




REVIEW

Sodium-glucose co-transporter 2 inhibitor therapy: use in chronic kidney disease and adjunctive sodium restriction

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Abstract

The global burden of chronic kidney disease (CKD) has increased significantly over the past few decades. This reflects the rising prevalence of type 2 diabetes mellitus (T2DM) and hypertension, two leading causes of CKD. Hypertension, which can also be a complication of CKD, accelerates renal disease progression and augments cardiovascular risk, especially in individuals with diabetic kidney disease. Hence, blood pressure (BP) reduction is a vital component of CKD management. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a relatively novel class of medications developed to treat T2DM by inducing glycosuria and hence, lowering glycaemia. Additionally, SGLT2 inhibitors are antihypertensive, renoprotective and cardioprotective, even in individuals without T2DM, making them effective therapeutic agents for CKD. Another therapy that has proven to be antihypertensive, renoprotective and cardioprotective is dietary sodium restriction. This review evaluates the potential combined benefits of SGLT2 inhibition and dietary sodium restriction on the BP and renal parameters of individuals with CKD.

Introduction

Chronic kidney disease (CKD) is a term encompassing all structural and functional renal defects that last longer than 3 months.¹ In 2017, CKD affected approximately 700 million individuals globally, and was responsible for almost 36 million disability-adjusted life-years worldwide.² The burden of CKD has risen significantly in recent decades, partially due to the increasing prevalence

of diabetes and hypertension,² which account for 38% and 13% of newly treated end-stage kidney disease (ESKD) cases in Australia, respectively.³ Hypertension accelerates renal disease progression and amplifies cardiovascular risk in people with CKD, particularly those with diabetic kidney disease (DKD).² Hence, intensive blood pressure (BP) control is a crucial component of CKD management.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, a relatively new class of type 2 diabetes medications, including empagliflozin, dapagliflozin, canagliflozin and ertugliflozin, have displayed antihypertensive, renoprotective and cardioprotective effects when added to standard care in individuals with and without diabetes.^{4–10} Moreover, dietary sodium restriction is an antihypertensive, renoprotective and cardioprotective adjunct therapy in CKD, significantly enhancing the antihypertensive and renoprotective effects of renin–angiotensin–aldosterone (RAAS) inhibitors and exhibiting additive effects in combination with hydrochlorothiazide in DKD patients on background RAAS inhibition.^{11–13} Additionally, a high-sodium diet was found

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state concentrations; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection with Empagliflozin; ESKD, end-stage kidney disease; HF, heart failure; HR, hazard ratio; mGFR, measured glomerular filtration rate; PWV, pulse wave velocity; RAAS, renin–angiotensin–aldosterone system; RCT, randomised controlled trial; SGLT, sodium-glucose co-transporter; T2DM, type 2 diabetes mellitus; TGF, tubuloglomerular feedback
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to attenuate the renoprotective effects of dapagliflozin in a murine model of DKD, indicating that sodium restriction may also enhance the actions of SGLT2 inhibitors.¹⁴ However, the combined effects of SGLT2 inhibition and sodium restriction remain to be investigated in a prospective clinical trial. Furthermore, since SGLT2 is involved in renal sodium handling, there may be a mechanistic link between sodium intake and the efficacy of SGLT2 inhibitors, but this relationship is poorly elucidated. Hence, this combination warrants further investigation.

This review outlines the epidemiology of CKD in Australia, cardiovascular risk in people with CKD and type 2 diabetes mellitus (T2DM) and the management of CKD. The pharmacology of SGLT2 inhibitors and dietary sodium restriction as an adjunct therapy for CKD have also been described, with an emphasis on the antihypertensive and renoprotective effects of both therapies.

Epidemiology: CKD in Australia

In 2011–2012, CKD affected approximately 10% of Australians aged >25 years.³ There remains a paucity of data regarding the underlying causes of CKD; however, such data have been consistently obtained for patients with newly treated ESKD. Leading causes of newly treated ESKD in Australia include diabetes, glomerulonephritis, hypertension and polycystic kidney disease, accounting for 38%, 16%, 13% and 6.6% of cases, respectively.³

Chronic kidney disease, T2DM and cardiovascular risk

CKD is independently associated with increased cardiovascular risk. The risk is even greater among individuals with coexisting T2DM.¹⁵ An epidemiological study by Afkarian *et al.* indicated a 19.6% (95% confidence interval (CI), 14.7 to 24.4) standardised cumulative incidence of cardiovascular mortality in people with CKD and T2DM. In comparison, the standardised cumulative incidence was 6.7% (95% CI, 4.2 to 9.1) in participants with T2DM alone and 9.9% (95% CI, 7.9 to 11.9) in those with CKD alone.¹⁵ Similarly, Buyadaa *et al.* found that compared with people without CKD, the hazard ratio (HR) for death and major adverse cardiovascular events – non-fatal myocardial infarction, non-fatal stroke and cardiovascular death – was 2.38 (95% CI, 1.92 to 2.90) in people with T2DM and albuminuric CKD, and 1.42 (95% CI, 1.14 to 1.78) in people with T2DM and non-albuminuric CKD.¹⁶ This highlights the need for cardioprotection in CKD patients, especially those with albuminuric DKD, using approaches like BP control.

Management of chronic kidney disease

CKD management comprises a multi-pronged approach: lifestyle modification, BP control, lipid lowering, management of complications and treatment of underlying disease.¹⁷ Lifestyle modification involves increased physical activity, dietary adjustments, weight loss, smoking cessation and the avoidance of alcohol overconsumption. Dietary modification in CKD may involve limiting protein intake. Meanwhile, hypertension in people with CKD is commonly treated using RAAS inhibitors, diuretics and dietary sodium restriction.¹ Lipid lowering can be achieved using lifestyle modification and lipid-lowering pharmacotherapies. Finally, management of underlying disease often involves treating diabetes, hypertension, glomerulonephritis and/or polycystic kidney disease.¹⁷ Management of glomerulonephritis and polycystic kidney disease aims to treat symptoms and prevent complications, while the management of diabetes in CKD patients focuses on achieving glycaemic control – usually a glycated haemoglobin target of <7% using lifestyle modification and anti-hyperglycaemic agents – and ensuring renoprotection, cardioprotection and weight loss.¹⁸ RAAS inhibitors slow DKD progression.¹⁷ Like RAAS inhibitors, SGLT2 inhibitors are beneficial in the management of both diabetic and non-diabetic nephropathy.^{7,8} This is due to their pleiotropic effects – in addition to lowering glycaemia, SGLT2 inhibitors cause natriuresis, osmotic diuresis, BP reduction and weight loss, which are all beneficial in CKD.¹⁹ Hence, based on evidence from clinical trials, SGLT2 inhibitors are becoming an increasingly important part of the CKD management armamentarium. During later stages of CKD, management involves preparation for renal replacement therapy.¹⁷

SGLT2 inhibition

Pharmacokinetics

Overall, the pharmacokinetic profiles of SGLT2 inhibitors are similar (Table 1). Single oral doses of empagliflozin, dapagliflozin, canagliflozin and ertugliflozin display linear pharmacokinetics at their therapeutic doses in healthy populations. These medications are rapidly absorbed, reaching peak plasma concentrations within 2 h of oral administration. SGLT2 inhibitors are primarily metabolised through glucuronidation. Their half-lives make them suitable for once-daily dosing.^{20,21}

Exposure to SGLT2 inhibitors, denoted as area under the plasma concentration-time curve under steady-state conditions (AUC_{ss}), increases with worsening renal

Table 1 Pharmacokinetic profiles of SGLT2 inhibitors.^{20,21}

Parameter	Empagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
Dose (mg/day)	10, 25	10	100, 300	5, 15
Food effect	Clinically insignificant	Clinically insignificant	Clinically insignificant	Clinically insignificant
t_{max} (h)	1–2	2	1–2	1
Apparent volume of distribution (L)	73.8	118	119	85.5
Plasma protein binding (%)	86	91	98	94
$t_{1/2}$ (h)	12.4	12.9	100 mg: 10.6 300 mg: 13.1	16.6
Metabolism	Predominantly through direct glucuronidation and to a smaller degree, oxidation	Undergoes extensive glucuronidation, minimal oxidation and dealkylation	Undergoes extensive glucuronidation, minimal oxidation	Predominantly through direct glucuronidation, minimal oxidation
Elimination	Urinary (54%) and faecal (41%), with 28.6% and 34.2% of the administered dose excreted unchanged in the urine and faeces respectively	Urinary (75%) and faecal (21%), with 1–2% and 15–16% of the administered dose excreted unchanged in the urine and faeces respectively	Urinary (33%) and faecal (52%), with <1% and 38.7% of the administered dose excreted unchanged in the urine and faeces respectively	Urinary (50%) and faecal (41%), with 1.5% and 33.8% of the administered dose excreted unchanged in the urine and faeces respectively

SGLT2, sodium-glucose co-transporter 2; $t_{1/2}$, half-life; t_{max} , time taken to reach the maximum plasma concentration of the drug.

function. Nevertheless, in people with renal impairment, AUC_{ss} does not surpass twofold that of people with intact renal function.²¹ The anti-hyperglycaemic efficacy of SGLT2 inhibitors declines when patients have an estimated glomerular filtration rate (eGFR) lower than 45 mL/min/1.73 m²; however, the renoprotective and cardioprotective effects of these medications remain intact in individuals with an eGFR as low as 20 mL/min/1.73 m².^{8–10}

Pharmacodynamics

Mechanism of action

SGLT2 inhibitors were developed for T2DM management. In normoglycaemic individuals, the glucose load filtered at the glomerulus is entirely reabsorbed through SGLT. SGLT are transporters located in the proximal tubule. SGLT2 reabsorbs approximately 90% of the filtered glucose load, while SGLT1 reabsorbs the remainder.⁹ However, in T2DM patients, the glucose load often exceeds the renal threshold for reabsorption, causing glycosuria. SGLT2 is upregulated in response to chronic hyperglycaemia, a maladaptive mechanism to increase glucose reabsorption.⁹ Hence, SGLT2 is a suitable therapeutic target in T2DM. SGLT2 inhibitors competitively inhibit glucose and sodium reabsorption, resulting in glycosuria,²² natriuresis and osmotic diuresis (Fig. 1). They prevent 40–50% of glucose reabsorption.

Antihypertensive effects

BP reduction is an established effect of SGLT2 inhibitor therapy. A meta-analysis by Mazidi *et al.* involving participants with T2DM reported that SGLT2 inhibitors are associated with an average BP reduction of 2.46/1.46 mmHg.⁴ This meta-analysis included studies examining the effects of these medications on office, home and 24-h ambulatory BP. Meanwhile, a meta-analysis by Baker *et al.* involving participants treated with SGLT2 inhibitors examined the effects of these medications on 24-h ambulatory BP, which offers a more accurate representation of BP and cardiovascular risk than office BP. SGLT2 inhibitor use was associated with a mean 3.76/1.83 mmHg reduction in 24-h ambulatory BP.⁵ Additionally, SGLT2 inhibitors reduce central (aortic) BP,⁹ a more accurate prognostic indicator of cardiovascular events than peripheral (brachial) BP.

The modest antihypertensive effect of SGLT2 inhibitors suggests that they would be effective adjunct therapies for hypertension. In fact, a secondary analysis of Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE), a large randomised controlled trial (RCT) examining the effects of canagliflozin on the renal outcomes of people with T2DM and CKD, reported a consistent reduction in systolic BP within the treatment group, replacing the need for additional antihypertensive therapy in this population.⁶

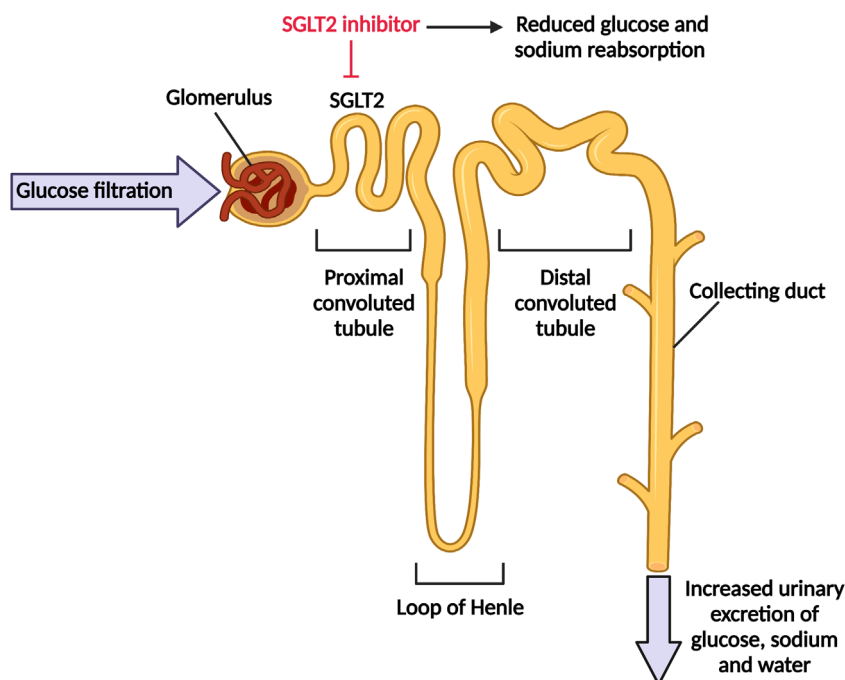


Figure 1 Mechanism of action of SGLT2 inhibitors. SGLT2 inhibitors selectively inhibit SGLT2 in the proximal tubule of the nephron, preventing 40–50% of glucose reabsorption.⁹ As a result, there is increased urinary glucose excretion and a consequent fall in plasma glucose concentrations.²² Additionally, SGLT2 inhibitors cause increased sodium and water excretion – natriuresis and diuresis, respectively. SGLT2, sodium-glucose co-transporter 2. Created with [BioRender.com](https://www.biorender.com).

Mechanisms of blood pressure reduction. The BP-lowering effects of SGLT2 inhibitors are largely attributed to their natriuretic and osmotic diuretic properties. However, these medications are purported to reduce BP through numerous mechanisms (Table 2).⁹

Renoprotective effects

The renoprotective effects of SGLT2 inhibition have been observed in renal outcome trials for dapagliflozin and canagliflozin, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) and CREDENCE (Table 3), respectively. In DAPA-CKD, dapagliflozin was found to reduce the risk of ESKD onset, doubling of the serum creatinine concentration, or renal or cardiovascular death when compared with placebo (HR, 0.61; 95% CI, 0.51 to 0.72), irrespective of T2DM diagnosis.⁸ This suggests that the renoprotective effects of SGLT2 inhibitors are independent of their glucose-lowering efficacy. Similarly, in CREDENCE, the intervention group benefitted in terms of the primary outcome of a $\geq 50\%$ deterioration in eGFR, ESKD onset, or renal or cardiovascular death, when compared with placebo (HR, 0.70; 95% CI, 0.59 to 0.82).⁷ SGLT2 inhibitors are also associated with a 30% reduction in albuminuria in people with DKD.²⁴

Mechanisms of renoprotection. The mechanisms responsible for the renal benefits of SGLT2 inhibition are poorly elucidated. However, one prominent hypothesis suggests

Table 2 Proposed mechanisms of blood pressure reduction by SGLT2 inhibitors.^{9,19}

Proposed mechanisms	Outcome(s)
Osmotic diuresis leads to extracellular fluid volume contraction	Reduced stroke volume (reduced preload) → reduced cardiac output → reduced blood pressure
Weight loss due to urinary calorie excretion	Reduced blood pressure
Activation of voltage-gated potassium channels and protein kinase G, leading to reduced arterial stiffness	Reduced total peripheral resistance → reduced blood pressure and reduced afterload
SGLT2i interact with non-classic RAAS pathways, leading to the activation of the AT ₂ receptor and angiotensin 1–7	Reduced blood pressure, positive inotropic effects, cardiac remodelling, anti-arrhythmic effects, anti-hypertrophic effects, anti-proliferative effects, natriuresis
SGLT2i lower plasma urate concentrations	Reduced blood pressure

AT₂ receptor, angiotensin II receptor type 2; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

that changes to renal haemodynamics play a central role. In a RCT involving participants with T2DM, compared with gliclazide, which had no consistent effects on renal haemodynamics, dapagliflozin produced declines in intraglomerular pressure, measured glomerular filtration rate (mGFR) and renal vascular resistance.²⁵ Together, a

Table 3 Large renal outcome trials of SGLT2 inhibitors

Trial parameter	CREDESCENCE ⁷	DAPA-CKD ⁸	EMPA-KIDNEY ²³
Intervention	100 mg of canagliflozin once daily versus placebo	10 mg of dapagliflozin once daily versus placebo	10 mg of empagliflozin once daily versus placebo
Population (n)	4401	4304	6609
Population characteristics	Adults aged ≥ 30 years with T2DM and albuminuric CKD	Adults with or without T2DM with albuminuric CKD	Adults with or without T2DM
Mean follow up (years)	2.62	2.4	3.1
Baseline UACR (mg/mmol)	33.9–565	22.6–565	≥ 22.6
HbA _{1c} at baseline (%)	6.5–12.0	–	–
Baseline eGFR (mL/min/1.73 m ²)	30–60	25–75	20–90
Primary outcome	ESKD onset, doubling of serum creatinine concentration, or renal or CV death (HR 0.70; 95% CI, 0.59–0.82)	$\geq 50\%$ decline in GFR, ESKD onset, or death from renal or CV causes (HR 0.61; 95% CI, 0.51–0.72)	Time to first occurrence of kidney disease progression or CV death
All-cause mortality	HR 0.83; 95% CI, 0.68–1.02	HR 0.69; 95% CI, 0.53–0.88	–
Cardiovascular mortality	HR 0.78; 95% CI, 0.61–1.00	HR 0.81; 95% CI, 0.58–1.12	–
ESKD	HR 0.68; 95% CI, 0.54–0.86	HR 0.64; 95% CI, 0.50–0.82	–
Notes	–	–	Study in progress

CI, confidence interval; CKD, chronic kidney disease; CREDESCENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection with Empagliflozin; ESKD, end-stage kidney disease; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; SGLT2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio.

decrease in mGFR and renal vascular resistance suggest postglomerular vasodilation, which is thought to be caused by the activation of tubuloglomerular feedback (TGF). TGF is activated when an increased concentration of sodium is delivered to the macula densa, a region of specialised cells within the distal tubule. By inhibiting proximal tubular sodium reabsorption, SGLT2 inhibitors activate TGF. As a result, adenosine is released from the macula densa. Adenosine binds to A1 receptors in the afferent arteriole, causing vasoconstriction, and the efferent arteriole, causing vasodilation.²⁵

In the same study, dapagliflozin was associated with increased excretion of the vasodilators prostaglandin E₂ and I₂.²⁵ Prostaglandin release inhibits adenosine-mediated afferent arteriolar vasoconstriction and promotes efferent arteriolar vasodilation, causing a decline in renal vascular resistance, intraglomerular pressure, mGFR and effective renal plasma flow. In the long term, these effects would lead to reduced albuminuria, eGFR stabilisation and improved renal outcomes. It is important to note that SGLT2 inhibition results in RAAS activation. Angiotensin II causes significant efferent arteriolar vasoconstriction. Hence, these haemodynamic effects of SGLT2 inhibition would be most prominent in T2DM patients on background RAAS inhibitor therapy (Fig. 2). Other renoprotective mechanisms may include

reduced production of reactive oxygen species, interactions with the sodium-hydrogen exchanger 3, improved renal oxygenation due to increased erythropoietin production and increased haematocrit, reduced arterial stiffness, a decline in total peripheral resistance, neurohormonal factors, lowering of serum urate concentrations, reduced BP, weight loss, increased serum glucagon concentrations and activation of hypoxia-inducible factor 1.^{9,19,25}

Cardioprotective effects

The cardioprotective effects of SGLT2 inhibition include lower rates of hospitalisation for heart failure (HF) or cardiovascular death in patients who have HF with reduced ejection fraction, regardless of underlying T2DM.⁹ The recent Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction reported that empagliflozin reduced the combined risk of cardiovascular death and hospitalisation for HF in patients with HF with preserved ejection fraction, regardless of underlying diabetes, when compared with placebo.¹⁰ This was particularly significant since there were no effective pharmacotherapies for HF with preserved ejection fraction until this point. The cardioprotective effects of SGLT2 inhibition and their proposed mechanisms have been discussed in other reviews.⁹

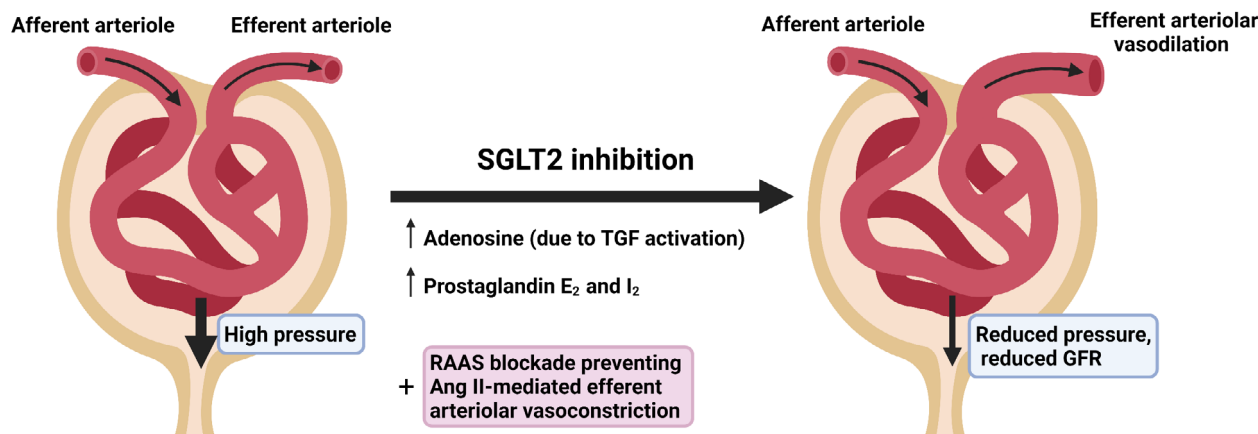


Figure 2 Hypothesised mechanisms of sodium-glucose co-transporter 2 (SGLT2) inhibitor-induced renal haemodynamic alterations in people with type 2 diabetes mellitus (T2DM) without overt nephropathy. Most patients with T2DM have high intraglomerular pressure. SGLT2 inhibition activates tubuloglomerular feedback (TGF) by increasing sodium delivery to the macula densa, which results in increased adenosine release. SGLT2 inhibition is also hypothesised to cause increased prostaglandin release. Together, these produce efferent arteriolar vasodilation, which leads to reduced intraglomerular pressure and estimated GFR, especially in patients taking renin–angiotensin–aldosterone system (RAAS) inhibitors.²⁵ Ang II, angiotensin II; GFR, glomerular filtration rate. Created with [BioRender.com](https://www.biorender.com).

Dietary sodium restriction

The World Health Organization recommends a maximum sodium intake of 2 g/day (approximately 87 mmol/day) for the general population,²⁶ which equates to a salt intake of approximately 5 g/day. Despite this, the average Australian has a sodium intake of approximately 170 mmol/day.²⁶ High sodium intake is associated with elevated BP and albuminuria, increased cardiovascular risk, and CKD progression.²⁷ Hence, reducing dietary sodium intake decreases BP and albuminuria in CKD,^{12,13,28} and augments the effects of antihypertensive and renoprotective medications.^{11–13}

Antihypertensive effects

The LowSALT study investigated the effects of dietary sodium restriction in patients with stage 3 and 4 CKD, of which approximately 40% had diabetes. There was a mean 24-h ambulatory BP decrease of 9.7/3.9 mmHg between moderate- (180 mmol/day) and low- (60 mmol/day) sodium periods.²⁸ In a meta-analysis of RCT, Suckling *et al.* found similar results – a 140 mmol/day reduction in sodium intake produced a 6.90/2.87 mmHg mean BP decrease in participants with type 2 diabetic nephropathy.²⁹ The magnitude of sodium restriction-associated BP reduction in these studies is greater than that of SGLT2 inhibitor-induced BP reduction.^{4–6}

Arterial stiffness, a determinant of central BP, is elevated in patients with CKD.³⁰ Pulse wave velocity

(PWV) is a marker that rises with increasing arterial stiffness. In the LowSALT study, the difference in PWV between the moderate- and low-salt periods was insignificant (0.5 m/s; 95% CI, –0.2 to 1.2).²⁸ Conversely, a meta-analysis of RCT found that an 89.3 mmol decrease in 24-h urinary sodium excretion was associated with a significant PWV reduction (–2.84%; 95% CI, –5.08 to –0.51).³¹ The meta-analysis involved both CKD and non-CKD patients.

Mechanisms of blood pressure reduction

There is a well defined correlation between high sodium intake and increased BP in salt-sensitive populations. Salt sensitivity is characterised by impaired sodium excretion.³² The aetiology of salt-sensitive hypertension is multifactorial and varies between patients. Key mechanisms include blunted RAAS suppression, renal sympathetic nervous system overactivity, endothelial dysfunction and oxidative stress.^{32,33} More recently, immune system involvement and epigenetic modifications, including DNA methylation, have been implicated.^{32,33} Kawarazaki and Fujita³² have suggested that various mechanisms may be activated during different life periods and interact with one another to cause salt-sensitive hypertension (Fig. 3). Most individuals with CKD, insulin resistance and obesity are salt-sensitive,^{32,33} and hence, likely to experience BP reductions in response to dietary sodium restriction.

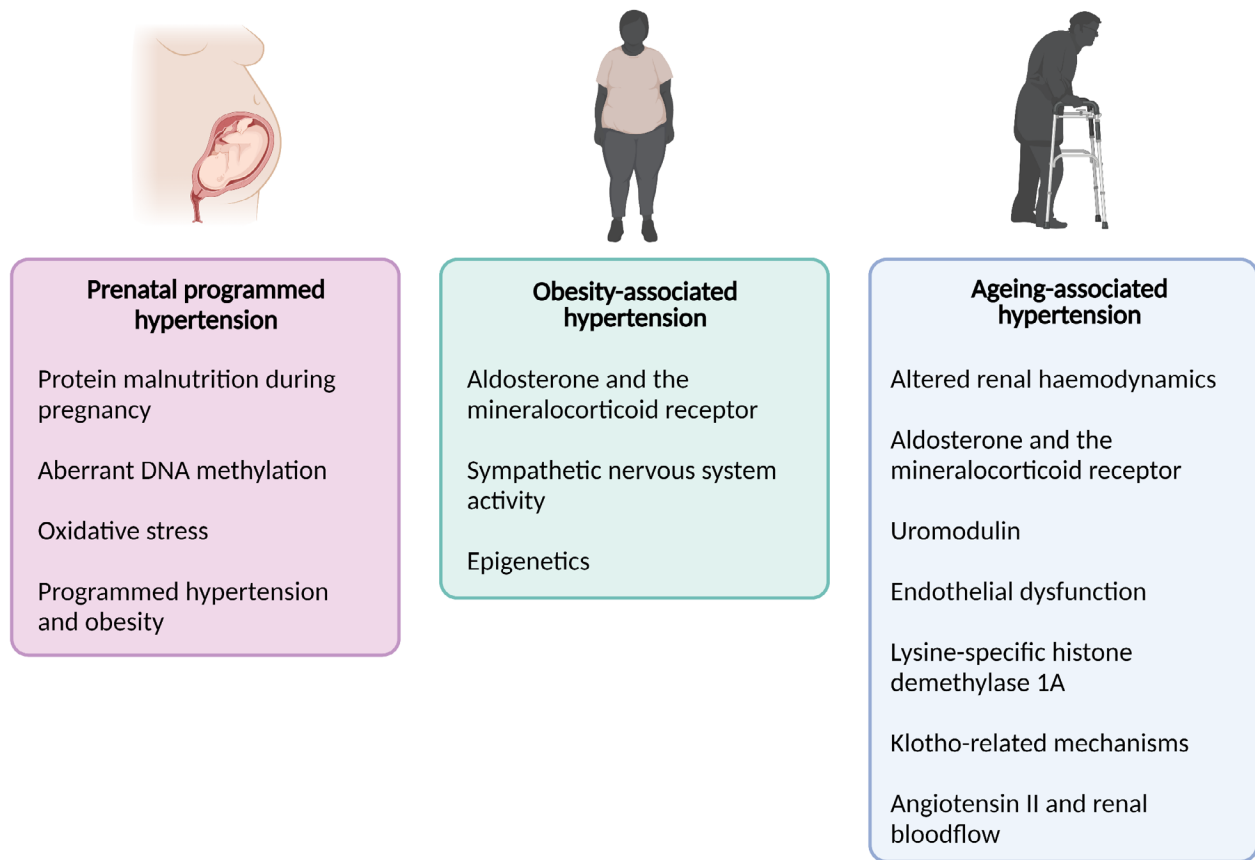


Figure 3 Postulated mechanisms of salt-sensitive hypertension throughout life.³² Created with BioRender.com.

Renoprotective effects

The LowSALT study found that the low-salt diet led to a 40–50% decrease in proteinuria and albuminuria as compared to the moderate-salt diet. Additionally, the low-salt diet reduced glomerular hyperfiltration when compared with the moderate-salt diet.²⁸ However, a meta-analysis by Smyth *et al.* found that while a high sodium intake (>200 mmol/day) was associated with a reduction in eGFR and an increase in proteinuria in participants with CKD, a low sodium intake (<100 mmol/day) was not more renoprotective than a moderate sodium intake (100–200 mmol/day).³⁴ Reducing sodium intake also slows CKD progression by reducing glomerular inflammation and glomerulosclerosis, and interstitial fibrosis in salt-sensitive individuals.^{35,36}

Mechanisms of renoprotection

As discussed, increased sodium intake is associated with BP elevation in salt-sensitive individuals. The kidneys are protected from systemic hypertension through

autoregulatory mechanisms which stabilise renal blood flow and glomerular hydrostatic pressure by constricting and dilating renal microvasculature.³⁷ However, these protective mechanisms are only intact within a certain BP range. Once the upper limit is exceeded, the kidneys are no longer guarded. This results in glomerular hypertension and consequent glomerular hyperfiltration, which manifests clinically as a normal or elevated eGFR. Glomerular hypertension is also a source of mechanical stress to glomerular cells. Hence, prolonged hyperfiltration may damage the glomerular filtration barrier, allowing plasma proteins, such as albumin to leak into urine.³⁸ Additionally, tubular alterations and vascular endothelial dysfunction have been implicated in the pathogenesis of hypertension-induced albuminuria.³⁸ Moreover, a recent study has shown that high salt intake is associated with renal damage in salt-sensitive individuals with controlled hypertension, signifying the presence of BP-independent mechanisms of sodium-induced renal injury.³⁵ There was an association between serum C-reactive protein concentrations and albuminuria,

suggesting that glomerular inflammation may contribute to albuminuria via increased vascular permeability. Furthermore, a rat study demonstrated that high salt intake is associated with increased renal collagen deposition and interstitial fibrosis.³⁶ Therefore, reducing dietary sodium intake leads to reductions in eGFR and albuminuria, and slows renal disease progression.

Cardioprotective effects

In addition to BP reduction, dietary sodium restriction causes a reduction in left ventricular hypertrophy, which is associated with increased cardiovascular morbidity and mortality.³⁹ Moreover, since sodium restriction reduces blood volume, it is beneficial in conditions associated with volume overload, including HF. The mechanisms responsible for these effects are discussed in other literature.³⁹ Furthermore, Ma *et al.* recently described a linear relationship between dietary sodium intake and cardiovascular risk. Sodium intake was estimated using 24-h urinary sodium excretion. It was observed that for each 1000 mg increase in urinary sodium excretion, there was an 18% increase in cardiovascular risk.⁴⁰ Similarly, a recent RCT examining cardiovascular and safety outcomes associated with a salt substitute (75% sodium chloride, 25% potassium chloride) compared with regular salt (100% sodium chloride) in individuals who had a history of stroke or were at least 60 years old and had hypertension, found that rates of stroke, major cardiovascular events and all-cause mortality were reduced in the group consuming the salt substitute compared with regular salt.⁴¹

Dietary sodium restriction as an adjunct therapy

Houlihan *et al.* found that the antihypertensive and proteinuria-reducing effects of the angiotensin receptor blocker, losartan, were enhanced with dietary sodium restriction in patients with T2DM, hypertension and albuminuria.¹¹ Moreover, according to Slagman *et al.*, dietary sodium restriction added to angiotensin-converting enzyme inhibitor therapy is more effective at reducing BP and proteinuria when compared with combined angiotensin receptor blocker and angiotensin-converting enzyme inhibitor therapy in patients with non-diabetic nephropathy.¹² Meanwhile, Kwakernaak *et al.* investigated the effects of the diuretic, hydrochlorothiazide and dietary sodium restriction in patients with type 2 diabetic nephropathy on background RAAS inhibition. The combination had additive effects in terms of reducing albuminuria and BP.¹³

Combined effects of SGLT2 inhibition and sodium restriction

A recent study investigated the effects of dapagliflozin in diabetic mice, with and without a high-salt diet. A normal-salt diet was defined as 0.5% salt, while a high-salt diet was defined as 4.0% salt. The dapagliflozin and normal-salt diet group had a mean urine albumin-to-creatinine ratio of 200 mg/mmol \pm 100 (standard error of the mean), the dapagliflozin and high-salt diet group had a mean ratio of 800 mg/mmol \pm 300 and the control group (diabetic mice administered saline only) had a mean ratio of 1800 mg/mmol \pm 1600.¹⁴ A high-salt diet also interfered with dapagliflozin's ability to reduce SGLT2 expression and diminished the dapagliflozin-induced amelioration of energy metabolism within proximal tubular endothelial cells in this murine model of DKD.¹⁴

To our knowledge, only one study has evaluated the impact of dietary sodium intake on the effects of SGLT2 inhibition in humans. The study is a retrospective analysis of a randomised trial investigating the antihypertensive and anti-albuminuric effects of dapagliflozin in Japanese individuals with albuminuric DKD.⁴² Participants with a higher basal sodium intake experienced greater improvements in home BP profile than those with a lower basal sodium intake. There was no difference between groups in terms of improvements in albuminuria. However, estimations of sodium intake were based on a single spot urine sample rather than a series of 24-h urine samples, which more accurately reflect daily sodium intake.⁴³ Moreover, participants' sodium intake was not controlled during the study.⁴² Additionally, given the retrospective nature of the study, it is difficult to establish causal relationships between participants' basal sodium intake and the effects of dapagliflozin on BP and albuminuria.

Further research is warranted to investigate the effect of sodium restriction in humans treated with SGLT2 inhibitors, given the conflicting results of the aforementioned studies. Likewise, more research is needed to illuminate the mechanistic relationship between SGLT2 inhibition and sodium handling. The safety profile of this combination therapy should also be explored.

SGLT2 inhibition and dietary sodium restriction both have antihypertensive, renoprotective and cardioprotective effects (Table 4). While their combined effects in people with CKD are unknown, it is expected that the combination would have more pronounced BP- and albuminuria-lowering effects than SGLT2 inhibitor therapy alone, based on the results of the murine and Kwakernaak *et al.* studies.^{13,14} Like thiazide diuretics, SGLT2 inhibitors mainly

Table 4 Effects of SGLT2 inhibition and dietary sodium restriction

Effects	SGLT2 inhibitor	Dietary sodium restriction
Antihypertensive	Reduces office blood pressure by an average of 2.46/1.46 mmHg ⁴ Reduces arterial stiffness ⁹	Reducing dietary sodium intake by 140 mmol/day induces a mean blood pressure reduction of 6.90/2.87 mmHg ²⁹ Reduced arterial stiffness reported in one meta-analysis ³¹
Renoprotective	Leads to a 30% reduction in albuminuria in people with diabetic kidney disease ²⁴ Reduces renal disease progression or death from cardiovascular or renal causes ^{7,8}	Reducing dietary sodium intake by 120 mmol/day leads to a 40–50% reduction in albuminuria in people with CKD ²⁸ Reducing dietary sodium intake reduces renal disease progression by reducing albuminuria, fibrosis and inflammation ^{35,36} Facilitates the full effects of RAAS inhibitors and diuretics ^{11–13}
Cardioprotective	Lowers rates of cardiovascular death or hospitalisation for HF ^{9,10}	Reduces and slows left ventricular hypertrophy ³⁹ Facilitates the full effects of RAAS inhibitors and diuretics ^{11–13} Reduces volume overload in HF ³⁹

CKD, chronic kidney disease; HF, heart failure; RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose co-transporter 2.

exert their antihypertensive effects through natriuresis and osmotic diuresis during initial weeks of therapy. Hence, it is expected that when combined with dietary sodium restriction, SGLT2 inhibitor therapy would have a greater antihypertensive effect. Based on existing research regarding combination therapy in the management of hypertension, we anticipate that the combination will have additive antihypertensive effects.⁴⁴

This combination is also expected to have renoprotective effects, including reduced intraglomerular hypertension and hyperfiltration, manifesting clinically as reduced eGFR and albuminuria. Moreover, sodium restriction is expected to maximise the effects of SGLT2 inhibitors on renal tubular energy metabolism. However, it is likely that adjunctive dietary sodium restriction would reduce the effects of SGLT2 inhibition on TGF. Dietary sodium restriction causes a fall in urinary sodium excretion.³¹ Therefore, it is expected that dietary sodium restriction would be associated with a lower concentration of sodium reaching the macula densa, and hence, may not activate TGF. Nevertheless, the loss of a single mechanism may not be significant, given the fact that the two therapies achieve their renoprotective effects through a range of distinct mechanisms. Hence, this combination has the potential to produce synergistic effects in the context of renal health. Moreover, it is anticipated that SGLT2 inhibition and dietary sodium restriction would work in concert to slow the progression of HF, a common comorbidity in CKD patients, since the

therapies produce their cardioprotective effects through unique mechanisms.

Conclusion

SGLT2 inhibitors, a class of medications originally developed to treat T2DM, have antihypertensive, renoprotective and cardioprotective effects, making them effective agents for slowing CKD progression. Adjunctive dietary sodium restriction is another measure which has antihypertensive, renoprotective and cardioprotective effects. Although the effects of this combination are yet to be investigated in a prospective clinical trial, it is postulated that SGLT2 inhibition with adjunctive sodium restriction would be more beneficial for cardiorenal outcomes in CKD than SGLT2 inhibition alone.

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