman's space
P <sub>G</sub>	Intraglomerular capillary hydrostatic pressure
SGLT	Sodium–glucose cotransporter
SNGFR	Single-nephron GFR

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## Introduction

Inhibitors of sodium–glucose cotransporter (SGLT) 2 have a wide range of clinically relevant actions in those with type 2 diabetes. Although SGLT2 inhibitors are primarily indicated as glucose-lowering agents, the consequences of reducing the renal threshold for glucosuria extend beyond simply reducing plasma glucose levels. Most attention has focused on the pleiotropic effects of SGLT2 inhibitors on cardiac function and their potential benefits with regards to heart failure and mortality rates.

In this review, we examine the effects of SGLT2 inhibitors on glucose metabolism and also explore their glucose-independent actions on adiposity, renal function and blood pressure. These additional actions are clinically important as most individuals with type 2 diabetes struggle to reduce or maintain their weight, at least every second patient has chronic kidney disease (CKD) and the majority of people with type 2 diabetes also have hypertension. Consequently, an intervention that reduces hyperglycaemia, aids weight loss and blood pressure control, and modulates kidney function has an important place in the management of type 2 diabetes.

## SGLT2 inhibitors and glucose control

SGLT2 inhibitor therapy in type 2 diabetes reduces plasma glucose levels proportional to the ambient glucose concentration and the glomerular filtration of this glucose. In clinical trials, SGLT2 inhibitors are associated with a reduction in HbA<sub>1c</sub> by 7–10 mmol/mol (0.6–0.9%) vs placebo, regardless of background therapy [1]. This finding is similar in magnitude to results with other oral glucose-lowering agents. However, owing to elevated glucosuria and hyperfiltration, greater reductions may be seen in patients with poor glycaemic control, potentially to a greater extent than with other agents [1]. As most clinical studies have been performed in participants with poor glycaemic control, it is often suggested that add-on therapy to SGLT2 inhibitors has superior efficacy compared with SGLT2 inhibitor monotherapy [2]. However, smaller reductions in HbA<sub>1c</sub> following SGLT2 inhibitor treatment are observed in participants with better control at baseline, especially at a low dose [3–5], and these reductions may be less than those with use of other agents for which the mechanism of action is not glucose-dependent.

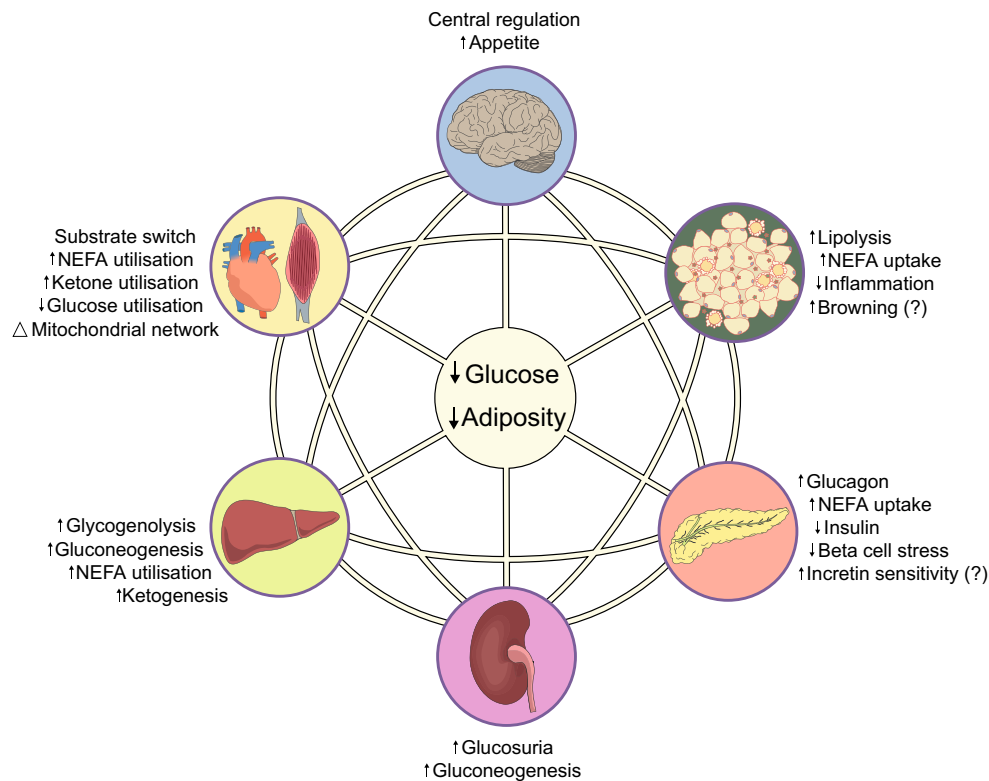
SGLT2 inhibitors reduce fasting plasma glucose (FPG) concentrations by 1–2 mmol/l, a greater reduction than that achieved with other glucose-lowering strategies [1]. This apparent advantage may partly reflect the marked elevation of FPG in patients with poor glucose control [6] and the greater glucosuria achieved following SGLT2 inhibitor therapy in this setting. SGLT2 inhibitors also reduce postprandial glucose levels and improve markers of blood glucose variability [7, 8], consistent with their mechanism of action.

The glucose-lowering effect of SGLT2 inhibitors is dose-dependent, at least in patients with HbA<sub>1c</sub> <64 mmol/mol (8%), in whom high-dose therapy produces superior glucose-lowering compared with low-dose formulations [1]. In those with poor glucose control, however, improvements in glycaemic control are statistically similar with both high- and low-dose SGLT2 inhibitors. This reflects the pharmacodynamic actions of SGLT2 inhibitors: the modest additional reduction in the threshold for glucosuria achieved by high-dose vs

low-dose formulations is most apparent when glucose filtration is closest to this threshold, and least apparent in patients with a very high HbA<sub>1c</sub>, in whom the filtered glucose load greatly exceeds the absorptive capacity for glucose. As a corollary, the preferred strategy is to initiate patients with poor glucose control with low-dose formulations of SGLT2 inhibitors, escalating to higher doses as clinically indicated; although this approach remains to be formally studied. In patients with only moderately elevated glucose levels, initiating treatment with high-dose formulations may be more appropriate for facilitating early efficacy and reinforcing ongoing adherence. Interestingly, the SGLT2 inhibitor canagliflozin (300 mg) has been associated with modestly greater effects on HbA<sub>1c</sub> and FPG compared with other SGLT2 inhibitors [1]. This is possibly due to its inhibitory actions on SGLT1 in the intestine [9] and activation of AMP-activated protein kinase (AMPK) [10], but also the higher dose used compared with other SGLT2 inhibitors. However, no head-to-head trials directly comparing individual SGLT2 inhibitors have been conducted to date.

Finally, the glucose-lowering effect of SGLT2 inhibitors also depends on the renal filtration of glucose; at the same ambient glucose levels, individuals with a high eGFR filter more glucose into their primary urine than those with a lower eGFR [11]. This further explains the greater degree of glucosuria seen with SGLT2 inhibitors in those with poor glucose control, as glucose-mediated hyperfiltration and ambient hyperglycaemia in these individuals combine to increase glucose filtration by the kidneys. By contrast, the glucose-lowering effects of SGLT2 inhibitors are attenuated in patients with eGFR <60 ml min<sup>-1</sup> [1.73 m]<sup>-2</sup> and almost absent when eGFR is <30 ml min<sup>-1</sup> [1.73 m]<sup>-2</sup> [11]. Hence, the use of SGLT2 inhibitors for glucose-lowering is not recommended or contraindicated in individuals with renal impairment. To maximise glucose-lowering effects in individuals with an eGFR <60 ml min<sup>-1</sup> [1.73 m]<sup>-2</sup>, initiating treatment with a high-dose formulation of an SGLT2 inhibitor may be preferred.

**Glucose lowering with SGLT2 inhibitor use is independent of insulin** The urinary excretion of glucose induced by SGLT2 inhibitors does not require insulin, so SGLT2 inhibitors also exert glucose-lowering effects in type 1 diabetes. Moreover, in type 2 diabetes, insulin requirements are modestly reduced following SGLT2 inhibition [12], while glucosuria and improved insulin sensitivity as a result of SGLT2 inhibition also causes a modest fall in endogenous insulin secretion [8, 13] (Fig. 1). Whether this reduced workload also preserves beta cell function beyond amelioration of glucose toxicity and peripheral insulin resistance remains to be established. However, the long-term sustainability of the glucose-lowering effects of SGLT2 inhibitors appears to be better than with sulfonylureas [14], with which beta cell exhaustion, as well as non-adherence due to hypoglycaemia or weight gain, often leads to a progressive loss of glycaemic control.



**Fig. 1** The nexus of metabolic changes contributing to reduced plasma glucose and adiposity following inhibition of SGLT2. SGLT2 inhibitor treatment triggers a reduction in insulin:glucagon ratio that increases hepatic glycogenolysis and gluconeogenesis. Renal gluconeogenesis is also modulated by SGLT2 inhibition. The unnecessary utilisation of glucose is constrained by increased peripheral oxidation of fat facilitated by increased lipolysis in adipose tissue and augmented NEFA uptake from the circulation. Ketones are also generated by the liver and act as an

alternative and efficient energy substrate for metabolism. Other efficacies in peripheral energy metabolism are also triggered, including changes in mitochondrial network homeostasis. SGLT2 inhibition increases hunger and modulates central regulation of glucose control and adiposity. In adipose tissue, altered fat utilisation may also reduce inflammation and augment fat browning. In the long term, there are additional effects in the pancreas to reduce beta cells stress and improve incretin sensitivity. This figure is available as part of a [downloadable slideset](#)

### Acute changes in glucagon, glycogen and gluconeogenesis

The loss of glucose into the urine following treatment with SGLT2 inhibitors triggers several compensatory pathways (Fig. 1). There is a rapid early increase in plasma glucagon following SGLT2 inhibitor use [13], likely arising from a reduction in (inhibitory) paracrine signalling within the islet, as well as central signals triggered by falling glucose levels. SGLT2 inhibitors may also act directly on alpha cells, at least in vitro and at high doses, to reduce SGLT1-dependent glucose uptake and promote glucagon release [15]. The resulting reduction in insulin:glucagon ratio triggers an increase in hepatic glucose production (HGP), mediated by glycogenolysis and subsequently gluconeogenesis [13]. Over time, the demand for increased glucose production is supplanted by other metabolic compensations and glucagon, hepatic glycogen and HGP return to normal [16]. Initiation of a low-carbohydrate diet induces similar dynamic metabolic changes. However, renal gluconeogenesis is also modulated following SGLT2 inhibition [17] and this may affect glucose control in the post-absorptive state, as gluconeogenesis-derived glucose is normally provided in almost equal amounts by the proximal tubule and the liver.

### Chronic shifts in metabolic substrate utilisation and ketogenesis

Depletion of liver glycogen [18, 19], and other signals that increase HGP following SGLT2 inhibition (Fig. 1), modulates the uptake and utilisation of glucose in peripheral tissues. Together, these actions protect the brain's glucose-dependent metabolism. Indeed, in this context SGLT2 inhibition may induce a state that is considered as 'pseudo-fasting'. As in the fasting state, any unnecessary utilisation of glucose is limited via increased peripheral oxidation of fat [20] due to increased lipolysis and NEFA uptake from the circulation. At the same time, NEFA is used by the liver to generate ketones, which can act as an alternative and efficient energy substrate for metabolism, and may be preferred by some tissues, such as the heart [13]. Unlike the transient changes in glucagon and HGP, the contribution of lipolysis and ketogenesis to overall energy metabolism strengthens with ongoing SGLT2 inhibitor treatment [13]. SGLT2 inhibition is also associated with changes in amino acid utilisation (as an alternative energy substrate) and protein catabolism (to provide amino acids) [21], although lean mass is not lost with SGLT2 inhibition.

## SGLT2 inhibitors and weight control

Most people with type 2 diabetes are obese, overweight or, at the very least, have increased fat deposition inside and around their internal organs. This ectopic fat has an important influence on health, illustrated by the profound effects of bariatric surgery on glycaemic control, insulin resistance, beta cell function, dyslipidaemia and hypertension, as well as broader effects on morbidity and mortality [22]. For overweight or obese individuals, it is widely recommended that an initial target of losing 5–10% of body weight is appropriate, with additional targets being set once this initial goal is met. Meeting these targets is challenging and can be made more difficult by the competing goal of glucose control and the addition of glucose-lowering agents that promote weight gain (e.g. sulfonylureas, insulin, thiazolidinediones). Hence, interventions to produce and sustain significant weight loss as well as glycaemic control in people with type 2 diabetes are held in high regard by patients and physicians alike.

**Glucosuria and weight loss** The presence and severity of glucosuria is associated with weight loss in people with uncontrolled diabetes. Weight loss is often a presenting feature of diabetes, alongside polyuria and polydipsia. In the second century AD, diabetes was described by the Greek physician, Aretaeus of Cappadocia, as a condition associated with ‘the wasting of flesh and limbs into urine’. The emaciated condition of people with type 1 diabetes prior to the discovery of insulin graphically demonstrates this phenomenon. Treatment with insulin, once it became available, resulted in lowered glucose levels, dramatic weight/fat gains and restoration of physical health, mainly due to elimination of glucosuria. In a seminal study performed in people with type 1 diabetes [23], it was estimated that 70% of the weight gained following intensive insulin treatment was due to improved renal conservation of ingested energy. Equally, in a randomised trial of night-time insulin and morning glipizide use in people with type 2 diabetes, the reduction in glucosuria largely accounted for the weight gain reported [24]. Moreover, people with type 2 diabetes presenting with little or no glucosuria do not present with weight loss [25].

**SGLT2 inhibitors and energy balance** While SGLT2 inhibitors are not licensed for use in weight loss therapy, it is apparent that, by promoting glucosuria, they provide an opportunity to achieve a negative energy balance. Consistent with this, a large number of clinical trials have reported that SGLT2 inhibitors are associated with a dose-dependent reduction in body weight [1, 26]. Initial weight loss may be rapid, with losses of 1 kg being observed within 7 days of starting therapy, and most studies reporting loss of 2–3 kg over the initial 6 months of treatment. High doses of canagliflozin may induce modestly greater weight loss than other SGLT2

inhibitors [1], possibly due to its additional actions [9, 10] and the higher dose used. Weight reduction is also greater in individuals with the highest HbA<sub>1c</sub> at baseline and is attenuated in those with good glucose control at baseline [27]. This is partly due to the magnitude of glucosuria resulting from SGLT2 inhibition and its impact on overall energy balance. In contrast, weight loss does not appear to be associated with baseline BMI, sex, race or background therapy [1].

**SGLT2 inhibitors and adiposity** Much of the early decline in body weight with SGLT2 inhibitor use follows depletion of hepatic glycogen and associated water loss. In the longer term, SGLT2 inhibitor-induced weight change mainly results from loss of fat mass, including reductions in steatosis and visceral and subcutaneous adipose tissue [28], mediated by enhanced fatty acid release from adipocytes to meet the demands for increased fatty acid oxidation (as detailed above). The potential for SGLT2 inhibition to specifically reduce hepatic fat accumulation, especially in individuals with fatty liver disease, remains under investigation. Increased fat use following SGLT2 inhibition could reduce hepatic fat stores. However, this may be offset by improved hepatic insulin sensitivity and increased uptake of NEFA liberated by peripheral lipolysis. Increased fat utilisation in white adipose tissue following SGLT2 inhibition may also reduce inflammation within fat and augment fat browning [29] (Fig. 1).

**Why isn't weight loss greater or ongoing following SGLT2 inhibitor use?** A daily loss of 60–80 g glucose into the urine every day equates to an energy loss of 1000–1300 kJ (230–310 kcal) per day, similar to that expended by running for 30 min each day. An individual with diabetes whose weight is stable (i.e. energy intake is equal to energy expenditure) beginning SGLT2 inhibitor treatment, might therefore be expected to generate a negative energy balance of 1000–1300 kJ (230–310 kcal) per day, and lose ~7 kg in body weight over 6 months if this negative balance were continued. However, the actual weight lost following SGLT2 inhibitor therapy is less than half this amount. Moreover, although clinical studies with SGLT2 inhibitors demonstrate an acute decline in body weight [1, 26], a nadir is reached after approximately 6 months and ongoing weight loss is not observed despite ongoing glucosuria and associated energy losses. This pattern implies that energy loss must be initially partly, and eventually fully, offset by other factors, as ultimately a new energy balance and stable weight is reached.

It has been suggested that SGLT2 inhibition may increase hunger (Fig. 1) [30], especially for sugar-rich foods [31], in a manner similar to exercise, low-carbohydrate diets and new-onset diabetes. Theoretically, a modest increase in energy intake may not balance initial heavy glucosuria, resulting in early weight loss with SGLT2 inhibitor use. However, as glucosuria declines with improving glucose control, (lesser)



energy losses may become fully offset by increased food intake, achieving a new energy balance and plateau in weight. Surprisingly, this would not require a large increase in energy intake—just the equivalent of one (1200 kJ) muffin extra every day, and such small dietary changes may be easily missed. At the same time, increased dietary adherence, such as that achieved when adopting a new diet, may help promote additional weight loss when starting SGLT2 inhibitor treatment, although caution is required with very-low-carbohydrate diets to prevent excessive ketogenesis.

People that adopt a low-carbohydrate diet experience an early increase in resting energy expenditure, almost half of which is due to the energy demands of gluconeogenesis [32]. This extra energy expenditure potentiates acute weight loss. By contrast, long-term adherence to a low-carbohydrate diet may be associated with a depressed metabolic rate [33] as energy-demanding gluconeogenesis is normalised and other energy-efficient compensations take over. These include changes in substrate utilisation, mitochondrial network homeostasis and downregulation of mammalian target of rapamycin complex 1 (mTORC1)-dependent pathways. One can speculate that similar changes occur following SGLT2 inhibition as well [21], whereby in the short term, glycogen depletion and enhanced energy-dependent HGP drive early weight loss. However, as gluconeogenesis normalises [16], hepatic glucagon receptors are downregulated [34] and energy-saving efficiencies are brought into force; a new steady state (weight) is reached with lower total energy expenditure, balancing ongoing energy losses associated with glucosuria.

**Weight loss in people with CKD** It is widely regarded that glucosuria, and its associated energy losses, is the primary driving factor for weight loss following SGLT2 inhibition. However, in people with reduced eGFR, impaired glomerular filtration of glucose reduces SGLT2 inhibitor-induced glucosuria, yet weight loss still occurs [11]. Hence, it is not simply the magnitude of glucosuria, but the magnitude of glucosuria per nephron, that potentially triggers feedback signals that initiate lipolysis and weight loss. However, the mechanisms that underlie this feedback pathway remain to be fully elucidated.

## SGLT2 inhibitors and renal function

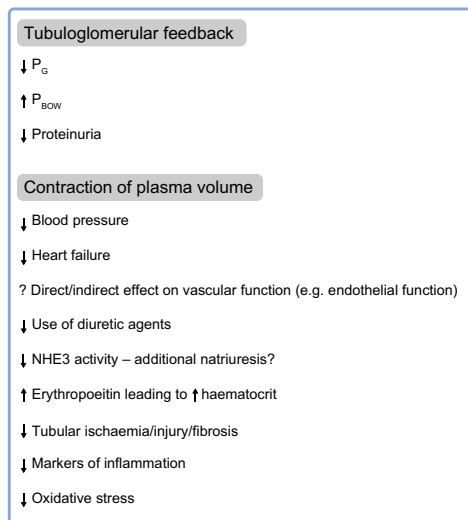
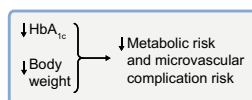
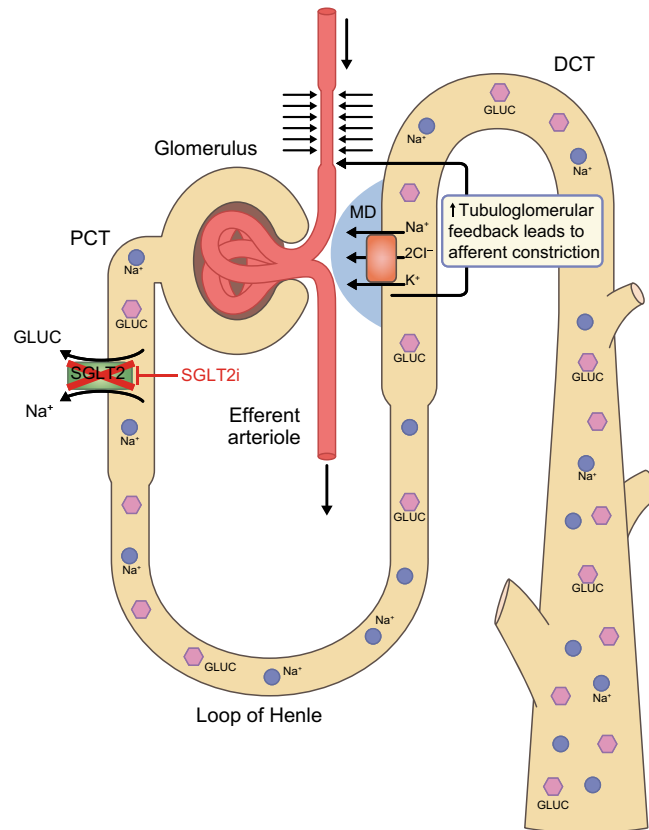
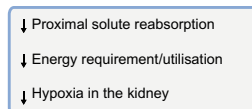
**Proximal tubular sodium handling** The glomeruli of the human kidney filter 400–600 g of sodium from the plasma every day; the proximal tubule subsequently reabsorbs between 60 and 80% of this. SGLT2 plays a small but significant role in this process, reabsorbing one  $\text{Na}^+$  ion for every glucose molecule from the lumen of the early proximal tubule. In the late proximal tubule, the high-affinity/low-capacity SGLT1 reabsorbs two  $\text{Na}^+$  ions for every glucose molecule but this

pathway is underused in the healthy kidney as >90% of the filtered glucose is reabsorbed via SGLT2. Overall, ~25 g of sodium (alongside ~180 g of glucose) is reabsorbed by SGLT-dependent pathways in the proximal tubule each day, amounting to 4–6% of the total filtered sodium load [35].

In diabetes, glucose-mediated renal hypertrophy, increased expression and activity of SGLT2 and full recruitment of SGLT1 mean that almost 50 g of sodium (over 10% of the filtered sodium load) may be reabsorbed via SGLT-dependent pathways [35]. Enhanced proximal sodium reabsorption strongly affects energy-dependent sodium transport further along the nephron, which is strongly impacted by sodium delivery to each segment. Of note, increased sodium reabsorption in the proximal tubule causes reduced sodium uptake at the macula densa (Fig. 2), activating tubuloglomerular feedback pathways to reduce synthesis of vasoconstrictive molecules, leading to augmented renal plasma flow and increased intraglomerular capillary hydrostatic pressure ( $P_G$ ) [36]. The ‘vacuum effect’ of enhanced proximal tubular sodium absorption also reduces the hydrostatic pressure in Bowman’s space ( $P_{Bow}$ ) [37, 38]. The higher pressure above and lower pressure below the filtration surface creates a pressure gradient (i.e. increased  $P_G - P_{Bow}$ ), so the filtration rate in each nephron (single-nephron GFR [SNGFR]) increases (Fig. 2).

SGLT2 inhibition has the opposite effect. Sodium and glucose that is not absorbed proximally via SGLT2 passes distally. Sodium and glucose retrieval by SGLT1 in the S2/3 segments of the proximal tubule partly compensates for this, albeit at limited capacity. In addition,  $\text{Na}^+/\text{H}^+$  exchanger-3 (NHE3)-dependent sodium uptake may also fail to compensate following SGLT2 inhibition [38], possibly due to overactivity of SGLT1. Together, these changes result in increased delivery of sodium to the macula densa, triggering a fall in  $P_G$  following SGLT2 inhibition [38–41]. Simultaneously, the osmotic effect of glucose and sodium also increases  $P_{Bow}$  to further reduce transglomerular pressure ( $P_G - P_{Bow}$ ) and SNGFR.

**SGLT2 inhibition and solute handling** In diabetes, energy-dependent sodium and glucose reabsorption in the proximal tubule increases hypoxia in the renal medulla, contributing to nephron dropout and functional decline. The high energy demands of the proximal tubule also make it sensitive to imbalances between renal oxygen delivery and oxygen consumption. This vulnerability is best illustrated by acute kidney injury (AKI), which occurs following volume depletion and is more common and severe in those with diabetes. By transferring some of the energy burden of sodium reabsorption away from the proximal tubule, SGLT2 inhibitors may protect against AKI. Indeed, in the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study [42], the incidence of AKI was lower in participants receiving empagliflozin when compared with

**a** Natriuresis**b** Glycosuria**c** Natriuresis + Glycosuria

**Fig. 2** Physiological mechanisms implicated in changes in renal function following inhibition of SGLT2. **(a)** Natriuresis activates tubuloglomerular feedback, which decreases  $P_G$  and increases  $P_{Bow}$ , thereby reducing the transcapillary pressure gradient, GFR and albuminuria. The natriuretic effects of SGLT2 inhibitors are also associated with a sustained contraction in plasma volume and enhanced distal delivery of solutes to medullary nephron segments. Increased energy requirements for solute reabsorption are offset by a compensatory increase in erythropoietin production, which raises the haemoglobin concentration. Finally, SGLT2 inhibition is also associated with suppression of tubular injury pathways, and

reduced circulating and tissue markers of inflammation and oxidative stress in experimental models. **(b)** Glucosuria is associated with improved glycaemic control and weight loss. **(c)** Sodium and glucose loss in urine may reduce proximal tubular ischaemia. This may also affect energy utilisation pathways in the medulla, thereby increasing erythropoietin production to enhance renal oxygen delivery. DCT, distal convoluted tubule; GLUC, glucose; MD, macula densa; PCT, proximal convoluted tubule; SGLT2i, SGLT2 inhibition. This figure is available as part of a [downloadable slideset](#)

placebo. However, volume depletion following SGLT2 inhibitor use may precipitate AKI in some settings [36, 43].

The sodium and glucose not absorbed in the proximal tubule following SGLT2 inhibition also influences solute handling elsewhere in the nephron. This distal shift in sodium reabsorptive burden following SGLT2 inhibition may increase medullary oxygen demand [44], possibly driving compensatory erythropoietin production (Fig. 2) [45]. In diabetes, however, erythropoietin production fails to increase despite renal hypoxia [46].

Tubular glucose can also be exchanged for uric acid by luminal GLUT9, which becomes more active in the presence of glucosuria [47]. The resulting uricosuria may explain the decline in plasma urate levels observed with SGLT2 inhibitor therapy [48]. Equally, SGLT2 inhibition is also associated with a reduction in phosphate clearance due to increased activity of the  $\text{Na}^+/\text{PO}_4^{3-}$  cotransporter, leading to a 3–5%

increase in serum phosphorous and compensatory effects on parathyroid hormone, fibroblast growth factor 23 and vitamin D [49]. SGLT2 inhibition has no direct impact on potassium homeostasis. The incidence of hyperkalaemia was reduced by SGLT2 inhibitor (empagliflozin) use in the EMPA-REG OUTCOME trial; although this was not observed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) [42, 50], possibly reflecting differences in incident renal impairment between the two trial cohorts (Fig. 3).

**SGLT2 inhibitors and kidney function** Realignment of renal sodium handling following SGLT2 inhibition is associated with a modest acute reduction in eGFR of  $3\text{--}4\text{ ml min}^{-1} [1.73\text{ m}]^{-2}$  [42, 50, 51]. This occurs after a single dose, persists with chronic dosing and is rapidly reversible after discontinuation of therapy [42]. Notably, a fall in eGFR following SGLT2 inhibitor use is also observed in individuals with

diabetes but without overt hyperfiltration, poor glycaemic control or CKD or, even, in those without diabetes altogether [45, 52], suggesting it is not merely an outcome of improved diabetic state or correction of hyperfiltration, or mediated by glucosuria.

SGLT2 inhibitors are also associated with a rapid reduction in urinary albumin excretion, independent of glycaemic effects [53]. It is likely that the reduction in  $P_G - P_{Bow}$ , which acutely reduces the eGFR, also reduces albuminuria [42, 53]. However, other changes in tubular endocytosis arising from changes in flow, intraluminal pressure or contact time with the primary urine following SGLT2 inhibition may also modulate handling of filtered protein in the proximal tubule (Fig. 1).

Long-term treatment with SGLT2 inhibitors is also associated with reduced progression of albuminuria and slower decline in renal function when compared with placebo [42, 50, 51]. Again, this appears to be independent of improvements in blood glucose levels, weight or blood pressure and occurs in individuals with and without CKD [53].

Although the number of renal events was small, fewer participants receiving SGLT2 inhibitor therapy (vs placebo) in the EMPA-REG OUTCOME study and CANVAS experienced doubling of serum creatinine, incident dialysis, renal transplantation and/or renal death (Fig. 3) [42, 50]. In addition, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study ([ClinicalTrials.gov](http://ClinicalTrials.gov) registration no. NCT02065791) was stopped prematurely due to clear benefits towards the primary composite endpoint of doubling of serum creatinine, incident dialysis, renal transplantation, renal or cardiovascular death.

## SGLT2 inhibitors and blood pressure control

Most people with type 2 diabetes have hypertension or require antihypertensive therapies to control blood pressure. Current guidelines recommend achieving a target blood pressure of <140/90 mmHg [54] to prevent micro- and macrovascular complications, disability and death [55]. However, lower targets may be appropriate for individuals with, or at high-risk of, cardiovascular disease or CKD [54].

Although not indicated as an antihypertensive agent, treatment with SGLT2 inhibitors is associated with sustained lowering of systolic and diastolic blood pressure by 4–6 mmHg and 1–2 mmHg, respectively [1, 56]. This reduction is observed in hypertensive and non-hypertensive individuals, regardless of background therapy, although the reduction may be greater in the former due to increased sodium/volume sensitivity in people taking vasodilators (rendered sodium/volume sensitive by sustained vasodilatation) [56]. A reduction in blood pressure is also observed in individuals with reduced eGFR [11], even though the glucose-lowering efficacy of SGLT2 inhibitors is attenuated in this setting. Furthermore,

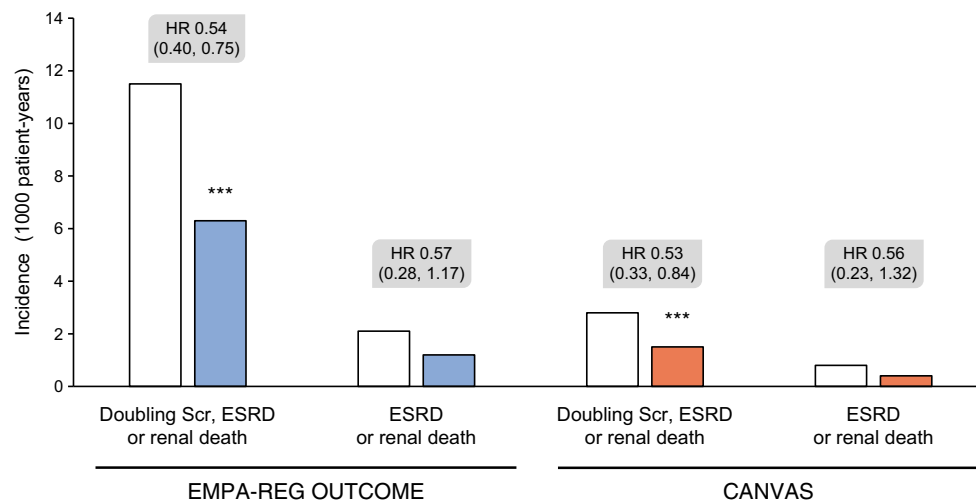
reductions in blood pressure with SGLT2 inhibitor use are also observed in renal transplant recipients, arguing against a direct neurogenic mechanism (as a transplanted kidney is denervated) [57]. Finally, a reduction in blood pressure is observed regardless of glucose control in both individuals with and without diabetes [45, 52], arguing that it does not represent reversal of renal or vascular pathology, at least in the short term. The most likely mechanism for the acute fall in blood pressure following SGLT2 inhibitor therapy is a sustained reduction in plasma volume (Fig. 2).

**SGLT2 inhibitors and plasma volume** Plasma volume is tightly controlled and rapidly recovers from imposed alterations through modulation of compensatory pathways. For example, a 5% reduction in plasma volume can activate the sympathetic nervous system and the renin–angiotensin–aldosterone system, and suppress natriuretic peptides, resulting in overall promotion of sodium and water reabsorption in the kidney and restoration of plasma volume. Increases in plasma osmolality also mobilise fluid into the extracellular space.

SGLT2 inhibitors cause an acute contraction in plasma volume within hours of therapy initiation, manifested by a 3–7% increase in haemoglobin, albumin and urea concentrations. Unlike other causes of plasma volume loss, that induced by SGLT2 inhibitors continues, even over years of therapy [42]. The underlying mechanism is not merely natriuresis, as the natriuresis associated with SGLT2 inhibition is modest when compared with conventional diuretics and is transient (24 h sodium excretion returns to pre-treatment levels within days, despite ongoing treatment) [58]. Nor is it dependent on the osmotic diuretic effects of glucosuria, since similar changes in plasma volume are observed in SGLT2 inhibitor-treated individuals without diabetes, and those with a reduced eGFR, despite minimal glucosuria [11, 45]. It is likely that, following SGLT2 inhibition, the osmotic effect of glucose and increased sodium flow beyond the early proximal tubule, are interpreted by the nephron as signs of excessive filtration, such as may occur following inappropriate expansion of plasma volume or sodium loading. However, plasma volume and sodium are not elevated. In fact, total body sodium is actually diminished following SGLT2 inhibition [59]. Nonetheless, these signs trigger homeostatic changes as if they were, including resetting of a new (reduced plasma volume) steady state.

## Conclusions

The spillover of sodium and glucose beyond the proximal nephron following SGLT2 inhibition triggers a dynamic and reversible realignment of energy metabolism, renal function and plasma volume. These acute changes have consequences for the health and survival of people with type 2 diabetes. The outcomes from recent cardiovascular safety studies in



**Fig. 3** Renal outcomes in the EMPA-REG OUTCOME trial [42] and CANVAS [50], which used empagliflozin (blue bars) and canagliflozin (orange bars), respectively (white bars, placebo). It should be noted that the event rate is low and this direct comparison of these trials should be interpreted with caution owing to differences in the study design,

populations and methodology. Data are shown as incidence per 1000 patient-years; \*\*\* $p < 0.001$  vs placebo. HR (95% CI) values are also shown. ESRD, end-stage renal disease requiring dialysis; Scr, serum creatinine. This figure is available as part of a [downloadable slideset](#)

participants with cardiovascular disease support this assertion [42, 50]. However, the much longer-term benefits of SGLT2 inhibitor use arising from improved glycaemic control, beta cell preservation, and reductions in adiposity, blood pressure and plasma volume, as well as better preservation of renal function may prove equally important and more broadly applicable.

Unlike the glucose-lowering effects of SGLT2 inhibitors, effects on weight, renal function and plasma volume do not rely on ongoing losses into the urine, and occur in the absence of significant glucosuria [11] or ongoing natriuresis [58]. Subtle changes in the solute/water/energy balance in the proximal tubule following SGLT2 inhibition cause the kidney to take control of a perceived imbalance, modulating not only eGFR and plasma volume, but also metabolic processes across the entire body. A better understanding of the precise biology underlying the acute actions of SGLT2 inhibitors in the kidney and how these are communicated to the body will likely lead to improved therapeutics, augmenting similar pathways in people with, and even without diabetes, to achieve augmented benefits.

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