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Review Article

Semaglutide in Chronic Kidney Disease: Current Evidence, Clinical Applications, and Future Perspectives

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ABSTRACT

Chronic kidney disease (CKD) is a progressive disorder associated with substantial morbidity, mortality, and cardiovascular complications worldwide. Type 2 diabetes mellitus remains the leading cause of CKD, emphasizing the importance of therapies that provide both glycaemic control and kidney protection. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), has demonstrated significant benefits beyond glucose lowering, including weight reduction, blood pressure improvement, anti-inflammatory effects, and cardiovascular risk reduction. Recent clinical trials have also highlighted its potential to slow CKD progression by reducing albuminuria, preserving estimated glomerular filtration rate (eGFR), and decreasing the incidence of major kidney outcomes. The renoprotective effects of semaglutide are mediated through multiple mechanisms, including improvement of metabolic parameters, reduction of oxidative stress, attenuation of renal inflammation and fibrosis, and enhancement of endothelial function. Although semaglutide is generally well tolerated, gastrointestinal adverse effects, dehydration, and acute kidney injury secondary to volume depletion require careful monitoring, particularly in patients with advanced CKD. Current evidence supports the integration of semaglutide into the management of CKD, especially in individuals with type 2 diabetes and obesity, while ongoing studies continue to evaluate its role in non-diabetic CKD. This review summarizes the pharmacology, mechanisms of renal protection, major clinical trial evidence, safety considerations, current guideline recommendations, and future directions of semaglutide therapy in chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive disorder characterized by irreversible structural or

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functional abnormalities of the kidneys that persist for more than three months. It is diagnosed by a sustained reduction in the estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m²) and/or the presence of markers of kidney damage, including albuminuria, abnormalities detected on imaging, or histological changes. CKD has become a major global public health concern because of its increasing prevalence, high healthcare costs, and its strong association with cardiovascular disease and premature mortality. Diabetes mellitus, hypertension, obesity, and aging are the leading contributors to CKD, with type 2 diabetes mellitus (T2DM) remaining the most common cause worldwide. Recent estimates indicate that more than 850 million people are affected by kidney disease globally, and CKD is projected to become one of the leading causes of death by 2040.

Progressive loss of kidney function results from persistent glomerular hyperfiltration, inflammation, oxidative stress, fibrosis, and activation of neurohormonal pathways. As kidney function declines, patients experience complications such as proteinuria, electrolyte disturbances, anemia, mineral and bone disorders, fluid overload, and an increased risk of cardiovascular events. Although renin–angiotensin–aldosterone system (RAAS) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors have significantly improved renal outcomes, many patients continue to experience progressive deterioration in kidney function despite receiving standard therapy. Therefore, additional therapeutic strategies capable of slowing CKD progression and reducing cardiovascular risk are urgently needed.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as an important class of antihyperglycemic agents with substantial cardiovascular and renal benefits beyond glucose lowering. Among them, semaglutide, a long-acting GLP-1 receptor agonist administered once weekly by subcutaneous injection or once daily as an oral formulation, has demonstrated remarkable efficacy in improving glycaemic control, promoting weight loss, reducing blood pressure, and lowering the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. Increasing evidence from randomized clinical trials and real-world studies suggests that semaglutide also provides significant renoprotective effects through multiple mechanisms independent of glycaemic control.

The renal benefits of semaglutide include reduction in albuminuria, slowing of eGFR decline, improvement in metabolic and inflammatory pathways, and attenuation of renal fibrosis. Recent landmark clinical trials have further strengthened its role in delaying CKD progression and reducing kidney-related outcomes in patients with type 2 diabetes and chronic kidney disease. These findings have led to the incorporation of GLP-1 receptor agonists into international clinical practice guidelines as an important component of comprehensive CKD management, particularly in patients with diabetes, obesity, or established cardiovascular disease.

This review summarizes the current evidence regarding semaglutide in chronic kidney disease, with emphasis on its pharmacological properties, mechanisms of renoprotection, major clinical trial findings, safety profile, current guideline recommendations, and future therapeutic perspectives. The aim is to provide an updated overview of the expanding role of semaglutide in improving renal and cardiovascular outcomes among patients with CKD.

1. SEMAGLUTIDE IN CHRONIC KIDNEY DISEASE

MECHANISM OF ACTION

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) structurally modified to resist degradation by dipeptidyl peptidase-4 (DPP-4), resulting in a prolonged half-life of approximately one week. It selectively binds to GLP-1 receptors expressed in the pancreas, gastrointestinal tract, cardiovascular system, kidneys, and central nervous system. Activation of these receptors enhances glucose-dependent insulin secretion while suppressing glucagon release, thereby improving glycaemic control with a low risk of hypoglycaemia.

In addition to its glucose-lowering action, semaglutide delays gastric emptying and increases satiety through central nervous system pathways, leading to significant weight reduction. It also exerts anti-inflammatory and antioxidant effects by reducing the production of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), while decreasing oxidative stress within renal tissues. Furthermore, semaglutide improves endothelial function, reduces intraglomerular pressure, and attenuates renal fibrosis, thereby contributing to preservation of kidney function. These pleiotropic actions explain its cardiovascular and renoprotective benefits beyond glycaemic control.

Therapeutic Role in Chronic Kidney Disease

Semaglutide has emerged as an important therapeutic option for patients with chronic kidney disease, particularly those with type 2 diabetes mellitus and obesity. Although initially developed as an antihyperglycaemic agent, accumulating evidence demonstrates that semaglutide provides substantial renal and cardiovascular protection independent of its glucose-lowering effects.

Clinical studies have shown that semaglutide significantly reduces urinary albumin excretion, slows the annual decline in estimated glomerular filtration rate (eGFR), lowers the risk of progression to kidney failure, and decreases major adverse cardiovascular events. Weight reduction, improved blood pressure control, better glycaemic management, and attenuation of systemic inflammation further contribute to its beneficial effects in CKD.

Current international guidelines recommend GLP-1 receptor agonists, including semaglutide, in patients with type 2 diabetes and chronic kidney disease who require additional glycaemic control or cardiovascular risk reduction despite receiving standard therapy such as RAAS inhibitors and SGLT2 inhibitors. Semaglutide may also be considered in patients unable to tolerate SGLT2 inhibitors or in those requiring additional weight reduction. Ongoing clinical trials are evaluating its effectiveness in non-diabetic CKD, potentially expanding its role in future nephrology practice.

2. RENOPROTECTIVE MECHANISMS OF SEMAGLUTIDE

Semaglutide exerts renoprotective effects through multiple complementary mechanisms that extend beyond glycaemic control. These mechanisms include improvement in metabolic parameters, reduction of glomerular hyperfiltration, attenuation of inflammation and oxidative stress, inhibition of renal fibrosis, and reduction in cardiovascular risk factors. Together, these effects contribute to slowing CKD progression and preserving long-term kidney function.

IMPROVEMENT OF GLYCAEMIC CONTROL

Persistent hyperglycaemia is a major contributor to diabetic kidney disease through activation of oxidative stress, advanced glycation end products (AGEs), protein kinase C, and inflammatory pathways. These processes lead to glomerular injury, mesangial expansion, podocyte dysfunction, and progressive nephron loss.

Semaglutide improves glycaemic control by stimulating glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying. Unlike insulin secretagogues, its glucose-dependent mechanism minimizes the risk of hypoglycaemia. Sustained reduction in HbA1c decreases chronic glucose toxicity and slows the progression of diabetic nephropathy.

Several cardiovascular outcome trials have demonstrated that semaglutide provides consistent reductions in HbA1c while simultaneously improving renal outcomes, suggesting that its kidney-protective effects extend beyond glucose lowering alone.

REDUCTION IN ALBUMINURIA

Albuminuria is an early marker of kidney damage and an important predictor of CKD progression and cardiovascular events. Persistent urinary albumin excretion reflects glomerular endothelial dysfunction and increased permeability of the filtration barrier.

Clinical studies have consistently demonstrated that semaglutide reduces urinary albumin excretion in patients with type 2 diabetes and CKD. The reduction in albuminuria is attributed to decreased intraglomerular pressure, improved endothelial integrity, reduced inflammation, and protection of podocytes.

Lower albuminuria is associated with slower CKD progression and reduced risk of kidney failure, making it an important therapeutic target during semaglutide treatment.

PRESERVATION OF ESTIMATED GLOMERULAR FILTRATION RATE (EGFR)

Declining eGFR is one of the strongest indicators of CKD progression. Semaglutide has demonstrated the ability to slow the annual decline in eGFR compared with standard therapy.

The preservation of kidney function is believed to result from improved renal haemodynamics, reduced glomerular hyperfiltration, better metabolic control, and attenuation of chronic inflammation. Recent randomized clinical trials have shown that patients receiving semaglutide experience a slower rate of kidney function decline and a lower incidence of major kidney outcomes.

These findings suggest that semaglutide may delay progression to end-stage kidney disease and reduce the need for dialysis or kidney transplantation.

ANTI-INFLAMMATORY EFFECTS

Chronic low-grade inflammation plays a central role in CKD progression. Increased production of inflammatory cytokines promotes glomerular injury, tubular damage, and renal fibrosis.

Experimental and clinical studies have shown that semaglutide suppresses inflammatory pathways by reducing the expression of cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1).

By limiting inflammatory cell infiltration and cytokine production, semaglutide protects renal tissue from progressive structural damage and preserves nephron function.

REDUCTION OF OXIDATIVE STRESS

Oxidative stress contributes significantly to kidney injury through excessive production of reactive oxygen species (ROS). Increased oxidative stress damages endothelial cells, podocytes, and renal tubular cells, accelerating CKD progression.

Semaglutide reduces oxidative stress by improving mitochondrial function and enhancing endogenous antioxidant defence mechanisms. Experimental studies have demonstrated reductions in oxidative biomarkers and improvements in endothelial function following GLP-1 receptor activation.

These antioxidant effects complement its anti-inflammatory actions and contribute to long-term preservation of renal function.

ANTI-FIBROTIC EFFECTS

Renal fibrosis represents the final common pathway leading to irreversible CKD progression. Persistent inflammation activates fibroblasts and stimulates excessive extracellular matrix deposition, resulting in progressive loss of functional nephrons.

Semaglutide inhibits several profibrotic signalling pathways, including transforming growth factor-beta (TGF-β), thereby reducing collagen deposition and renal scarring. Animal studies have demonstrated attenuation of glomerulosclerosis and tubulointerstitial fibrosis following semaglutide therapy.

These anti-fibrotic effects may contribute to slowing irreversible structural damage within the kidneys.

WEIGHT REDUCTION AND BLOOD PRESSURE CONTROL

Obesity and hypertension are important modifiable risk factors for CKD progression. Excess body weight increases glomerular hyperfiltration, while uncontrolled hypertension accelerates nephron loss.

Semaglutide produces clinically significant weight loss by reducing appetite and increasing satiety through central nervous system mechanisms. It also modestly lowers systolic blood pressure, likely secondary to weight reduction, natriuresis, and improved vascular function.

Improvement in these cardiometabolic risk factors indirectly contributes to renal protection and better long-term kidney outcomes.

CARDIOVASCULAR PROTECTION

Cardiovascular disease is the leading cause of mortality among patients with CKD. Semaglutide has consistently demonstrated significant reductions in major adverse cardiovascular events, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Improved endothelial function, reduced inflammation, weight loss, better blood pressure control, and favourable metabolic effects collectively reduce cardiovascular risk. Because renal and cardiovascular diseases are closely interconnected, cardiovascular protection further contributes to improved overall outcomes in CKD patients.

3. EVIDENCE FROM MAJOR CLINICAL TRIALS

Robust evidence from randomized controlled trials and large cardiovascular outcome studies has established semaglutide as an effective therapy for improving glycaemic control while providing significant cardiovascular and renal protection. Recent studies have demonstrated reductions in

albuminuria, slower decline in estimated glomerular filtration rate (eGFR), and lower incidence of kidney-related outcomes, supporting its role in the management of patients with chronic kidney disease (CKD), particularly those with type 2 diabetes mellitus.

SUSTAIN-6 Trial

The SUSTAIN-6 trial was a multicentre, randomized, double-blind, placebo-controlled cardiovascular outcomes trial designed to evaluate the long-term safety of once-weekly subcutaneous semaglutide in patients with type 2 diabetes who were at high cardiovascular risk.

A total of 3,297 patients were randomized to receive semaglutide (0.5 mg or 1.0 mg once weekly) or placebo for 104 weeks in addition to standard therapy. The primary endpoint was the occurrence of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

Beyond cardiovascular benefits, semaglutide significantly reduced the incidence of new or worsening nephropathy, mainly through a reduction in persistent macroalbuminuria. Patients receiving semaglutide also demonstrated a slower decline in kidney function compared with placebo. These findings provided the first strong clinical evidence suggesting that semaglutide possesses renoprotective properties beyond glucose lowering.

FLOW Trial

The FLOW trial is the first dedicated kidney outcomes trial evaluating semaglutide in patients with chronic kidney disease and type 2 diabetes mellitus.

The study enrolled patients with moderate-to-severe CKD receiving standard therapy, including renin–angiotensin system inhibitors whenever appropriate. Participants were randomized to receive once-weekly semaglutide or placebo and were followed for kidney and cardiovascular outcomes.

Results demonstrated that semaglutide significantly reduced the risk of the composite kidney endpoint, including persistent decline in eGFR, kidney failure, or death from renal or cardiovascular causes. The treatment group also showed slower annual decline in eGFR, significant reductions in albuminuria, and fewer cardiovascular events compared with placebo.

The FLOW trial represents a landmark study because it established semaglutide as a therapy capable of directly improving clinically meaningful kidney outcomes rather than only reducing surrogate markers such as albuminuria.

SELECT Trial

The SELECT trial evaluated the cardiovascular benefits of semaglutide in overweight or obese adults without diabetes but with established cardiovascular disease.

Participants received once-weekly semaglutide 2.4 mg or placebo alongside standard medical therapy. Besides significant weight reduction and cardiovascular risk reduction, exploratory analyses demonstrated favourable effects on kidney function.

Patients receiving semaglutide experienced lower rates of kidney disease progression, slower eGFR decline, and reductions in albuminuria compared with placebo. These findings suggest that the renal benefits of semaglutide may not be entirely dependent on improvements in glycaemic control and may extend to individuals without diabetes.

STEP Clinical Trial Programme

The STEP (Semaglutide Treatment Effect in People with Obesity) clinical trial programme primarily investigated the effectiveness of semaglutide for chronic weight management.

Across multiple STEP trials, semaglutide produced substantial and sustained weight reduction, accompanied by improvements in blood pressure, lipid profile, insulin sensitivity, and inflammatory markers. Since obesity is an independent risk factor for CKD progression, these metabolic improvements indirectly contribute to kidney protection.

Weight reduction achieved with semaglutide decreases glomerular hyperfiltration, improves metabolic health, and lowers cardiovascular risk, thereby supporting long-term preservation of renal function.

Real-World Evidence

In addition to randomized clinical trials, several real-world observational studies have confirmed the effectiveness of semaglutide in routine clinical practice.

Patients treated with semaglutide demonstrated:

- Significant reductions in HbA1c.
- Meaningful weight loss.
- Reduction in urinary albumin excretion.
- Slower decline in eGFR.
- Lower rates of hospitalization due to cardiovascular complications.

These studies also suggest that semaglutide maintains an acceptable safety profile across a broad range of CKD stages, provided appropriate monitoring is performed.

Clinical Implications

Collectively, evidence from SUSTAIN-6, FLOW, SELECT, STEP, and real-world studies demonstrates that semaglutide provides benefits extending well beyond glycaemic control. Its ability to reduce albuminuria, preserve kidney function, lower cardiovascular risk, and promote weight reduction makes it an important component of comprehensive CKD management.

Current evidence supports the use of semaglutide in patients with type 2 diabetes and CKD, particularly those at high cardiovascular risk or requiring additional metabolic control despite standard therapy. Ongoing clinical studies will further clarify its role in non-diabetic CKD and other kidney disorders.

4. SAFETY PROFILE AND ADVERSE EFFECTS OF SEMAGLUTIDE IN CHRONIC KIDNEY DISEASE

Semaglutide is generally well tolerated and has demonstrated a favorable safety profile in patients with type 2 diabetes mellitus and chronic kidney disease (CKD). Most adverse effects are mild to moderate in severity and occur during treatment initiation or dose escalation. Gastrointestinal adverse events are the most frequently reported and usually improve with continued therapy. However, careful monitoring is essential in CKD patients because dehydration secondary to gastrointestinal symptoms may precipitate acute kidney injury. Appropriate patient education, gradual dose escalation, and regular follow-up can minimize treatment-related complications.

Gastrointestinal Adverse Effects

Gastrointestinal adverse events are the most common side effects associated with semaglutide therapy. These include nausea, vomiting, diarrhea,

constipation, abdominal pain, dyspepsia, and decreased appetite. These symptoms occur because GLP-1 receptor activation delays gastric emptying and alters gastrointestinal motility.

The incidence of gastrointestinal adverse effects is highest during the initial weeks of therapy and gradually decreases as patients develop tolerance. Slow dose titration and consumption of smaller meals can significantly reduce symptom severity. Most patients are able to continue treatment without discontinuation.

Acute Kidney Injury (AKI)

Although semaglutide itself is not directly nephrotoxic, severe gastrointestinal symptoms may lead to dehydration, hypotension, and reduced renal perfusion, increasing the risk of acute kidney injury, particularly in patients with advanced CKD or those receiving diuretics and renin–angiotensin system inhibitors.

Patients presenting with persistent vomiting or diarrhea should undergo prompt assessment of renal function, serum electrolytes, and hydration status. Temporary interruption of semaglutide therapy may be necessary until fluid balance is restored.

Dehydration

Dehydration is an important clinical concern during semaglutide therapy because prolonged nausea, vomiting, or diarrhea can result in excessive fluid loss.

Patients with CKD have limited renal reserve and are therefore more susceptible to deterioration in kidney function following volume depletion. Adequate oral fluid intake should be encouraged, especially during treatment initiation and dose escalation. Patients should also be educated to seek medical attention if gastrointestinal symptoms become severe or persistent.

Hypoglycaemia

Semaglutide has a low intrinsic risk of hypoglycaemia because insulin secretion is stimulated only in the presence of elevated blood glucose concentrations.

However, the risk increases when semaglutide is administered together with insulin or sulfonylureas. In such cases, reduction of insulin or sulfonylurea doses may be required to minimize hypoglycaemic episodes. Regular blood glucose monitoring is recommended during treatment initiation and dose adjustment.

Diabetic Retinopathy

Rapid improvement in glycaemic control has been associated with temporary worsening of diabetic retinopathy in susceptible individuals.

Patients with pre-existing proliferative diabetic retinopathy or severe retinal disease should undergo ophthalmological evaluation before initiating semaglutide therapy. Regular retinal examinations should continue throughout treatment, particularly in patients experiencing rapid reductions in HbA1c.

Pancreatitis

Acute pancreatitis has been reported rarely during treatment with GLP-1 receptor agonists, although a definite causal relationship remains uncertain.

Patients should be advised to report persistent severe abdominal pain, particularly if radiating to the back or accompanied by vomiting. If pancreatitis is suspected, semaglutide should be discontinued immediately and appropriate diagnostic evaluation performed.

Gallbladder Disease

Weight loss associated with semaglutide therapy may increase the risk of gallstone formation and gallbladder disorders, including cholelithiasis and cholecystitis.

Patients should be monitored for symptoms such as right upper abdominal pain, fever, nausea, or jaundice. Early diagnosis and appropriate management are recommended if gallbladder disease develops.

Thyroid Safety

Animal studies demonstrated an increased incidence of thyroid C-cell tumors following prolonged exposure to GLP-1 receptor agonists. Although similar findings have not been confirmed in humans, semaglutide is contraindicated in individuals with a personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN2).

Patients should report symptoms including neck swelling, persistent hoarseness, dysphagia, or difficulty breathing for further evaluation.

Use in Patients with Chronic Kidney Disease

Semaglutide can be used in patients with mild, moderate, and severe CKD without routine dose adjustment. Nevertheless, renal function should be monitored regularly, particularly in patients experiencing significant gastrointestinal adverse effects or receiving concomitant nephrotoxic medications.

Clinical monitoring should include:

- Serum creatinine
- Estimated glomerular filtration rate (eGFR)
- Urinary albumin-to-creatinine ratio (UACR)
- Blood pressure
- HbA1c
- Body weight
- Hydration status
- Electrolytes when clinically indicated

Careful patient selection, gradual dose escalation, and routine monitoring improve the safety of semaglutide therapy in CKD patients.

Table 1. Adverse Effects and Management of Semaglutide

Adverse Effect	Mechanism	Clinical Impact	Management
Gastrointestinal symptoms	Delayed gastric emptying	Nausea, vomiting, diarrhea	Slow dose escalation, eat smaller meals
Acute kidney injury	Volume depletion secondary to GI symptoms	Rise in serum creatinine, fall in eGFR	Maintain hydration, monitor renal function, temporarily discontinue if severe
Dehydration	Excessive fluid loss	Hypotension, worsening CKD	Encourage adequate fluid intake, monitor hydration
Hypoglycaemia	Combination with insulin or sulfonylureas	Low blood glucose	Adjust insulin/sulfonylurea dose, monitor glucose
Diabetic retinopathy	Rapid HbA1c reduction	Worsening retinal disease	Regular ophthalmic examinations
Pancreatitis	Uncertain mechanism	Severe abdominal pain	Discontinue therapy and evaluate immediately

Gallbladder disease	Rapid weight loss	Cholelithiasis, cholecystitis	Monitor symptoms, perform imaging if required
Thyroid C-cell tumour risk	GLP-1 receptor stimulation (animal studies)	Potential thyroid neoplasia	Avoid use in patients with MTC or MEN2

5. CURRENT GUIDELINE RECOMMENDATIONS FOR SEMAGLUTIDE IN CHRONIC KIDNEY DISEASE

Recent international clinical practice guidelines recognize glucagon-like peptide-1 receptor agonists (GLP-1 RAs), particularly semaglutide, as an important therapeutic option for patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). These recommendations are based on evidence demonstrating improvements in glycaemic control, cardiovascular outcomes, body weight, and renal protection. Semaglutide is recommended as part of a comprehensive treatment strategy alongside lifestyle modification, renin–angiotensin system (RAS) blockade, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and optimal blood pressure control.

KDIGO 2024 Recommendations

The Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Clinical Practice Guideline recommends the use of long-acting GLP-1 receptor agonists in patients with T2DM and CKD who require additional glycaemic control despite treatment with metformin and an SGLT2 inhibitor or when these agents are contraindicated or not tolerated.

The guideline highlights semaglutide because of its proven cardiovascular benefits, reduction in albuminuria, and slowing of kidney function decline demonstrated in recent clinical trials. KDIGO also emphasizes individualized treatment based on kidney function, cardiovascular risk, and patient preference.

Key Recommendations:

- Use long-acting GLP-1 RAs after initiation of SGLT2 inhibitors when additional therapy is needed.
- Prioritize agents with proven cardiovascular benefit, including semaglutide.
- Continue treatment unless significant adverse effects occur.
- Regularly monitor renal function, HbA1c, body weight, and albuminuria.

American Diabetes Association (ADA) Standards of Care

The ADA Standards of Care recommend semaglutide for patients with T2DM and CKD who require improved glycaemic control and cardiovascular risk reduction.

The ADA recognizes semaglutide as one of the preferred GLP-1 receptor agonists because it provides:

- Effective HbA1c reduction.
- Significant weight loss.
- Lower risk of major adverse cardiovascular events.
- Reduction in albuminuria.

- Slower progression of diabetic kidney disease.

Combination therapy with SGLT2 inhibitors is recommended whenever appropriate because both drug classes provide complementary cardiovascular and renal benefits.

American Association of Clinical Endocrinology (AACE)

The AACE Clinical Practice Guidelines recommend GLP-1 receptor agonists as first-line injectable therapy for patients with type 2 diabetes requiring additional glucose lowering, particularly those with obesity, cardiovascular disease, or chronic kidney disease.

Semaglutide is considered one of the preferred agents because of:

- Superior glycaemic efficacy.
- Significant body weight reduction.
- Proven cardiovascular protection.
- Favorable renal outcomes.

The guideline also recommends individualized treatment based on patient comorbidities, renal function, and treatment goals.

European Society of Cardiology (ESC)

The European Society of Cardiology (ESC) recommends GLP-1 receptor agonists with proven cardiovascular benefit, including semaglutide, for patients with type 2 diabetes who have established cardiovascular disease or are at high cardiovascular risk.

Since cardiovascular disease is the leading cause of mortality in CKD, semaglutide is considered beneficial for reducing cardiovascular events while simultaneously slowing kidney disease progression.

The ESC emphasizes comprehensive risk reduction through:

- Blood pressure control.
- Lipid management.
- Weight reduction.
- Glycaemic optimization.
- Kidney protection.

Practical Clinical Recommendations

Based on current evidence and international guidelines, semaglutide should be considered in patients with CKD who have:

- Type 2 diabetes with inadequate glycaemic control.
- Persistent albuminuria despite standard therapy.
- High cardiovascular risk.
- Obesity requiring pharmacological weight management.
- Inability to tolerate SGLT2 inhibitors.

Treatment should always be individualized according to renal function, cardiovascular status, comorbidities, patient preference, and tolerability.

Key Points from Current Guidelines

- Long-acting GLP-1 receptor agonists are recommended in patients with T2DM and CKD requiring additional glucose lowering.

- Semaglutide is preferred because of its strong evidence for cardiovascular and renal protection.
- Combination therapy with SGLT2 inhibitors is encouraged whenever feasible.
- Routine monitoring of eGFR, urinary albumin-to-creatinine ratio (UACR), HbA1c, blood pressure, body weight, and adverse effects is recommended.
- Lifestyle modification, dietary counselling, and medication adherence remain essential components of CKD management.

6. NON-PHARMACOLOGICAL MANAGEMENT AND CLINICAL PHARMACIST ROLE

Pharmacological treatment alone is insufficient to achieve optimal outcomes in patients with chronic kidney disease (CKD). Lifestyle modification, nutritional management, regular physical activity, medication adherence, patient education, and multidisciplinary care are essential components of comprehensive CKD management. When combined with semaglutide therapy, these interventions further improve glycaemic control, body weight, cardiovascular health, and renal outcomes.

LIFESTYLE MODIFICATION

Lifestyle modification remains the foundation of CKD management. Patients should be encouraged to adopt healthy dietary habits, maintain an appropriate body weight, avoid tobacco use, and engage in regular physical activity. These interventions improve insulin sensitivity, reduce cardiovascular risk factors, and help delay CKD progression.

Smoking cessation is strongly recommended because smoking accelerates kidney function decline and increases cardiovascular morbidity. Excessive alcohol consumption should also be avoided, as it may worsen hypertension and interfere with glycaemic control.

MEDICAL NUTRITION THERAPY

Individualized nutritional counselling plays a crucial role in patients receiving semaglutide. A balanced diet helps improve metabolic control while reducing the progression of kidney disease.

General dietary recommendations include:

- Restrict sodium intake to help control blood pressure.
- Moderate protein intake according to CKD stage.
- Consume adequate fruits and vegetables while considering potassium restrictions when indicated.
- Limit processed foods rich in sodium, saturated fat, and refined sugars.
- Encourage whole grains, lean protein sources, and healthy fats.
- Maintain adequate hydration unless fluid restriction is indicated.

Patients receiving semaglutide should also be advised to consume smaller, more frequent meals to minimize gastrointestinal adverse effects.

PHYSICAL ACTIVITY AND WEIGHT MANAGEMENT

Regular physical activity improves insulin sensitivity, cardiovascular fitness, blood pressure, and quality of life.

Adults with CKD should be encouraged to perform at least 150 minutes of moderate-intensity aerobic exercise per week, together with muscle-strengthening exercises when appropriate.

Semaglutide promotes significant weight loss by reducing appetite and increasing satiety. Sustainable weight reduction decreases glomerular hyperfiltration, improves metabolic parameters, and lowers cardiovascular risk, thereby contributing to preservation of kidney function.

Exercise programmes should be individualized according to age, physical capacity, and CKD stage.

MEDICATION ADHERENCE

Medication adherence is essential for achieving optimal therapeutic outcomes. Poor adherence is associated with inadequate glycaemic control, accelerated CKD progression, increased hospitalization, and higher mortality.

Factors affecting adherence include:

- Polypharmacy.
- Complex dosing schedules.
- Adverse drug reactions.
- Financial constraints.
- Poor understanding of disease.
- Psychological factors.
- Limited health literacy.

Healthcare professionals should regularly assess adherence and address patient-specific barriers.

PATIENT EDUCATION AND COUNSELLING

Patient education improves self-management and enhances treatment adherence.

Patients receiving semaglutide should be counselled regarding:

- Proper administration technique for injectable or oral semaglutide.
- Importance of gradual dose escalation.
- Recognition and management of gastrointestinal adverse effects.
- Maintaining adequate hydration.
- Recognition of symptoms of hypoglycaemia when combined with insulin or sulfonylureas.
- Importance of regular blood glucose and kidney function monitoring.
- Benefits of healthy diet, physical activity, and weight reduction.
- Need for routine follow-up appointments.

Education should be reinforced during every clinical visit to improve long-term treatment success.

ROLE OF THE CLINICAL PHARMACIST

Clinical pharmacists play an important role in optimizing semaglutide therapy among patients with CKD.

Their responsibilities include:

- Reviewing medication regimens for potential drug interactions.
- Identifying contraindications and precautions.

- Educating patients regarding correct medication use.
- Monitoring medication adherence.
- Assessing adverse drug reactions.
- Recommending dose adjustments of concomitant medications when appropriate.
- Monitoring renal function and metabolic parameters.
- Providing lifestyle and nutritional counselling.
- Participating in multidisciplinary patient care.

Clinical pharmacist interventions have been shown to improve medication adherence, reduce medication-related problems, and enhance therapeutic outcomes.

MULTIDISCIPLINARY CARE

Optimal CKD management requires collaboration among multiple healthcare professionals.

The multidisciplinary team may include:

- Nephrologist
- Endocrinologist/Diabetologist
- Primary care physician
- Clinical pharmacist
- Renal dietitian
- Diabetes educator
- Nurse
- Physiotherapist

A coordinated team-based approach improves early detection of complications, optimizes medication therapy, promotes patient education, and enhances long-term renal and cardiovascular outcomes.

FUTURE PERSPECTIVES

Recent advances in nephrology suggest that semaglutide may have an expanding role beyond diabetic kidney disease. Ongoing clinical trials are evaluating its effectiveness in non-diabetic CKD, obesity-related kidney disease, and combination therapy with SGLT2 inhibitors and mineralocorticoid receptor antagonists. Future research focusing on personalized treatment strategies, biomarker-guided therapy, and long-term renal outcomes will further define the role of semaglutide in CKD management.

7. FUTURE PERSPECTIVES

The therapeutic role of semaglutide in chronic kidney disease (CKD) continues to evolve with emerging evidence from randomized clinical trials and real-world studies. Although current data strongly support its use in patients with type 2 diabetes mellitus and CKD, several important areas require further investigation to optimize patient outcomes and expand its clinical applications.

Recent studies suggest that the renoprotective effects of semaglutide extend beyond glycaemic control. Its anti-inflammatory, antioxidant, anti-fibrotic, and cardiometabolic benefits indicate that semaglutide may provide kidney protection even in patients without diabetes. Ongoing clinical trials are evaluating its efficacy in non-diabetic CKD, obesity-related kidney disease, and other proteinuric renal disorders. Positive findings from these studies may broaden future indications for semaglutide.

Combination therapy represents another promising area of research. The concurrent use of semaglutide with sodium-glucose cotransporter-2 (SGLT2) inhibitors and non-steroidal mineralocorticoid receptor antagonists such as finerenone may provide complementary mechanisms of renal protection. Future studies are needed to determine the long-term safety, efficacy, and cost-effectiveness of these combination strategies.

Precision medicine is expected to play an increasingly important role in CKD management. Identification of novel biomarkers capable of predicting treatment response may facilitate individualized therapy and improve clinical outcomes. Advances in genomics, proteomics, and metabolomics may further help identify patients who derive the greatest benefit from semaglutide therapy.

Long-term safety data are also essential. Although semaglutide has demonstrated a favourable safety profile in clinical trials, continued post-marketing surveillance is required to evaluate rare adverse events, treatment adherence, and effectiveness across diverse patient populations, including elderly individuals and those with advanced CKD.

Future research should also focus on health-related quality of life, patient-reported outcomes, healthcare utilization, and economic evaluations to determine the overall impact of semaglutide on CKD management. These findings will assist clinicians and policymakers in developing evidence-based treatment strategies that improve both renal and cardiovascular outcomes.

CONCLUSION

Chronic kidney disease remains a major global health challenge associated with progressive loss of kidney function, increased cardiovascular morbidity, and reduced quality of life. Despite significant advances in CKD management, many patients continue to experience disease progression, highlighting the need for therapies that provide comprehensive renal and cardiovascular protection.

Semaglutide has emerged as an important therapeutic option that offers benefits extending beyond glycaemic control. Through improvements in metabolic parameters, reduction of albuminuria, preservation of estimated glomerular filtration rate (eGFR), attenuation of inflammation and oxidative stress, promotion of weight loss, and reduction of cardiovascular risk, semaglutide contributes significantly to slowing CKD progression.

Evidence from major clinical trials, including SUSTAIN-6**,** FLOW**,** SELECT, and other contemporary studies, supports the renoprotective potential of semaglutide in patients with type 2 diabetes and chronic kidney disease. Current international guidelines recommend its use as part of an individualized treatment strategy, particularly in patients requiring additional glycaemic control, cardiovascular protection, or weight reduction despite standard therapy.

Although semaglutide is generally well tolerated, appropriate patient selection, gradual dose escalation, regular monitoring of renal function, and early recognition of adverse effects are essential to maximize treatment benefits and ensure patient safety. Lifestyle modification, medication adherence, and multidisciplinary care remain integral components of comprehensive CKD management.

Future clinical trials evaluating semaglutide in non-diabetic CKD, combination therapies, and personalized treatment approaches will further define its role in nephrology practice. Overall, semaglutide represents a promising advancement

in the management of chronic kidney disease, offering meaningful improvements in renal, cardiovascular, and metabolic outcomes while potentially delaying progression to kidney failure.

REFERENCES

1. Perkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med. 2024;391(2):109-121.
2. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834-1844.
3. Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017;377(9):839-848.
4. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and renal outcomes in type 2 diabetes (REWIND). Lancet. 2019;394:131-138.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(Suppl):S1-S314.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2022;102(Suppl):S1-S127.
7. American Diabetes Association. Standards of Care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1):S1-S350.
8. American Diabetes Association. Chronic kidney disease and risk management: Standards of Care in Diabetes—2025. Diabetes Care. 2025;48(Suppl 1):S239-S251.
9. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2024 consensus report by the ADA and EASD. Diabetes Care. 2024;47(1):20-42.
10. Rossing P, Baeres FMM, Bakris G, et al. Rationale, design and baseline characteristics of the FLOW trial. Nephrol Dial Transplant. 2023;38:2041-2050.
11. Mahaffey KW, Tuttle KR, Arici M, et al. Cardiovascular outcomes with semaglutide by severity of chronic kidney disease in type 2 diabetes: FLOW trial. Eur Heart J. 2025;46(12):1096-1108.
12. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384:989-1002.
13. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly semaglutide on weight maintenance. JAMA. 2021;325:1414-1425.
14. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide on body weight. JAMA. 2021;325:1403-1413.
15. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes (SELECT). N Engl J Med. 2023;389:2221-2232.
16. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in type 2 diabetes (PIONEER 6). N Engl J Med. 2019;381:841-851.
17. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER (SUSTAIN-3). Lancet Diabetes Endocrinol. 2017;5:341-354.
18. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide (SUSTAIN-7). Lancet Diabetes Endocrinol. 2018;6:275-286.
19. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of semaglutide monotherapy (SUSTAIN-1). Lancet Diabetes Endocrinol. 2017;5:251-260.
20. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin

(SUSTAIN-5). J Clin Endocrinol Metab. 2018;103:2291-2301.
21. Bain SC, Mosenzon O, Arechavaleta R, et al. Cardiovascular safety of oral semaglutide. Diabetes Obes Metab. 2020;22:2057-2066.
22. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality and kidney outcomes with GLP-1 receptor agonists: systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2021;9:653-662.
23. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular and kidney outcomes with GLP-1 receptor agonists. Lancet Diabetes Endocrinol. 2019;7:776-785.
24. Tuttle KR, Rayner B, Lakshmanan MC, et al. Clinical use of GLP-1 receptor agonists in diabetic kidney disease. Kidney Int Rep. 2023;8:1203-1216.
25. de Boer IH, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO diabetes guideline. Kidney Int. 2022;102:990-999.
26. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on CKD outcomes in type 2 diabetes. N Engl J Med. 2020;383:2219-2229.
27. Pitt B, Filippatos G, Agarwal R, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. N Engl J Med. 2021;385:2252-2263.
28. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in CKD. N Engl J Med. 2020;383:1436-1446.
29. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in CKD (EMPA-KIDNEY). N Engl J Med. 2023;388:117-127.
30. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and renal outcomes (CREDENCE). N Engl J Med. 2019;380:2295-2306.
31. Wheeler DC, Stefansson BV, Batiushin M, et al. DAPA-CKD trial outcomes. Kidney Int. 2021;99:143-155.
32. American Association of Clinical Endocrinology. AACE Clinical Practice Guideline for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2022;28:923-1049.
33. Cosentino F, Grant PJ, Aboyans V, et al. ESC Guidelines on diabetes, pre-diabetes and cardiovascular disease. Eur Heart J. 2023;44:4043-4140.
34. Rossing P. GLP-1 receptor agonists in diabetic kidney disease. Nat Rev Nephrol. 2023;19:617-629.
35. Tuttle KR, McKinney TD. GLP-1 receptor agonists for kidney protection. Clin J Am Soc Nephrol. 2024;19:1012-1022.
36. Bakris GL. Management of diabetic kidney disease. N Engl J Med. 2023;388:1201-1212.
37. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges and opportunities. Clin J Am Soc Nephrol. 2021;16:203-215.
38. Heerspink HJL, Stefansson BV. Kidney protection beyond glycaemic control. Nat Rev Nephrol. 2022;18:145-156.
39. Sattar N, McGuire DK. Pathophysiology and treatment of diabetic kidney disease. Lancet. 2023;401:1209-1224.
40. Levin A, Stevens PE, Bilous RW, et al. Kidney disease: improving global outcomes. Kidney Int. 2023;104:45-68.
41. Zelniker TA, Braunwald E. Cardiorenal benefits of GLP-1 receptor agonists. Circulation. 2021;143:1200-1212.
42. Muskiet MHA, Tonneijck L, Smits MM, et al. GLP-1 receptor agonists and renal physiology. Diabetes Obes Metab. 2020;22(Suppl 1):82-99.
43. Brown E, Heerspink HJL, Cuthbertson DJ, et al. SGLT2 inhibitors and GLP-1 receptor agonists in diabetic kidney disease. Diabetologia. 2021;64:2265-2278.
44. Tuttle KR, Brosius FC. Kidney disease in diabetes. N Engl J Med. 2021;385:2140-2151.
45. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and CKD. Am J Kidney Dis. 2022;79:S1-S127.
46. Kidney Disease Outcomes Quality Initiative. KDOQI Nutrition Guideline. Am J Kidney Dis. 2020;76:S1-S107.
47. Perkovic V, Jardine MJ. Advances in diabetic kidney disease. Kidney Int. 2022;101:1123-1135.
48. McGuire DK, Shih WJ, Cosentino F, et al. GLP-1 receptor agonists and cardiovascular disease. Circulation. 2022;145:1449-1462.

49. Drucker DJ. Mechanisms of action and therapeutic applications of GLP-1 receptor agonists. Cell Metab. 2023;35:32-52.
50. Nauck MA, Meier JJ. GLP-1 receptor agonists in type 2 diabetes. Lancet. 2019;394:2180-2193.
51. Buse JB, Wexler DJ, Tsapas A, et al. Pharmacologic approaches to glycemic treatment. Diabetes Care. 2025;48(Suppl 1):S181-S206.

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