

Mini Review

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GLP-1 Receptor Agonists and SGLT2 Inhibitors in Diabetes, Obesity, and Kidney Disease: a Global Perspective



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Abstract

Type 2 diabetes mellitus (T2DM) and obesity are major drivers of chronic kidney disease (CKD) worldwide, with disproportionate impact in low- and middle-income countries. Although glycemic control, blood pressure optimization, and renin-angiotensin system blockade remain central to care, substantial residual kidney and cardiovascular risk persist.

This review summarizes the evolving evidence for sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RA), and discusses implementation from a global perspective. Landmark SGLT2i trials (CREDENCE, DAPA-CKD, EMPA-KIDNEY) consistently show reduced CKD progression and cardiovascular events, including in non-diabetic CKD, supporting their role as foundational therapy at eGFR ≥ 20 mL/min/1.73m². GLP-1 RA trials initially demonstrated renal benefits in secondary outcomes; the FLOW trial has now provided dedicated kidney outcome evidence for semaglutide, alongside cardiovascular and survival benefits.

A pragmatic strategy is sequential, combining lifestyle and risk-factor optimization with SGLT2i first, GLP-1 RA when additional metabolic/cardiovascular or kidney benefit is needed, and finer none for persistent albuminuria in T2DM. The major barrier is no longer evidence but equitable access. Expanding affordability, formulary inclusion, and health-system implementation is essential to deliver global benefit.

Keywords: Receptor; Inhibitors; Diabetes; Obesity; kidney disease; Glycemic Control

Abbreviations: T2DM: Type 2 diabetes mellitus; CKD: Chronic kidney disease; RAS: Renin-Angiotensin System; SGLT2i: Sodium-Glucose Co-Transporter-2 Inhibitors; GIP: Glucose-dependent Insulinotropic Polypeptide

Introduction

Type 2 diabetes mellitus (T2DM) and obesity are major contributors to chronic kidney disease (CKD) worldwide. Current estimates suggest over 530 million adults live with diabetes, projected to reach 643 million by 2030 [1]. CKD represents one of the fastest growing causes of death globally, particularly in low- and middle-income countries [2].

Traditional strategies- glycemic control, renin-angiotensin system (RAS) blockade, and blood pressure management-remain essential but leave considerable residual risk. Two drug classes have emerged with benefits extending beyond glucose lowering: sodium-glucose co-transporter-2 inhibitors (SGLT2i) show Reno protective and cardioprotective effects, whilst glucagon-like peptide-1 receptor agonists (GLP-1 RA) offer metabolic,

cardiovascular, and increasingly, kidney benefits.

This review examines current evidence, mechanisms, and implementation challenges, drawing on guidance from KDIGO, the American Diabetes Association, and the International Society of Nephrology.

The Obesity-Diabetes-CKD Axis

Obesity promotes CKD through multiple pathways: glomerular hyperfiltration, podocyte injury, and obesity-related glomerulopathy [3]. As an endocrine organ, adipose tissue produces adipokines and inflammatory mediators that worsen insulin resistance and drive fibrosis. The convergence of obesity and T2DM has become a leading cause of end-stage kidney disease worldwide.

SGLT2 Inhibitors: Evidence and Mechanisms

Clinical trials

Three trials established the renal benefits of SGLT2 inhibitors:

CRENCE demonstrated that canagliflozin reduced kidney failure or cardiovascular death by 30% in patients with T2DM and CKD [4]. DAPA-CKD showed dapagliflozin reduced the composite of sustained eGFR decline, ESKD, or renal/cardiovascular death by 44%, with benefits in both diabetic and non-diabetic CKD [5]. EMPA-KIDNEY confirmed empagliflozin reduced CKD progression or cardiovascular death across a broad spectrum of disease severity, including patients without diabetes and those with eGFR as low as 20 mL/min/1.73m² [6].

Mechanisms of action

SGLT2 inhibitors work through multiple pathways beyond glucose reduction. They restore tubule glomerular feedback, reducing intraglomerular pressure and the hyperfiltration injury characteristic of diabetic kidney disease. Additional benefits include systemic blood pressure reduction, decreased uric acid levels, and improved tubular energetics [7].

Current recommendations

KDIGO 2022 recommends SGLT2 inhibitors as foundational therapy for T2DM with CKD when eGFR ≥ 20 mL/min/1.73m² [8]. The ADA 2025 Standards of Care supports their use in CKD or heart failure independent of glycemic targets [9]. This represents a shift from glucose-centric prescribing to organ protection.

GLP-1 Receptor Agonists: from Cardiovascular to Renal Benefits

Evolution of the evidence

Renal benefits emerged as secondary outcomes in cardiovascular trials. LEADER showed liraglutide reduced new or worsening nephropathy by 22% [10], SUSTAIN-6 demonstrated semaglutide reduced nephropathy risk by 36% [11], and REWIND found dulaglutide slowed eGFR decline [12]. However, these studies were not powered for kidney outcomes and used composite endpoints with varying clinical significance.

The FLOW Trial

The FLOW trial (2024) provided definitive evidence. As the first dedicated kidney outcome trial of a GLP-1 RA, it showed semaglutide significantly reduced kidney failure, sustained eGFR decline, and renal death in patients with T2DM and CKD. Cardiovascular events and all-cause mortality were also reduced [13]. This trial addressed limitations of earlier studies by using hard renal endpoints in a CKD population.

Mechanisms

The renal benefits likely arise from multiple mechanisms. Weight loss reduces glomerular hyperfiltration, blood pressure

reduction decreases intraglomerular pressure, and natriuretic effects may improve fluid balance. Anti-inflammatory pathways and potential direct renal effects are under investigation, though their relative contributions remain unclear [14].

Guideline integration

KDIGO 2022 recommends GLP-1 RA when SGLT2 inhibitors and metformin are insufficient or contraindicated in patients with T2DM and CKD [8]. ADA 2025 emphasizes their role when cardiovascular risk is high or when weight loss is a treatment goal [9]. Post-FLOW, these recommendations may evolve to reflect stronger kidney outcome data.

Dual incretin therapy

Tripeptide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, has shown superior glycemic control and weight loss compared with selective GLP-1 RA in the SURPASS programs. Post-hoc analysis of SURPASS-4 suggested slower eGFR decline and reduced albuminuria [15], but dedicated kidney outcome trials are needed before drawing firm conclusions about renal protection.

Integration into clinical practice

Sequential treatment approach

A pragmatic framework combines these therapies stepwise:

Begin with lifestyle modification, optimize blood pressure control, initiate RAS blockade, and start statin therapy. Add an SGLT2 inhibitor for eligible patients (eGFR ≥ 20 mL/min/1.73m²), regardless of diabetes status. Consider a GLP-1 RA when additional glycemic control, weight loss, or cardiovascular benefit is needed, or when SGLT2 inhibitors are unsuitable. In T2DM with persistent albuminuria despite RAS blockade, add a non-steroidal mineralocorticoid receptor antagonist such as finerenone [16].

Safety profile

SGLT2 inhibitors carry risks of genital mycotic infections, volume depletion, and rarely, euglycemic diabetic ketoacidosis [17]. Patient education about sick day management and ketone monitoring is essential, particularly during intercurrent illness.

GLP-1 RA commonly cause gastrointestinal side effects-nausea, vomiting, diarrhea-which may lead to dehydration. Dose titration can minimize these effects. Semaglutide does not require dose adjustment in renal impairment [18], simplifying use in CKD populations.

The global access challenge

Trial evidence has outpaced implementation. In high-income countries, regulatory approvals and reimbursement decisions have increased uptake, though significant gaps remain. In low- and middle-income countries, access is severely limited by cost, supply chain constraints, and absence from essential medicines lists.

The ISN Global Kidney Health Atlas identifies SGLT2 inhibitors as priority medicines for CKD [2], yet many health systems cannot afford them. GLP-1 RA remain even less accessible. Generic production, price negotiation, and inclusion in WHO and national formularies are essential to bridge this gap. Without concerted action, the benefits of these therapies will remain confined to wealthy populations.

Future directions

Several questions warrant investigation. Kidney outcome trials of dual and triple agonists, including tripeptide and retatrutide, will clarify whether incretin combinations offer additive renal benefits. Studies optimizing multi-drug regimens-SGLT2 inhibitors, GLP-1 RA, non-steroidal MRAs-are needed to guide clinical decision-making. Mechanistic research should distinguish direct renal effects from those mediated by weight loss and blood pressure reduction. Finally, implementation research must address the barriers preventing adoption in resource-limited settings.

Conclusion

The converging epidemics of obesity, diabetes, and CKD require therapies targeting multiple disease mechanisms. SGLT2 inhibitors have transformed CKD management by slowing progression and reducing mortality in diabetic and non-diabetic populations. GLP-1 receptor agonists, supported by dedicated kidney outcome data from FLOW, now offer proven renal benefits alongside metabolic and cardiovascular protection. Dual incretin therapies represent an evolving area of investigation.

The challenge ahead is implementation, not evidence. Ensuring equitable global access so that patients in all countries can benefit from these advances must be a priority for the nephrology community.

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