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REVIEW

Chronic kidney disease in type 1 diabetes: translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes

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Abstract

Current management of chronic kidney disease (CKD) in type 1 diabetes centres on glycaemic control, renin–angiotensin system inhibition and optimisation of risk factors including blood pressure, lipids and body weight. While these therapeutic approaches have significantly improved outcomes among people with type 1 diabetes and CKD, this population remains at substantial elevated risk for adverse kidney and cardiovascular events, with limited improvements over the last few decades. The significant burden of CKD and CVD in type 1 diabetes populations highlights the need to identify novel therapies with the potential for heart and kidney protection. Over the last decade, sodium–glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists and non-steroidal mineralocorticoid receptor antagonists have emerged as potent kidney-protective and/or cardioprotective agents in type 2 diabetes. The consistent, substantial kidney and cardiovascular benefits of these agents has led to their incorporation into professional guidelines as foundational care for type 2 diabetes. Furthermore, introduction of these agents into clinical practice has been accompanied by a shift in the focus of diabetes care from a 'glucose-centric' to a 'cardiorenal risk-centric' approach. In this review, we evaluate the potential translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes with the lens of preventing the development and progression of CKD.

Keywords Cardiorenal · Chronic kidney disease · Glucagon-like peptide 1 receptor agonist · Mechanisms · Review · Sodium–glucose cotransporter-2 inhibitor · Therapeutics · Type 1 diabetes

Abbreviations

ARB	Angiotensin receptor blocker
CKD	Chronic kidney disease
CRP	C-reactive protein
DKA	Diabetic ketoacidosis
DKD	Diabetic kidney disease

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ERA	Endothelin receptor antagonist
ESKD	End-stage kidney disease
GIP	Glucose-dependent insulinotropic polypeptide
GLP1	Glucagon-like peptide 1
GLP1-RA	Glucagon-like peptide 1 receptor agonist
HF	Heart failure
hsCRP	High-sensitivity C-reactive protein
MACE	Major adverse cardiovascular events
MRA	Mineralocorticoid receptor antagonist
NO	Nitric oxide
RAS	Renin–angiotensin system
sGC	Soluble guanylate cyclase
SGLT2i	Sodium–glucose cotransporter-2 inhibitor(s)
UACR	Urine albumin to creatinine ratio

Burden of chronic kidney disease in type 1 diabetes: an unmet clinical need

Similar to type 2 diabetes, hyperglycaemia in type 1 diabetes increases the risk of end-organ damage, including chronic kidney disease (CKD). CKD can be classified and prognosticated using eGFR and albuminuria (quantified using the urine albumin to creatinine ratio [UACR]) [1]. The relative risks of complications, including progression of CKD to end-stage kidney disease (ESKD), CVD and mortality, are increased with both reduced eGFR and elevated UACR levels [1]. The prevalence of CKD in type 1 diabetes increases with diabetes duration, with approximately 33% and 25% of adults developing albuminuria and eGFR <60 ml/min per 1.73 m^2, respectively, after >40 years of diabetes; overall, the lifetime risk of ESKD is 10–30% [2, 3]. Notably, there was a decrease in the cumulative incidence of severe albuminuria in individuals diagnosed with type 1 diabetes in the 1980s compared with those diagnosed in the 1970s in Finland, although no further improvement was apparent in the 1990–1999 diagnosis cohort [4]. This study also showed that, from the onset of recurrent albuminuria screening in 1980 until 2020, the cumulative incidence of moderate albuminuria had shown no signs of decrease. The decrease between the 1970s and the 1980s coincided with the emergence of renin–angiotensin system (RAS) blockers, but the conspicuous lack of further improvements after the 1980s highlights the need for additional kidney-protective medications [4]. In a similar analysis of the Swedish National Diabetes Register, a decreasing trend in standardised incidence rates of diabetic nephropathy in people with type 1 diabetes was observed from 2001 to 2019, with no changes in the rates of ESKD over the same period [5]. Additionally, CVD remains a leading cause of morbidity and mortality in type 1 diabetes. Compared with matched controls, individuals diagnosed with type 1 diabetes between 0 and 10 years of age have a nearly 30 times increased risk of coronary heart disease, with greater than seven times the risk of cardiovascular death [6].

While the prevalence of CVD is similar in individuals with type 1 diabetes and those with type 2 diabetes, the risk of CKD may be greater in those with type 1 diabetes. Following age stratification, the risk of CKD was 1.4- to 3.0-fold higher in individuals with type 1 diabetes at all ages than in those with type 2 diabetes [7]. Additionally, in Scandinavian cohort studies, event rates of heart failure (HF), stroke, incident CKD and 'cardiorenal'-related death were higher in type 1 diabetes than in type 2 diabetes [7]. Consistent with these results, age-, sex- and socioeconomic status-adjusted data from national Scottish registries demonstrated that incident HF hospitalisations were higher among those with type 1 diabetes than those with type 2 diabetes [8]. Importantly, underuse of therapies directed at heart and kidney protection was noted in individuals with type 1 diabetes compared with those with type 2 diabetes in the Scandinavian cohort [7]. Fewer people with type 1 diabetes than type 2 diabetes were on CVD medication (53.9% vs 82.1%), ACE inhibitors (22.5% vs 32.0%) and angiotensin receptor blockers (ARB) (16.7% vs 31.3%).

The significant burden of CKD and CVD in type 1 diabetes highlights the need to identify novel therapies with the potential for heart and kidney protection. Although significant therapeutic advances have been made for people living with type 2 diabetes, similar benefits have yet to be achieved in those with type 1 diabetes. In this review, we evaluate the potential translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes with the lens of preventing the development and progression of CKD.

Mechanistic underpinnings of CKD in diabetes

The development and progression of CKD in diabetes is driven by metabolic and haemodynamic factors, which contribute to endothelial dysfunction and activation of inflammatory and pro-fibrotic pathways [9, 10]. These processes interact with one another in a pathological feed-forward cycle, ultimately yielding functional and structural kidney abnormalities characteristic of diabetic kidney disease (DKD) (Fig. 1).

Persistent hyperglycaemia induces deleterious changes in kidney cellular metabolism and function through a variety of mechanisms. Hyperglycaemia differentially affects energy metabolism across kidney cell types, for example impeding glycolysis in glomerular epithelial cells (where glucose is the preferred energy substrate) while enhancing glycolysis in proximal tubular epithelial cells (which typically rely on fatty acid oxidation) [11]. Changes in glucose metabolism culminate in endothelial dysfunction and the activation of

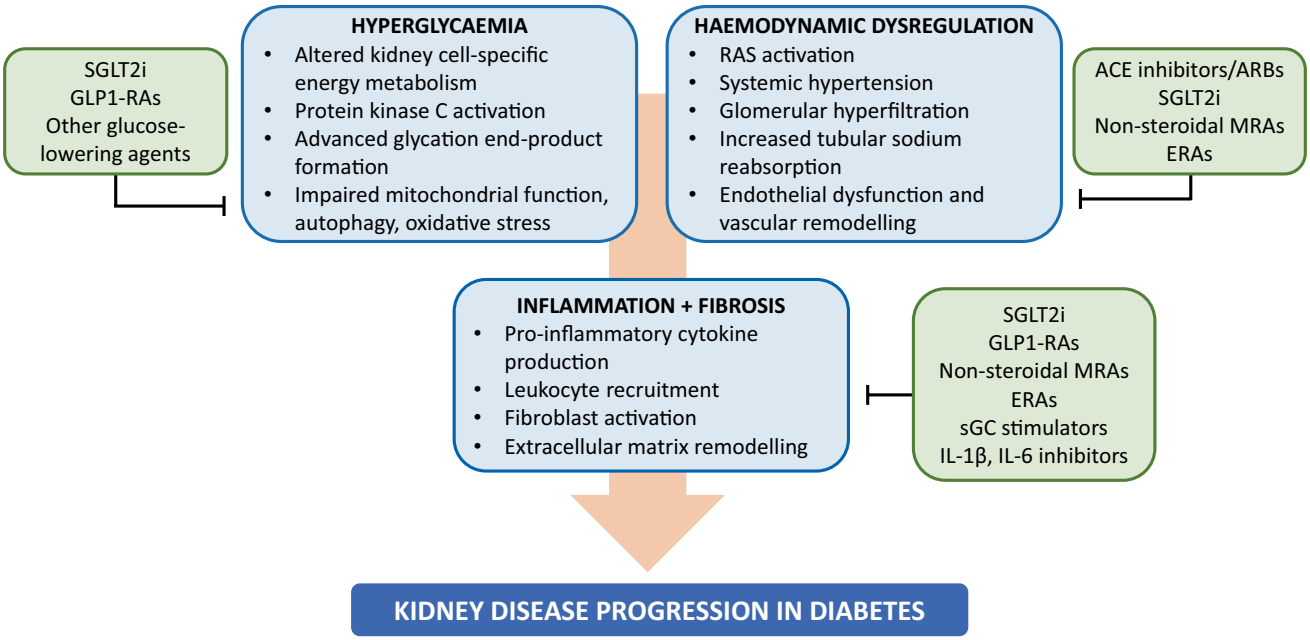

Fig. 1 Mechanisms underlying kidney disease progression in diabetes. Processes contributing to kidney disease progression in diabetes are summarised in the blue boxes. Pharmacological agents targeting these processes are shown in the green boxes. ERA, endothelin receptor antagonist; sGC, soluble guanylate cyclase. This figure is available as a downloadable slide

downstream inflammatory and pro-fibrotic pathways involving immune cell recruitment and TGF-β1 production. These changes are also accompanied by mitochondrial dysfunction, impaired autophagy and oxidative stress. Additionally, non-enzymatic binding of glucose to circulating proteins results in generation of AGEs. AGEs cause injury by binding to AGE-specific receptors and alteration of cellular structures and protein metabolism, augmenting inflammation and oxidative stress [12].

Haemodynamic factors, RAS overactivation and hypertension are central to CKD development and progression in diabetes. Diabetes-associated excess kidney tissue RAS activation increases angiotensin II-mediated glomerular efferent arteriolar vasoconstriction and glomerular hyperfiltration, tubular sodium reabsorption, and signalling through intracellular pathways, resulting in inflammation and oxidative stress [13]. Additionally, angiotensin II contributes to endothelial dysfunction by inducing expression of vascular endothelial growth factor and increasing reactive oxygen species, which reduce the bioavailability of vasodilators (such as nitrous oxide) responsible for maintaining normal glomerular vascular tone [14]. Hyperglycaemia also disrupts tubuloglomerular feedback, causing afferent arteriolar vasodilation and exacerbating glomerular hyperfiltration. Excess aldosterone, in addition to increasing tubular sodium reabsorption, activates inflammatory and pro-fibrotic pathways and promotes vascular remodelling [15]. Elevated systemic blood pressure, exacerbated by RAS activation and transmitted to the glomerular capillary system in the context of impaired autoregulation, further worsens glomerular endothelial injury and dysfunction.

Together, the combined outcomes of these metabolic and haemodynamic factors and their downstream inflammatory and pro-fibrotic effects result in glomerular and tubular injury, amounting to clinical and histopathological disease. This manifests as progressively worsening albuminuria and eGFR decline, with glomerular mesangial expansion, podocyte effacement, segmental glomerulosclerosis and tubular injury, which progress to diffuse glomerular and tubulointerstitial fibrosis [10].

Current pharmacological treatment landscape

Current management of CKD in type 1 diabetes centres on glycaemic control, RAS inhibition and optimisation of risk factors including blood pressure, lipids and body weight [1, 16]. Insulin-based glycaemic control is the pharmacological cornerstone in type 1 diabetes and delays the onset and progression of kidney disease. The benefits of intensive insulin therapy for kidney and other microvascular complications, cardiovascular outcomes and mortality in adults with type 1 diabetes were comprehensively demonstrated in the DCCT/

EDIC study [17]. In DCCT, participants were randomised to either intensive or conventional insulin therapy (achieving a median HbA_{1c} level of 7% vs 9% [53 vs 75 mmol/mol], respectively) and followed for a mean of 6.5 years. In the observational follow-up study EDIC, all participants were encouraged to attempt intensive glycaemic control and were followed for >15 years. Intensive therapy resulted in a reduced risk of albuminuria and eGFR decline, extending beyond the randomisation period, indicating the importance of early glycaemic control in preventing long-term adverse kidney outcomes [18].

RAS inhibition using an ACE inhibitor or an ARB is recommended for adults with type 1 diabetes and albuminuria, with numerous placebo-controlled trials demonstrating a reduced risk of albuminuria progression and eGFR decline independent of blood pressure-lowering effects [19, 20]. Overall, in adults with type 1 diabetes and CKD, RAS inhibition reduces the risks of progression of microalbuminuria to macroalbuminuria by approximately 50% and of serum creatinine doubling by 20–30% [21]. However, RAS inhibition has not yet been found to prevent kidney disease among those with type 1 diabetes, normal blood pressure and without albuminuria, and also does not prevent the progression of histological changes associated with DKD at the early stage of disease [22].

Hypertension is highly prevalent in individuals with CKD and contributes to disease progression. Blood pressure management is important for reducing the risk of kidney disease and CVD in type 1 diabetes, with 2023 ADA guidelines recommending a target goal of <130/80 mmHg [16]. Hyperlipidaemia treatment and weight loss are additionally part of foundational type 1 diabetes care.

While glycaemic control, RAS inhibition and risk factor management have significantly improved outcomes among people with type 1 diabetes and CKD, this population remains at substantial elevated risk for adverse kidney and cardiovascular events. In the aforementioned RAS inhibition trials, 20–40% of participants randomised to ACE inhibitors or ARBs still experienced the primary kidney endpoint [19, 20]. More recently, in the PERL trial of adults with type 1 diabetes and CKD, iohexol-based GFR declined by ~3 ml/min per 1.73 m^2 per year, despite 90% of participants using RAS inhibitors [23]. Treatment strategies for type 1 diabetes and CKD have remained largely unchanged over the last 30 years, with RAS inhibitors introduced in 1993. There is therefore a critical need for the development and implementation of novel therapies that not only address residual kidney and cardiovascular risk in this population but also target metabolic, haemodynamic, inflammatory and profibrotic processes that contribute to kidney disease onset and progression. Concurrently, more sensitive screening methods and biomarkers for DKD are warranted, considering the limitations of albuminuria and eGFR in detecting early disease.

Pharmacological advancements in type 2 diabetes and CKD and translation to type 1 diabetes and CKD

Over the last decade, sodium–glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP1-RAs) and non-steroidal mineralocorticoid receptor antagonists (MRAs) have emerged as potent kidney- and/or cardioprotective agents in type 2 diabetes. The consistent substantial kidney and cardiovascular benefits of these agents has led to their incorporation into professional guidelines as foundational care for the management of CKD in type 2 diabetes [1, 24]. Furthermore, introduction of these agents into clinical practice has been accompanied by a shift in the focus of diabetes care from a 'glucose-centric' to a 'cardiorenal risk-centric' approach. However, SGLT2i, GLP1-RAs and non-steroidal MRAs have yet to be integrated into standard type 1 diabetes practice because of their limited availability or absence of clinical trial data in this population. In the following sections we discuss the potential for translation of SGLT2i, GLPA1-RAs and MRAs to people living with type 1 diabetes and CKD (Table 1, Fig. 1).

Sodium–glucose cotransporter-2 inhibitors SGLT2i block kidney proximal tubular sodium–glucose cotransport and were initially used as glucose-lowering agents. SGLT2i have consistently demonstrated kidney and cardiovascular benefits in people with type 2 diabetes across numerous large randomised placebo-controlled clinical trials evaluating primary kidney and cardiovascular clinical outcomes [25]. The dedicated kidney outcomes trials include the CREDENCE trial, conducted in adults with type 2 diabetes and CKD, and the DAPA-CKD and EMPA-KIDNEY trials, conducted in adults with CKD and including people with and without type 2 diabetes [26–28]. In each of these studies, SGLT2i were associated with a ~30–40% reduction in the risk of eGFR decline, progression to ESKD or death due to kidney or CVD.

The mechanisms by which SGLT2i exert their kidney-protective effects are multifactorial, related to their metabolic, haemodynamic and anti-inflammatory effects [29]. In addition to improving glycaemic control and inducing weight loss, SGLT2i may ameliorate hyperglycaemia-related kidney cell-specific changes in energy metabolism, thereby modulating mitochondrial function and autophagy [29]. SGLT2i also have prominent haemodynamic effects, normalising tubuloglomerular feedback and reducing glomerular hyperfiltration by increasing distal tubular sodium delivery.

Table 1 Summary of select clinical studies of SGLT2i, GLP1-RAs and MRAs in individuals with type 1 diabetes

Study	Participant cohort	Treatment	Findings
SGLT2i			
inTandem1 and 2 (pooled) [33]	Adults (>18 years) with type 1 diabetes (diagnosis ≥1 year) HbA_{1c} 7.0–11.0%	Sotagliflozin 200 mg/day (n=524) or 400 mg/day (n=525) or placebo (n=526) for 52 weeks	Mean (95% CI) HbA_{1c} reduction at 24 weeks: • Sotagliflozin 200 mg: −0.36% (−0.44, −0.29) (−3.9 mmol/mol [−4.8, −3.2]) • Sotagliflozin 400 mg: −0.38% (−0.45, −0.31) (−4.2 mmol/mol [−4.9, −3.4]) • All p<0.001 vs placebo • Sustained effects through week 52 Mean (95% CI) difference in fat mass between treatments and placebo at 52 weeks: • Sotagliflozin 200 mg: −1.70 kg (−2.70, −0.69), p=0.001 • Sotagliflozin 400 mg: −2.12 kg (−3.11, −1.14), p<0.001
inTandem3 [34]	Adults with type 1 diabetes (diagnosis ≥1 year) HbA_{1c} 7.0–11.0% eGFR ≥45 ml/min per 1.73 m^2	Sotagliflozin 400 mg/day (n=699) or placebo (n=703) for 24 weeks	Mean HbA_{1c} reduction at 24 weeks: • Sotagliflozin 400 mg: −0.79% (−8.6 mmol/mol) • Placebo: −0.33% (−3.6 mmol/mol) • p<0.001 Mean weight reduction at 24 weeks: • Sotagliflozin 400 mg vs placebo: difference −2.98 kg, p<0.001 Insulin reductions from baseline with sotagliflozin 400 mg (placebo corrected) at 24 weeks: • Mean daily total: −5.3 units (−9.7%) • Bolus: −2.8 units (−12.3%) • Basal: −2.6 units (−9.9%) • All p<0.001 Mean SBP pressure reduction at 24 weeks: • Sotagliflozin 400 mg vs placebo: difference −3.5 mmHg, p=0.002

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
EASE-2 and -3 (pooled) [35]	Adults with type 1 diabetes (diagnosis ≥1 year) HbA_{1c} 7.5–10.0% eGFR ≥30 ml/min per 1.73 m^2 Fasting C-peptide <0.23 nmol/l	EASE-2: empagliflozin 10 mg/day (n=243) or 25 mg/day (n=244) or placebo (n=243) for 52 weeks EASE-3: empagliflozin 2.5 mg/day (n=241), 10 mg/day (n=248) or 25 mg/day (n=245) or placebo (n=241) for 26 weeks	Mean (95% CI) placebo-subtracted HbA_{1c} changes at 26 weeks: • Empagliflozin 2.5 mg: −0.28% (−0.42, −0.15) (−3.1 mmol/mol [−4.6, −1.6]) • Empagliflozin 10 mg: −0.54% (−0.65, −0.42) (−5.9 mmol/mol [−7.1, −4.6]) • Empagliflozin 25 mg: −0.53% (−0.65, −0.42) (−5.8 mmol/mol [−7.1, −4.6]) • All p<0.0001. Mean weight change at 26 weeks: • Empagliflozin 2.5 mg: −1.8 kg • Empagliflozin 10 mg: −3.0 kg • Empagliflozin 25 mg: −3.4 kg • All p<0.0001 Mean total daily insulin dose change at 26 weeks: • Empagliflozin 2.5 mg: −6.4% • Empagliflozin 10 mg: −13.3% • Empagliflozin 25 mg: −12.7% • All p<0.0001 Mean SBP change at 26 weeks: • Empagliflozin 2.5 mg: −2.1 mmHg • Empagliflozin 10 mg: −3.9 mmHg • Empagliflozin 25 mg: −3.7 mmHg • All p<0.05
DEPICT-1 and -2 (pooled) [36]	Adults (18–75 years) with type 1 diabetes, taking insulin for ≥12 months HbA_{1c} 7.5–10.5% C-peptide <0.23 nmol/l	Dapagliflozin 5 mg/day (n=548) or 10 mg/day (n=566) or placebo (n=532) for 52 weeks	Mean (95% CI) HbA_{1c} difference vs placebo at 52 weeks: • Dapagliflozin 5 mg: −0.26% (−0.37, −0.16) (−2.8 mmol/mol [−4.0, −1.7]) • Dapagliflozin 10 mg: −0.30% (−0.41, −0.20) (−3.3 mmol/mol [−4.5, −2.2]) Mean body weight difference at 52 weeks: • Dapagliflozin 5 mg: −2.57 kg • Dapagliflozin 10 mg: −3.34 kg • Placebo: 0.44 kg Mean insulin dose difference vs placebo at 52 weeks: • Dapagliflozin 5 mg: −9.57% (−12.01, −7.07) • Dapagliflozin 10 mg: −11.75% (−14.13, −9.30) Mean SBP difference vs placebo at 52 weeks: • Dapagliflozin 5 mg: −3.72 mmHg (−7.76, −0.31) • Dapagliflozin 10 mg: −4.24 mmHg (−8.43, −0.05)

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
GLP1-RAs			
ADJUNCT ONE [53]	Adults (18–75 years) with type 1 diabetes (clinically diagnosed >12 months before visit) Taking insulin for ≥6 months HbA_{1c} 7.0–10.0% BMI ≥20 kg/m^2	Liraglutide 0.6 mg/day (n=350), 1.2 mg/day (n=346) or 1.8 mg/day (n=346) or placebo (n=347) for 26 weeks	Placebo-subtracted HbA_{1c} changes at 52 weeks (ETD [95% CI]): • Liraglutide 0.6 mg: −0.1% (−0.21, 0.03) (−1.1 mmol/mol [−2.3, −0.3]), p=0.13 • Liraglutide 1.2 mg: −0.15% (−0.27, −0.03) (−1.6 mmol/mol [−3.0, −0.3]), p=0.02 • Liraglutide 1.8 mg: −0.2% (−0.32, −0.07) (−2.2 mmol/mol [−3.5, −0.8]), p=0.002 Placebo-subtracted change in body weight (ETD [95% CI]): • Liraglutide 0.6 mg: −2.2 kg (−2.9, −1.5) • Liraglutide 1.2 mg: −3.6 kg (−4.3, −2.8) • Liraglutide 1.8 mg: −4.9 kg (−5.7, −4.2) • All p<0.0001 Ratio of rate of symptomatic hypoglycaemic events with liraglutide vs placebo (ERR [95% CI]): • Liraglutide 0.6 mg: 1.17 (0.97, 1.43), p=0.11 • Liraglutide 1.2 mg: 1.27 (1.03, 1.55), p=0.02 • Liraglutide 1.8 mg: 1.31 (1.07, 1.59), p=0.008 Ratio of total insulin dose with liraglutide vs placebo at 52 weeks (ETR [95% CI]): • Liraglutide 0.6 mg: 1.00 (0.96, 1.04), p=0.96 • Liraglutide 1.2 mg: 0.95 (0.91, 0.99), p=0.015 • Liraglutide 1.8 mg: 0.92 (0.88, 0.96), p<0.0001
ADJUNCT TWO [54]	Adults (>18 years) with type 1 diabetes Taking insulin for ≥6 months and a stable insulin dose for at least 3 months HbA_{1c} 7.0–10.0% BMI ≥20 kg/m^2	Liraglutide 0.6 mg/day (n=350), 1.2 mg/day (n=346) or 1.8 mg/day (n=346) or placebo (n=347) for 26 weeks	Placebo-subtracted HbA_{1c} changes at 52 weeks (ETD [95% CI]): • Liraglutide 0.6 mg: −0.24% (−0.39, −0.10) (−2.6 mmol/mol [−4.3, −1.1]), p=0.001 • Liraglutide 1.2 mg: −0.23% (−0.38, −0.08) (−2.5 mmol/mol [−4.2, −0.9]), p=0.002 • Liraglutide 1.8 mg: −0.35% (−0.50, −0.20) (−3.8 mmol/mol [−5.5, −2.2]), p<0.0001 Change in body weight from baseline to week 26: • Liraglutide 0.6 mg: −2.5 kg • Liraglutide 1.2 mg: −4.0 kg • Liraglutide 1.8 mg: −5.1 kg • Placebo: −0.2 kg • All p<0.0001 Ratio of rate of symptomatic hypoglycaemic events with liraglutide vs placebo (ERR [95% CI]): • Liraglutide 0.6 mg: NS • Liraglutide 1.2 mg: 1.31 (1.03, 1.68), p=0.03 • Liraglutide 1.8 mg: NS Ratio of total insulin dose with liraglutide vs placebo at 26 weeks (ETR [95% CI]): • Liraglutide 0.6 mg: 0.95 (0.92, 0.99), p=0.0075 • Liraglutide 1.2 mg: 0.93 (0.90, 0.96), p<0.0001 • Liraglutide 1.8 mg: 0.90 (0.86, 0.93), p<0.0001

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
MRAs			
Schjoedt et al [63]	Adults (>18 years) with type 1 diabetes Albuminuria (>300 mg/24 h) eGFR >30 ml/min per 1.73 m^2 Taking ACEi or ARB Diabetic retinopathy Absence of clinical/laboratory evidence consistent with non-DKD Plasma potassium <4.5 mmol/l	Crossover trial with *n*=22 participants assigned to spironolactone 25 mg/day and placebo in random order for 2 months each	Geometric mean of albuminuria (95% CI): • Spironolactone 25 mg: 584 mg/24 h (441, 829) • Placebo: 831 mg/24 h (624, 1106) • % mean difference: −30% (−41, −17), $p<0.001$ Geometric mean of fractional albumin clearance (95% CI): • Spironolactone 25 mg: 129×10^{-6} θ_{Alb} (78, 210) • Placebo: 197×10^{-6} θ_{Alb} (122, 317) • % mean difference: −35% (−46, −20), $p<0.001$ Mean (95% CI) difference in 24 h blood pressure with spironolactone vs placebo: • SBP: −8 mmHg (−17, 1) • DBP: −3 mmHg (−7, 0.2) • p=NS Mean (95% CI) difference in measured GFR with spironolactone vs placebo: • −3 ml/min per 1.73 m^2 (−7, 0.1), p=NS
Schjoedt et al [64]	Adults (>18 years) with type 1 or type 2 diabetes Nephrotic range albuminuria (>2500 mg/24 h ×3 collections) eGFR >30 ml/min per 1.73 m^2 Taking ACEi or ARB Diabetic retinopathy Absence of clinical/laboratory evidence consistent with non-DKD Plasma potassium <4.5 mmol/l	Crossover trial with *n*=20 participants assigned to spironolactone 25 mg/day and placebo in random order for 2 months each	Geometric mean of albuminuria (95% CI): • Spironolactone 25 mg: 2510 mg/24 h (1831, 3441) • Placebo: 3718 mg/24 h (2910, 4749) • % mean difference: −32% (−42, −21), $p<0.001$ Mean (95% CI) difference in 24 h blood pressure with spironolactone vs placebo: • SBP: −6 mmHg (−10, −2) • DBP: −4 mmHg (−6, −2) • $p<0.01$ for all Mean (95% CI) difference in daytime blood pressure with spironolactone vs placebo: • SBP: −7 mmHg (−12, −3) • DBP: −5 mmHg (−7, −3) • $p<0.01$ for all Mean (95% CI) difference in measured GFR with spironolactone vs placebo: • −3 ml/min per 1.73 m^2 (−6, 1), p=NS

Table 1 (continued)

Study	Participant cohort	Treatment	Findings
Schjoedt et al [65]	Adults (>18 and <70 years) with type 1 diabetes Hypertension (>135/90 but <170/100 mmHg) Normoalbuminuria and normal kidney function (plasma creatinine <88 μmol/l in women, <100 μmol/l in men) Plasma potassium <4.8 mmol/l No recent cardiovascular events	Crossover trial with *n*=17 participants assigned to spironolactone 25 mg/day and placebo in random order for 1 month each	Change in measured GFR induced by i.v. clonidine injection (indication of impaired autoregulation [95% CI]): • Spironolactone 25 mg: −15 ml/min per 1.73 m^2 (−19, −11) • Placebo: −11 ml/min per 1.73 m^2 (−17, −5) • Mean difference: −4 ml/min per 1.73 m^2 (−10, −3), *p*=NS Change in mean arterial pressure induced by i.v. clonidine injection (95% CI): • Spironolactone 25 mg: −19 mmHg (−21, −17) • Placebo: −17 mmHg (−21, −13) • Mean difference: −2 mmHg (−6, −2), *p*=NS Correlation between clonidine-induced GFR changes (indication of impaired autoregulation) and diabetes duration among placebo group: • *R*=0.67, *p*<0.01
Nielsen et al [62]	Adults (>18 and <80 years) with type 1 diabetes Microalbuminuria (30–300 mg/24 h in at least two of three urine samples) Taking ACEi or ARB HbA_{1c} <10% Plasma potassium <4.6 mmol/l Without severe hypertension (<160/100 mmHg)	Crossover trial with *n*=21 participants assigned to spironolactone 25 mg/day and placebo in random order for 60 days each	Geometric mean of urinary albumin excretion rate (95% CI): • Spironolactone 25mg: 35 mg/24 h (16, 72) • Placebo: 90 mg/24 h (61, 121) • % mean difference: −60% (−80, −21), *p*=0.011 Mean (95% CI) difference in 24 h blood pressure with spironolactone vs placebo: • SBP: −3 mmHg (−8, 3) • DBP: 0 mmHg (−3, 3) • *p*=NS for all Mean (95% CI) difference in measured GFR with spironolactone vs placebo: • −5 ml/min per 1.73 m^2 (−8, −2), *p*=0.003 % difference in tubular injury biomarkers with spironolactone vs placebo (95% CI): • Urinary NGAL/Cr: 22% (−153, 76) • Urinary LFABP/Cr: −26% (−46, 241) • Urinary KIM1/Cr: −61% (−43, 358) • *p*=NS for all

Adapted with permission from Liu et al [46]

ACEi, ACE inhibitor; Cr, creatinine; DBP, diastolic blood pressure; ERR, estimated rate ratio; ETD, estimated treatment difference; ETR, estimated treatment ratio; KIM1, kidney injury molecule-1; LFABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; SBP, systolic blood pressure

In inducing natriuresis, SGLT2i improve blood pressure. Furthermore, SGLT2i have been demonstrated to reduce kidney tissue hypoxia and inflammation in experimental models and in humans [30, 31]. The very similar benefits seen in people with CKD with or without diabetes suggests that the effect on hyperglycaemia is of minor importance for the kidney benefit [32].

In type 1 diabetes, SGLT2i have principally been investigated as glucose-lowering therapies used in conjunction with insulin (Table 1). The EASE, DEPICT and inTandem (studying the SGLT1 and 2 inhibitor sotagliflozin) trial programmes each consisted of a series of randomised placebo-controlled trials assessing the effects of SGLT2i on HbA_{1c} levels in adults with type 1 diabetes over 24–52 weeks' follow-up [33–36]. SGLT2i use was consistently associated with improvements in HbA_{1c}, as well as with reductions in total daily insulin dose, weight and blood pressure. Moreover, SGLT2i did not increase hypoglycaemia risk; rather, these agents reduced participant-reported symptomatic hypoglycaemic events, particularly nocturnal episodes [35].

While no RCTs have examined the effects of SGLT2i on primary kidney outcomes in type 1 diabetes, post hoc analyses of the EASE, DEPICT and inTandem trial programmes have yielded findings suggesting similar physiological effects in people with type 1 diabetes as in those with type 2 diabetes or with non-diabetic CKD. In pooled analyses from each of these three type 1 diabetes trial programmes, among people with a UACR >3 mg/mmol at baseline, SGLT2i resulted in a reduction in UACR of as much as 30% over 52 weeks' follow-up [37–39]. Additionally, these studies noted an acute 'dip' in eGFR with SGLT2i, suggesting a therapeutic reduction in glomerular hypertension. Furthermore, increases in haematocrit and uric acid-lowering effects were observed, which is relevant because these biochemical alterations are closely linked statistically as 'mediators' of clinical benefits of SGLT2i in kidney and cardiovascular outcome trials [40, 41]. These concordant effects on mediators of cardiorenal benefits support the hypothesis that physiological mechanisms of cardiorenal protection may also be pertinent in individuals with type 1 diabetes treated with SGLT2i. In line with this hypothesis, an observational study of 200 adults with type 1 diabetes demonstrated improvements in albuminuria and in eGFR with SGLT2i use over 12 months among adults with a baseline eGFR <90 ml/min per 1.73 m^2 [42]. In another post hoc analysis of the inTandem trials using predictive modelling, sotagliflozin was reported to reduce the estimated risk of CVD and ESKD [43].

Despite apparent kidney and cardiovascular benefits, associations between SGLT2i and increased risk of diabetic ketoacidosis (DKA) have limited the implementation of this drug class in type 1 diabetes. A meta-analysis of 18 RCTs including >7000 participants identified a 2.8-fold greater risk of DKA with SGLT2i use compared with placebo in adults with type 1 diabetes [44]. Notably, DKA risk increased with higher SGLT2i doses and was modified by various factors including BMI and insulin resistance. Specifically, SGLT2 inhibition tends to be associated with euglycaemic DKA, which is more difficult to detect in the absence of regular ketone monitoring. More widespread use of SGLT2i in type 1 diabetes will necessitate implementation of strategies to assess and mitigate DKA risk, including preventative measures, patient education and continuous ketone monitoring, as well as a better understanding of the potential benefits for clinical cardiorenal outcomes, especially in high-risk populations such as people with CKD (Table 2) [46, 47].

Glucagon-like peptide 1 receptor agonists GLP1-RAs promote glucose-dependent insulin secretion and decrease glucagon secretion, providing glycaemic benefits. With respect to non-glycaemic outcomes, GLP1-RAs promote weight loss and have been investigated in randomised placebo-controlled trials focusing on cardiovascular outcomes in adults with type 2 diabetes and high cardiovascular risk. In these trials, GLP1-RAs have consistently demonstrated benefits for both primary cardiovascular and secondary kidney outcomes. Specifically, a meta-analysis of the ELIXA, LEADER, SUSTAIN-6, EXSCEL, REWIND and AMPLITUDE-O trials in type 2 diabetes estimated a 21% reduction in the risk of new-onset macroalbuminuria, eGFR decline, progression to ESKD or death attributable to kidney causes with GLP1-RAs compared with placebo [48]. Kidney benefits may be even greater among those with CKD at baseline [49]. The ongoing FLOW trial (NCT03819153) will be the first large multinational randomised placebo-controlled trial to primarily investigate the effects of a GLP1-RA, once-weekly subcutaneous semaglutide, on major kidney outcomes in adults with type 2 diabetes and CKD [50].

The kidney-protective effects of GLP1-RAs are believed to result from reductions in inflammation and oxidative stress, in part through direct binding to glucagon-like peptide 1 (GLP1) receptors present on kidney glomerular and tubular cells [51]. A study conducted using a rat model of type 1 diabetes demonstrated reduced inflammatory cell infiltration and decreased glomerular expression of inflammatory markers, including TGF-β1 and intercellular adhesion molecule-1, with administration of exendin-4 [51]. Notably, reduced inflammation was accompanied by decreased glomerular hypertrophy, mesangial expansion and type IV collagen deposition. In another study using a rat model of diabetes, GLP1-RAs reduced markers of oxidative stress in the kidney and ameliorated AGE-induced injury [52]. Furthermore, GLP1-RAs are effective at inducing body weight loss and improving insulin sensitivity, which may have kidney and cardiovascular benefits in type 1 diabetes.

Table 2 Strategies to mitigate risk of DKA with SGLT2i use in people with type 1 diabetes

Intervention	Details
Appropriate patient selection	Select patients with no history of reoccurring DKA, normal blood ketone levels (<0.6 mmol/l), low DKA risk factors, good adherence to treatment plans and good lifestyle/behavioural factors [45]. Current label indications in Europe and Japan call for selection of patients with a BMI ≥27 kg/m^2 and a total daily insulin dose of at least 0.5 U kg^{-1} day^{-1}
Enhanced patient education	All patients should be well informed about treatment protocols, DKA risk factors and sick day management Patients should work together with healthcare providers to optimise insulin doses and create a consistent and healthy diet to minimise risk of DKA
Lower dose of SGLT2i	Lower doses of SGLT2i may still be effective while also decreasing risk of DKA [35] Initiate SGLT2 inhibitors at lower doses and titrate up in those with a good response
Limited insulin dose reductions	Reduce basal and prandial insulin after initiation of SGLT2 inhibition by 10–20% in patients with good glycaemic control to mitigate risk of hypoglycaemia Lower or no reductions in insulin may be required for patients with less intensive glycaemic control Too high a reduction in insulin may lead to DKA
Close follow-up	Adjust insulin doses accordingly with close follow-up by healthcare provider based on blood glucose and ketone monitoring
Glucose monitoring	Frequent manual glucose monitoring or continuous glucose monitoring should be carried out to enable quick readjustment of insulin dose if required
Ketone monitoring	Self-testing of β-hydroxybutyrate levels with a blood ketone meter should be carried out routinely, as euglycaemic DKA cannot be detected by glucose monitoring alone. Unlike ketone monitoring in type 1 diabetes populations without SGLT2i use, among SGLT2i users, ketone levels should be tested in the event of symptoms of DKA regardless of the level of blood glucose Urine ketone testing can be used if necessary but this only measures acetoacetate and not β-hydroxybutyrate and will be an estimation of average concentrations since the last void In future clinical practice, continuous ketone monitoring will play a role in the surveillance of ketogenesis and DKA

Adapted with permission from Liu et al [46]

In type 1 diabetes, studies of GLP1-RAs as an adjunctive therapy to insulin have focused on glycaemic control and body weight reduction (Table 1). The ADJUNCT ONE and ADJUNCT TWO trials together randomised >2000 adults with type 1 diabetes to once-daily subcutaneous injections of liraglutide compared with placebo in addition to insulin for 26 and 52 weeks, respectively [53, 54]. Overall, the ADJUNCT programme demonstrated dose-dependent improvements in HbA_{1c}, a decrease in the daily insulin dose and a reduction in body weight with liraglutide compared with placebo. A meta-analysis of five randomised placebo-controlled trials of liraglutide in type 1 diabetes validated these findings and additionally demonstrated no association of liraglutide with severe hypoglycaemia or DKA [55]. Among the GLP1-RA agents, once-weekly semaglutide may be especially promising in type 1 diabetes, as this agent has demonstrated superiority over other GLP1-RAs in terms of glycaemic control and weight loss in type 2 diabetes, as well as good tolerability [56]. The effects of semaglutide on kidney oxygenation, albuminuria and eGFR will be assessed in people with type 1 diabetes as part of the REMODEL-T1D mechanistic trial (NCT05822609).

With the results of the FLOW trial anticipated next year, as well as high rates of obesity and CVD in type 1 diabetes, there remains an unmet need for additional mechanistic and CVD/kidney outcome studies of GLP1-RAs in the population with type 1 diabetes and CKD [50]. Interest in this area similarly applies to dual GLP1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists such as tirzepatide, which have profound effects on glycaemic control and body weight (e.g. 11 kg body weight reduction in the SURPASS-4 trial), preserve the eGFR slope and reduce the UACR [57, 58]. Concurrently, triple GIP, GLP1 and glucagon receptor agonists such as retatrutide are around the corner, which have impressive effects on glycaemic control, obesity and fatty liver disease [59, 60].

Mineralocorticoid receptor antagonists MRAs act by preventing aldosterone binding to mineralocorticoid receptors. The steroidal MRAs spironolactone (first generation) and eplerenone (second generation) were the first to enter clinical practice and act as potassium-sparing diuretics with potent antihypertensive effects. Reductions in morbidity and mortality with steroidal MRA use among individuals with HF with reduced ejection fraction have led to these agents being included as cornerstones of medical therapy for HF [61].

Kidney effects of steroidal MRAs have primarily been investigated in type 2 diabetes and CKD, although several small crossover studies have been performed in adults with type 1 diabetes and CKD, where use of spironolactone resulted in a 30–60% reduction in albuminuria compared

with placebo (Table 1) [62–65]. In a meta-analysis of 16 RCTs of adults with diabetes and CKD (four of which included people with type 1 diabetes), spironolactone added to standard therapy was associated with a reduction in 24 h urinary albumin/protein excretion [66]. However, assessment of long-term, hard clinical kidney endpoints has been limited by the three- to fivefold higher risk of hyperkalaemia with spironolactone use [66]. For this reason, steroidal MRA use is discouraged in severe CKD.

Over the last few years, novel non-steroidal MRAs such as finerenone have been developed that demonstrate greater mineralocorticoid receptor selectivity and other pharmacokinetic differences compared with steroidal MRAs [67]. In safety and tolerability studies conducted in adults with CKD, finerenone was associated with lowering of albuminuria compared with placebo, and a reduced risk of hyperkalaemia compared with spironolactone [68]. Subsequently, in the large randomised placebo-controlled FIDELIO-DKD trial including adults with type 2 diabetes and CKD, finerenone reduced the risk of the primary kidney outcome (a composite of kidney failure, sustained eGFR decline ≥40% or kidney death) by ~20% [69]. While hyperkalaemia occurred more frequently with finerenone than with placebo, this was often mild or moderate and resulted in few drug discontinuations (2.3% vs 0.9%, respectively), despite study participants also being on maximum-tolerated RAS inhibitor therapy. Additionally, finerenone demonstrated significant cardiovascular benefits in adults with type 2 diabetes and CKD, evaluated in the FIGARO-DKD trial [70]. Notably, kidney and cardiovascular benefits of finerenone were apparent even in combination with SGLT2i and GLP1-RA use in secondary analyses of the FIDELIO-DKD and FIGARO-DKD trials [71, 72]. The ongoing CONFIDENCE trial (NCT05254002) is an international randomised controlled double-blind trial that will directly assess the effects of finerenone plus empagliflozin on albuminuria and characterise the efficacy and safety of this drug combination in the setting of type 2 diabetes.

Finerenone's kidney-protective effects likely stem from suppression of inflammatory and pro-fibrotic pathways [73]. Compared with steroidal MRAs, non-steroidal MRAs exert stronger anti-inflammatory and anti-fibrotic effects, probably related to their distinct effects on tissue-specific gene activation [67]. In animal models finerenone reduced the expression of genes encoding monocyte chemoattractant protein-1, matrix metalloproteinase-2 and plasminogen activator inhibitor-1 (related to tissue remodelling and fibrosis) in the kidney, and additionally demonstrated beneficial immunomodulatory effects [73]. While non-steroidal MRAs have not yet been investigated in type 1 diabetes, based on their observed benefits in type 2 diabetes and their mechanism of action, similar kidney-protective effects are anticipated, emphasising the need for dedicated studies with finerenone in people with type 1 diabetes and CKD, including their use in combination with other 'repurposed' therapies such as SGLT2i and GLP1-RAs.

Potential future treatments for CKD in type 1 diabetes

Beyond the classes of medication discussed above, additional pharmacological treatments are being investigated for use in DKD that may be suitable for use in type 1 diabetes.

Endothelin receptor antagonists (ERAs) have been studied in diabetes and CKD for over a decade, with early studies ending prematurely because of complications associated with fluid retention. Newer ERAs have since been designed that preferentially target endothelin A receptors, associated with inflammation and podocytopathy, over endothelin B receptors, associated with vasodilation and natriuresis [74]. The largest trial of ERAs, SONAR, including 2648 participants with type 2 diabetes and proteinuric CKD, demonstrated that atrasentan on top of RAS inhibition significantly lowered the risk of a doubling of serum creatinine or ESKD compared with placebo by 35% [75]. Since then, more potent endothelin A-specific ERAs have been under development for use in CKD. The combination of these agents with SGLT2 inhibition is particularly interesting considering the natriuresis and protection against HF outcomes associated with SGLT2i [76]. Specifically, a study of zibotentan, a highly selective endothelin A ERA, in combination with dapagliflozin in participants with type 2 diabetes (NCT05570305) is currently underway, with similar phase 2 trials in type 1 diabetes being proposed.

Another potential novel therapeutic option for the treatment of CKD in diabetes is the use of soluble guanylate cyclase (sGC) activators. sGC is an enzyme that catalyses the formation of cGMP after nitric oxide (NO) binding [77]. Reduced NO bioavailability and associated impairments in NO–sGC–cGMP signalling have been associated with CKD onset and progression in diabetes. Preclinical models have suggested that stimulation of sGC in diabetes can increase cGMP formation, with resultant improvements in kidney inflammation/fibrosis, glomerular permeability and kidney blood flow [78]. In a Phase II study of 156 individuals with type 2 diabetes and UACR >22.6 and <565 mg/mmol, the sGC stimulator praliciguat demonstrated a non-statistically significant placebo-adjusted decrease in UACR of 15%, accompanied by reductions in blood pressure [79]. Other sGC stimulators and activators are currently in development for the treatment of CKD (NCT04507061, NCT04750577), with at least one study including participants with type 1 diabetes.

Targeting inflammatory pathways, specifically the NLR family pyrin domain containing 3 (NLRP3)/IL-1β/IL6/C-reactive protein (CRP) pathway, has emerged as another strategy for improving cardiorenal outcomes in high-risk

populations. This was emphasised in the CANTOS trial, in which a monoclonal antibody targeting IL-1β in individuals with established atherosclerotic CVD and evidence of systemic inflammation reduced the risk of major adverse cardiovascular events (MACE) by 15–17%, an effect that was likely to be mediated by reductions in serum CRP concentrations [80, 81]. A similar effect size was also observed in a substudy of participants with eGFR <60 ml/min per 1.73 m^2 [82]. The Phase II RESCUE trial subsequently evaluated targeting the more downstream IL-6 with ziltivekimab in participants with CKD and elevated high-sensitivity CRP (hsCRP) [83]. Compared with placebo, ziltivekimab reduced hsCRP concentrations by up to 92%, prompting the formal cardiovascular outcome trial, ZEUS (NCT05021835). ZEUS will enrol 6200 participants with stage 3 or 4 CKD and elevated hsCRP levels, with a primary MACE outcome and secondary kidney endpoints including kidney disease progression, UACR reductions and eGFR slope. ZEUS will also include participants with type 1 diabetes. Additional trials are also underway in participants with type 1 diabetes targeting diverse pathways including oxidative stress, using nicotinamide adenine dinucleotide phosphate oxidase (Nox)-1/4 inhibitors, and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, using bardoxolone (NCT03366337, NCT03550443) [84, 85].

Considering the mechanistic overlap in the development and progression of CKD in type 1 and type 2 diabetes, there exists a strong rationale for simultaneously developing novel CKD therapies for use in both type 1 diabetes and type 2 diabetes and studying the repurposing of existing type 2 diabetes CKD therapies for the treatment of CKD in people with type 1 diabetes.

Conclusion

With the completion of several cardiovascular and kidney outcome trials involving an increasing number of therapeutic agents, tremendous progress has been made in the management of individuals with type 2 diabetes and CKD. Regrettably, people with type 1 diabetes have not been able to benefit from this expanded armamentarium of therapeutic agents and remain at unacceptably high risk of kidney and cardiovascular complications. The translation of these and other novel therapies under development into the clinical care of individuals with type 1 diabetes with established complications requires a concerted demonstration of efficacy and safety in dedicated and properly designed cardiorenal outcome trials.

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