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Research article

Type 2 diabetes mellitus with chronic kidney disease: an updated narrative review of pathophysiology, diagnosis, and contemporary cardio-renal management

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ABSTRACT

Type 2 diabetes mellitus complicated by chronic kidney disease represents a high-risk cardio-renal-metabolic condition associated with progressive kidney function decline, cardiovascular events, heart failure, hospitalization, therapeutic complexity, and premature mortality. Although diabetic kidney disease was traditionally viewed as a microvascular complication mainly driven by chronic hyperglycemia, current evidence indicates that its development and progression result from complex interactions among metabolic, hemodynamic, inflammatory, fibrotic, and cardiovascular mechanisms. Persistent hyperglycemia, insulin resistance, glomerular hyperfiltration, renin–angiotensin–aldosterone system activation, oxidative stress, endothelial dysfunction, podocyte injury, tubular damage, and interstitial fibrosis collectively contribute to albuminuria, reduced estimated glomerular filtration rate, and eventual kidney failure.

Early detection is essential because kidney damage may remain clinically silent for years. Assessment using both estimated glomerular filtration rate and urinary albumin-to-creatinine ratio provides more accurate risk stratification than either parameter alone. As kidney function declines, glycemic assessment and treatment become increasingly complex because anaemia, altered red blood cell turnover, reduced insulin clearance, drug accumulation, comorbidities, and frailty may increase glycemic variability and hypoglycemia risk.

Recent therapeutic advances have shifted management from glucose-centred treatment toward comprehensive cardio-renal-metabolic protection. Sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists provide clinically meaningful benefits beyond glycemic control, including slowing kidney disease progression, reducing albuminuria, lowering heart failure risk, and improving cardiovascular outcomes. This review summarises current understanding of the epidemiology, pathophysiology, diagnosis, risk stratification, and contemporary management of type 2 diabetes complicated by chronic kidney disease, emphasizing early screening, individualized therapy, multidisciplinary care, and long-term organ protection.

Keywords: Type 2 diabetes mellitus, Chronic kidney disease, Diabetic kidney disease, Albuminuria, SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, Cardio-renal-metabolic disease.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide and represents a major public health challenge because of its progressive nature, lifelong treatment requirements, and multisystem complications. Beyond hyperglycemia, T2DM is characterized by insulin resistance, β-cell dysfunction, chronic low-grade inflammation, dysregulated lipid metabolism, endothelial dysfunction, and increased cardiometabolic risk. These abnormalities contribute not only to impaired glucose homeostasis but also to structural and functional injury in multiple organs, including the kidneys, heart, blood vessels, retina, and peripheral nerves. Among these complications, chronic kidney disease (CKD) is particularly important because it is strongly associated with cardiovascular events, kidney failure, hospitalization, reduced quality of life, and premature mortality.

CKD in patients with T2DM has traditionally been described as diabetic nephropathy or diabetic kidney disease. In classical descriptions, diabetic kidney disease develops after years of persistent hyperglycemia and follows a relatively predictable course, beginning with glomerular hyperfiltration, progressing to microalbuminuria, then overt proteinuria, declining estimated glomerular filtration rate (eGFR), and eventually kidney failure. However, this traditional model does not fully reflect the clinical heterogeneity observed in contemporary practice. Many patients with T2DM develop reduced eGFR without marked albuminuria, while others present with albuminuria before a measurable decline in kidney filtration. In addition, hypertension, obesity, aging, dyslipidemia, atherosclerosis, heart failure, recurrent acute kidney injury, and exposure to nephrotoxic medications may all contribute to kidney dysfunction in people with diabetes.

For this reason, T2DM complicated by CKD should be understood as a heterogeneous cardio-renal-metabolic disorder rather than a purely glucose-driven microvascular complication. The interaction between diabetes and kidney disease is bidirectional and self-amplifying. Hyperglycemia and insulin resistance promote glomerular and tubular injury, while declining kidney function worsens metabolic instability, increases the risk of hypoglycemia, alters drug clearance, promotes volume overload, and intensifies cardiovascular risk. Albuminuria reflects not only kidney damage but also systemic endothelial dysfunction and increased vascular permeability. Similarly, reduced eGFR is not only a measure of impaired filtration but also a marker of higher risk for anaemia, mineral and bone disorders, electrolyte abnormalities, cardiovascular disease, and medication-related adverse events.

The burden of T2DM with CKD is clinically significant because kidney dysfunction substantially changes the management of diabetes. As renal function declines, the pharmacokinetics and safety profiles of many glucose-lowering agents are altered. Insulin clearance decreases, some oral antidiabetic drugs require dose adjustment or discontinuation, and the risk of hypoglycemia increases. At the same time, conventional glycemic markers such as glycated hemoglobin may become less reliable in advanced CKD because of anemia, altered red blood cell lifespan, iron therapy, erythropoiesis-stimulating agents, and other CKD-related factors. Therefore, diabetes management in CKD requires individualized interpretation of glycemic indices, careful drug selection, and close monitoring of both efficacy and safety.

Early detection of CKD in patients with T2DM is essential because kidney damage can remain clinically silent for years. Serum creatinine alone is insufficient for early detection, especially in patients with preserved filtration or low muscle mass. Current clinical practice, therefore, emphasises the combined use of eGFR and urinary albumin-to-creatinine ratio (UACR) for screening, staging, and risk stratification. eGFR provides an estimate of filtration capacity, while UACR identifies abnormal albumin excretion and early glomerular or endothelial injury. The combination of these two markers allows clinicians to classify CKD severity, estimate the risk of progression, guide treatment intensity, determine monitoring frequency, and identify patients who may benefit from nephrology referral.

Over the past decade, the therapeutic landscape for T2DM complicated by CKD has changed substantially. Earlier management strategies focused mainly on glycemic control, blood pressure reduction, lipid management, and renin–angiotensin system blockade. Although these interventions remain foundational, they are no longer sufficient as the only approach to long-term risk reduction. Large randomized controlled trials have demonstrated that several newer drug classes provide clinically meaningful kidney and cardiovascular protection beyond their glucose-lowering effects. In particular, sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce intraglomerular pressure, albuminuria, kidney disease progression, heart failure hospitalization, and major cardio-renal outcomes in patients with CKD, including those with and without diabetes.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have also become increasingly important in the management of T2DM with CKD, especially in patients with obesity, poor glycemic control, or high cardiovascular risk. These agents improve glucose control, promote weight reduction, reduce major adverse cardiovascular events in selected high-risk populations, and may provide kidney protection through reductions in albuminuria, inflammation, body weight, and blood pressure. More recently, kidney outcome data have strengthened the role of GLP-1 RAs as part of a broader cardio-renal-metabolic treatment strategy rather than simply as glucose-lowering therapies.

Another important therapeutic advance is the use of nonsteroidal mineralocorticoid receptor antagonists, particularly finerenone. Mineralocorticoid receptor overactivation contributes to inflammation, oxidative stress, fibrosis, endothelial dysfunction, and cardiovascular remodeling. In patients with T2DM and CKD, finerenone has demonstrated significant benefits in reducing kidney disease progression and cardiovascular events when added to optimized standard therapy, especially among patients with persistent albuminuria despite renin–angiotensin system inhibition. These findings illustrate the growing importance of targeting inflammatory and fibrotic pathways in addition to metabolic and hemodynamic mechanisms.

The current treatment paradigm, therefore, emphasises comprehensive cardio-renal-metabolic protection. This model integrates glycemic control, blood pressure management, lipid lowering, albuminuria reduction, kidney function preservation, heart failure prevention, cardiovascular risk reduction, lifestyle intervention, and patient-centered care. Rather than treating

diabetes, kidney disease, and cardiovascular disease as separate clinical problems, modern management recognizes their biological and prognostic interdependence. This integrated approach is reflected in recent international guidelines, which recommend early CKD screening, risk-based monitoring, SGLT2 inhibitor therapy for eligible patients, individualized glycemic targets, consideration of GLP-1 RAs and finerenone in appropriate clinical contexts, and multidisciplinary coordination.

Despite major advances, important gaps remain between evidence and real-world practice. Albuminuria testing is still underused in many healthcare systems, resulting in delayed CKD recognition and missed opportunities for early intervention. Newer organ-protective therapies may be underprescribed because of cost, limited access, uncertainty about indications, concerns regarding adverse effects, or lack of coordination among primary care, endocrinology, nephrology, and cardiology services. In low- and middle-income settings, these barriers may be compounded by limited laboratory infrastructure, fragmented follow-up, financial constraints, and late presentation. Addressing these gaps requires not only clinical awareness but also system-level strategies to improve screening, risk stratification, medication access, patient education, and continuity of care.

This review aims to provide an updated and clinically oriented synthesis of T2DM complicated by CKD. Specifically, it discusses the epidemiological and clinical burden of the condition, summarizes key mechanisms involved in disease initiation and progression, reviews current diagnostic and risk stratification approaches, evaluates contemporary evidence-based treatment strategies, and highlights real-world implementation challenges. By emphasizing early detection and integrated cardio-renal-metabolic management, this review seeks to support a more comprehensive approach to reducing kidney failure, cardiovascular events, and premature mortality among patients with T2DM and CKD.

Epidemiology and clinical burden

Global burden of type 2 diabetes mellitus

Type 2 diabetes mellitus has become one of the most important noncommunicable diseases worldwide. Its increasing prevalence is driven by population ageing, urbanization, sedentary lifestyles, excess body weight, dietary transition, socioeconomic change, and improved survival of people living with chronic cardiometabolic conditions. According to the International Diabetes Federation Diabetes Atlas, the global burden of diabetes continues to rise, with recent estimates showing that approximately 590 million people worldwide are living with diabetes, and the number is expected to increase substantially in the coming decades [9]. Because type 2 diabetes accounts for the majority of diabetes cases globally, its complications have become a major driver of long-term morbidity, healthcare utilization, and premature mortality.

The burden of type 2 diabetes is not limited to hyperglycemia itself. Rather, the major clinical and economic consequences arise from chronic complications affecting the kidneys, cardiovascular system, eyes, nerves, and peripheral vasculature. Among these, chronic kidney disease is especially important because it often develops silently, progresses over years, and substantially increases the risk of cardiovascular events and death. In many patients, CKD is detected only after albuminuria or reduced estimated glomerular filtration rate has already become established. This delayed recognition reduces the opportunity for early intervention, particularly in settings where routine urinary albumin-to-creatinine ratio testing is not consistently implemented.

Diabetes is a leading cause of chronic kidney disease

Diabetes is one of the leading causes of chronic kidney disease worldwide. Epidemiological evidence suggests that up to 40% of people living with diabetes may develop CKD during their lifetime. The International Diabetes Federation has also highlighted that new cases of CKD among people with type 2 diabetes increased markedly between 1990 and 2017, reflecting both the rising prevalence of diabetes and the long-term survival of affected individuals.

The relationship between type 2 diabetes and CKD is clinically significant because the presence of kidney disease changes the natural history of diabetes. Patients with diabetes and CKD are more likely to experience progressive decline in kidney function, resistant hypertension, fluid overload, electrolyte disturbances, anemia, mineral and bone disorders, cardiovascular complications, and medication-related adverse events. As kidney function worsens, treatment becomes increasingly complicated because many glucose-lowering drugs require dose adjustment or discontinuation, and the risk of hypoglycemia rises due to reduced renal insulin clearance and altered drug metabolism.

CKD in type 2 diabetes is also heterogeneous. Some patients present with the classic albuminuric phenotype, characterized by progressive albuminuria followed by a decline in eGFR. Others develop a non-albuminuric phenotype, in which eGFR declines despite absent or only mildly increased albuminuria. This heterogeneity may reflect differences in underlying pathophysiology, including vascular disease, ageing-related nephron loss, hypertensive nephrosclerosis, tubulointerstitial injury, obesity-related kidney stress, or previous episodes of acute kidney injury. Therefore, reliance on either eGFR or albuminuria alone may underestimate the burden of kidney disease in patients with type 2 diabetes.

Global burden of chronic kidney disease

Chronic kidney disease itself has become a major global health problem. Recent Global Burden of Disease analyses indicate that CKD is now among the leading causes of death worldwide. A 2025 Lancet analysis reported that CKD was the ninth leading cause of death globally in 2023, accounting for approximately 1.48 million deaths, and was also a major contributor to disability-adjusted life years.

The growing burden of CKD is especially concerning because, unlike some cardiovascular conditions whose mortality rates have declined in many regions, CKD-related mortality is projected to remain high or increase in several populations. This reflects persistent gaps in prevention, early diagnosis, risk-factor control, and access to kidney-protective therapies. Diabetes, hypertension, obesity, and ageing are central contributors to this burden. Among these risk factors, type 2 diabetes is particularly important because it combines metabolic injury, vascular dysfunction, inflammation, and hemodynamic stress, all of which accelerate kidney damage.

The burden of CKD is also unevenly distributed. Low- and middle-income countries face a particularly difficult challenge because they often experience rapid increases in diabetes prevalence while having limited access to early CKD screening, nephrology care, newer cardio-renal-protective medications, dialysis, and kidney transplantation. In these settings, many patients present late, and CKD may remain undiagnosed until advanced stages. This creates a large hidden burden of disease and increases the risk of preventable kidney failure and cardiovascular death.

Cardiovascular burden in patients with type 2 diabetes and CKD

The coexistence of type 2 diabetes and CKD greatly amplifies cardiovascular risk. Patients with both conditions are more likely to develop coronary artery disease, stroke, peripheral artery disease, heart failure, arrhythmias, and sudden cardiac death than patients with diabetes alone. This risk is driven by overlapping mechanisms, including endothelial dysfunction, chronic inflammation, oxidative stress, arterial stiffness, volume overload, dyslipidemia, hypertension, autonomic dysfunction, anemia, and mineral metabolism abnormalities.

Albuminuria and reduced eGFR are both independent predictors of cardiovascular events and mortality. Albuminuria reflects glomerular injury but also serves as a marker of systemic vascular dysfunction. Reduced eGFR indicates loss of kidney filtration capacity and is associated with accumulation of uremic toxins, sodium retention, neurohormonal activation, anemia, and vascular calcification. When albuminuria and reduced eGFR coexist, cardiovascular risk increases substantially. This is why KDIGO classifies CKD prognosis by combining GFR categories and albuminuria categories, ranging from low risk to very high risk.

Heart failure is particularly important in this population. Type 2 diabetes increases the risk of both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction, while CKD further worsens volume regulation, blood pressure control, and myocardial stress. Conversely, heart failure may accelerate kidney dysfunction through reduced renal perfusion, venous congestion, neurohormonal activation, and repeated exposure to diuretics or hemodynamic instability. This bidirectional relationship explains why current management increasingly emphasizes cardio-renal-metabolic protection rather than isolated treatment of hyperglycemia.

Kidney disease progression and risk of kidney failure

Progression of CKD in patients with type 2 diabetes varies considerably. Some patients remain stable for years, while others experience a rapid decline in kidney function. Important predictors of progression include high baseline albuminuria, lower eGFR, poor blood pressure control, persistent hyperglycemia, smoking, obesity, dyslipidemia, history of acute kidney injury, heart failure, and lack of kidney-protective therapy. Severe albuminuria is particularly important because it often indicates active glomerular injury and high risk of future decline.

The risk of kidney failure has major implications for patients and healthcare systems. Advanced CKD may require dialysis or kidney transplantation, both of which are associated with high cost, complex logistics, reduced quality of life, and increased mortality. For patients with type 2 diabetes, the transition to kidney failure is often accompanied by extensive comorbidity, including cardiovascular disease, neuropathy, retinopathy, foot complications, frailty, infection risk, and polypharmacy. Therefore, preventing or delaying CKD progression is a central goal of diabetes care.

The modern therapeutic objective is not merely to delay dialysis, but to preserve kidney function, reduce albuminuria, prevent cardiovascular events, avoid heart failure hospitalization, maintain functional status, and reduce treatment-related harm. This broader view is consistent with current guideline recommendations, which emphasize early detection, risk stratification, and evidence-based organ-protective therapy [1].

Clinical complexity and treatment burden

Patients with type 2 diabetes and CKD often require complex, long-term management. They may need medications for glycemic control, blood pressure, lipid lowering, albuminuria reduction, antiplatelet therapy, heart failure, anemia, mineral metabolism disorders, acidosis, and fluid balance. This creates a high risk of polypharmacy, drug-drug interactions, medication nonadherence, and adverse events.

Glycemic management becomes more difficult as kidney function declines. Insulin and some insulin secretagogues have increased hypoglycemia risk in CKD because of reduced renal clearance and impaired counter-regulatory responses. Metformin use depends on eGFR and must be reassessed when kidney function declines or when acute illness occurs. Some glucose-lowering agents require dose adjustment, while others may be preferred because of cardiovascular or kidney benefits. In addition, HbA1c may be less reliable in advanced CKD due to anemia, altered red blood cell turnover, iron therapy, erythropoiesis-stimulating agents, and other CKD-related factors.

This complexity requires individualized treatment goals. A younger patient with early CKD, preserved functional status, and low hypoglycemia risk may benefit from more intensive glycemic

management. In contrast, an older patient with advanced CKD, frailty, cardiovascular disease, and recurrent hypoglycemia may require less stringent glycemic targets and simplified therapy. Therefore, treatment should be guided not only by HbA1c but also by kidney function, albuminuria, cardiovascular risk, life expectancy, comorbidities, patient preferences, and safety.

Economic and health-system burden

The economic burden of type 2 diabetes complicated by CKD is substantial. Costs arise from outpatient visits, laboratory monitoring, medications, cardiovascular events, hospitalizations, emergency care, dialysis, transplantation, rehabilitation, and long-term management of complications. As CKD progresses, healthcare costs increase sharply, especially when patients reach advanced stages or require kidney replacement therapy.

Hospitalization is a major driver of cost. Patients with diabetes and CKD are frequently admitted for heart failure, acute kidney injury, uncontrolled hyperglycemia or hypoglycemia, infection, cardiovascular events, fluid overload, electrolyte abnormalities, and foot complications. These admissions often lead to functional decline, medication changes, and further kidney injury. Recurrent hospitalization also disrupts continuity of care and increases the burden on families and caregivers.

From a health-system perspective, the most effective strategy is early identification and risk-based intervention. Routine screening with eGFR and UACR, timely use of kidney-protective medications, blood pressure control, lipid management, smoking cessation, patient education, and multidisciplinary care can reduce long-term complications. However, implementation remains inconsistent, especially in resource-limited settings. This gap between evidence and practice is one of the major challenges in reducing the global burden of diabetic CKD.

Implications for clinical practice

The epidemiological and clinical burden of type 2 diabetes with CKD supports several important practice implications. First, CKD screening should be performed systematically in patients with type 2 diabetes, even when serum creatinine appears normal. Second, eGFR and UACR should be interpreted together because they provide complementary information on filtration capacity and kidney damage. Third, albuminuria should be treated as a clinically meaningful risk marker, not simply a laboratory abnormality. Fourth, cardiovascular risk reduction should be integrated into kidney care from the earliest stages of CKD. Finally, evidence-based therapies with kidney and cardiovascular benefits should be initiated early when indicated, rather than reserved for advanced disease.

Overall, type 2 diabetes complicated by CKD represents a high-burden, high-risk, and highly modifiable clinical condition. Its impact extends beyond nephrology and endocrinology, involving cardiology, primary care, pharmacy, nutrition, nursing, and public health. The rising global prevalence of diabetes and CKD makes early detection and integrated cardio-renal-metabolic management a major priority for modern healthcare systems.

Pathophysiology

Overview of disease mechanisms

The pathophysiology of chronic kidney disease in patients with type 2 diabetes mellitus is complex and multifactorial. Although chronic hyperglycemia remains a central initiating factor, diabetic kidney disease cannot be fully explained by glucose toxicity alone. Its development and progression involve a dynamic interaction among metabolic dysregulation, glomerular hemodynamic changes, renin–angiotensin–aldosterone system activation, oxidative stress, inflammation, podocyte injury, endothelial dysfunction, tubular injury, renal hypoxia, mitochondrial dysfunction, and progressive fibrosis. These mechanisms affect both glomerular and tubulointerstitial compartments, ultimately leading to albuminuria, declining estimated glomerular filtration rate, and progressive loss of functional nephron mass.

A modern understanding of diabetic kidney disease has moved beyond the classical glomerular-centered model. Traditionally, diabetic kidney disease was described as a sequence beginning with glomerular hyperfiltration, followed by microalbuminuria, overt proteinuria, progressive reduction in eGFR, and finally kidney failure. However, contemporary clinical observations show that this sequence is not universal. Some patients develop declining eGFR without substantial albuminuria, whereas others have persistent albuminuria despite relatively preserved filtration. This heterogeneity suggests that vascular, tubular, inflammatory, and metabolic pathways may contribute differently across patient subgroups.

Recent reviews emphasize that diabetic kidney disease is characterized by glomerular and tubular hypertrophy, podocyte injury, albuminuria, hyperfiltration, oxidative stress, inflammation, renal hypoxia, mitochondrial injury, and epigenetic changes. In parallel, KDIGO 2024 continues to recommend classification of CKD by cause, GFR category, and albuminuria category, reflecting the concept that both kidney filtration and kidney damage markers are necessary to understand disease severity and prognosis.

Hyperglycemia-mediated metabolic injury

Persistent hyperglycemia is one of the earliest and most important drivers of kidney injury in type 2 diabetes. High intracellular glucose levels activate several damaging biochemical pathways, including formation of advanced glycation end products, activation of protein kinase C, increased polyol pathway flux, oxidative stress, mitochondrial dysfunction, and dysregulated inflammatory signaling. These processes impair endothelial function, alter extracellular matrix turnover, promote mesangial expansion, and damage the glomerular filtration barrier.

Advanced glycation end products accumulate in glomerular and vascular tissues and alter the structure and function of proteins such as collagen and laminin. This contributes to

glomerular basement membrane thickening, increased vascular stiffness, and impaired cellular signaling. Binding of advanced glycation end products to their receptors also promotes oxidative stress and inflammation, further amplifying tissue injury. Over time, these changes contribute to glomerulosclerosis and tubulointerstitial fibrosis.

Hyperglycemia also increases oxidative stress by promoting excessive production of reactive oxygen species. Reactive oxygen species damage cellular proteins, lipids, and DNA, while also activating inflammatory and profibrotic pathways. In podocytes, oxidative injury contributes to cytoskeletal disruption, foot process effacement, apoptosis, and detachment from the glomerular basement membrane. In tubular epithelial cells, oxidative stress contributes to mitochondrial dysfunction, endoplasmic reticulum stress, cellular senescence, and inflammatory cytokine production.

Metabolic injury is not limited to glucose toxicity. Insulin resistance, dyslipidemia, and ectopic lipid accumulation also contribute to kidney injury. Lipotoxicity in renal cells can trigger mitochondrial dysfunction, oxidative stress, apoptosis, and inflammatory activation. These mechanisms are particularly relevant in patients with type 2 diabetes, obesity, metabolic syndrome, and nonalcoholic fatty liver disease, in whom kidney injury may reflect a broader cardio-renal-metabolic phenotype.

Glomerular hyperfiltration and altered tubuloglomerular feedback

Glomerular hyperfiltration is a key early hemodynamic abnormality in diabetic kidney disease. In type 2 diabetes, increased filtered glucose leads to increased glucose and sodium reabsorption in the proximal tubule through sodium–glucose cotransporter 2. As a result, less sodium chloride reaches the macula densa. The macula densa interprets this as reduced effective filtration and triggers afferent arteriolar dilation through altered tubuloglomerular feedback. This leads to increased intraglomerular pressure and glomerular hyperfiltration.

Initially, hyperfiltration may appear compensatory because eGFR can remain normal or even elevated. However, sustained intraglomerular hypertension imposes mechanical stress on the glomerular capillary wall, mesangial cells, podocytes, and filtration barrier. Over time, this promotes podocyte loss, albumin leakage, mesangial expansion, and segmental glomerulosclerosis. As nephron injury progresses, remaining nephrons undergo adaptive hyperfiltration, creating a vicious cycle of further mechanical stress and nephron loss.

This mechanism also helps explain the kidney-protective effect of SGLT2 inhibitors. By reducing proximal tubular glucose and sodium reabsorption, SGLT2 inhibitors increase sodium delivery to the macula densa, restore tubuloglomerular feedback, promote afferent arteriolar vasoconstriction, reduce intraglomerular pressure, and lower hyperfiltration-related injury. Reviews of SGLT2 inhibitor mechanisms highlight activation of tubuloglomerular feedback and reduction of hyperfiltration-mediated kidney injury as central pathways for kidney protection. These effects are partly independent of glucose lowering, explaining why SGLT2 inhibitors reduce kidney outcomes even in some patients with lower eGFR or without diabetes.

Renin–angiotensin–aldosterone system activation

Activation of the renin–angiotensin–aldosterone system is another major mechanism in diabetic kidney disease. Angiotensin II causes preferential efferent arteriolar constriction, which increases intraglomerular pressure and contributes to hyperfiltration, albuminuria, and progressive glomerular injury. Angiotensin II also promotes inflammation, oxidative stress, endothelial dysfunction, mesangial cell proliferation, and extracellular matrix deposition. These effects contribute to glomerulosclerosis and tubulointerstitial fibrosis.

Aldosterone further contributes to kidney and cardiovascular injury through sodium retention, blood pressure elevation, oxidative stress, inflammation, and fibrosis. Mineralocorticoid receptor activation in kidney and cardiovascular tissues promotes profibrotic signaling, macrophage infiltration, endothelial dysfunction, and vascular remodeling. This pathway is clinically relevant because patients with type 2 diabetes and CKD often have persistent albuminuria despite angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy.

The importance of this pathway is reflected in current therapeutic strategies. Renin–angiotensin system inhibitors remain foundational in patients with diabetes, hypertension, and albuminuria. More recently, nonsteroidal mineralocorticoid receptor antagonists such as finerenone have been shown to reduce kidney and cardiovascular outcomes in patients with type 2 diabetes and CKD. This supports the concept that inflammatory and fibrotic mineralocorticoid receptor signaling is not merely a secondary feature but an active contributor to disease progression.

Podocyte injury and disruption of the glomerular filtration barrier

Podocytes are highly specialized epithelial cells that maintain the integrity of the glomerular filtration barrier. They wrap around glomerular capillaries and form slit diaphragms, which prevent excessive leakage of albumin and other plasma proteins into the urine. In diabetic kidney disease, podocytes are injured by hyperglycemia, mechanical stretch from intraglomerular hypertension, oxidative stress, advanced glycation end products, angiotensin II, inflammatory cytokines, and mitochondrial dysfunction.

Podocyte injury results in cytoskeletal remodeling, foot process effacement, reduced slit diaphragm integrity, apoptosis, and detachment from the glomerular basement membrane. Because podocytes have limited regenerative capacity, podocyte loss is a critical and often irreversible event. Once podocyte density falls

below a critical threshold, the glomerular capillary wall becomes more permeable, albuminuria develops, and progressive glomerulosclerosis may follow.

Albuminuria therefore reflects more than passive leakage of protein. It is a sign of structural injury to the filtration barrier and a marker of ongoing glomerular stress. Persistent albuminuria is strongly associated with future kidney function decline and cardiovascular risk. This explains why UACR is used together with eGFR for CKD staging and prognosis in current guidelines.

Tubular injury and tubulointerstitial fibrosis

Although diabetic kidney disease was historically viewed as a primarily glomerular disease, tubular injury is now recognized as a major determinant of progression. The proximal tubule is exposed to high filtered loads of glucose, sodium, fatty acids, albumin, and other metabolic stressors. In diabetes, increased proximal tubular reabsorption increases oxygen consumption and creates a mismatch between oxygen demand and oxygen supply. This contributes to renal cortical and medullary hypoxia.

Tubular epithelial cells exposed to high glucose and lipid accumulation develop oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, inflammatory activation, and cellular senescence. A recent review of tubular injury in diabetic kidney disease noted that high glucose and lipid accumulation contribute to tubular injury through oxidative stress, endoplasmic reticulum stress, inflammation, apoptosis, and fibrotic remodeling [2]. Tubular injury can occur early and may contribute to kidney function decline even before heavy albuminuria becomes apparent.

Tubulointerstitial fibrosis is one of the strongest pathological correlates of progressive eGFR decline. Injured tubular cells release cytokines, chemokines, and profibrotic mediators that recruit inflammatory cells and activate fibroblasts. Activated fibroblasts and myofibroblasts produce extracellular matrix proteins, leading to interstitial expansion, capillary rarefaction, nephron loss, and irreversible scarring. Once fibrosis is established, kidney recovery becomes increasingly limited. Therefore, prevention of tubular injury and fibrosis is a major target of modern kidney-protective therapy.

Inflammation and immune activation

Inflammation plays a central role in the initiation and progression of diabetic kidney disease. Hyperglycemia, oxidative stress, advanced glycation end products, lipotoxicity, hypertension, and mechanical stress activate inflammatory pathways within glomerular, tubular, endothelial, and interstitial cells. These cells produce cytokines, chemokines, adhesion molecules, and profibrotic mediators that recruit macrophages, lymphocytes, and other immune cells into kidney tissue.

Inflammatory mediators contribute to endothelial dysfunction, increased vascular permeability, podocyte injury, tubular damage, and activation of fibroblasts. Chronic low-grade inflammation also promotes progressive extracellular matrix accumulation and fibrosis. In addition, inflammatory pathways interact closely with oxidative stress and mitochondrial dysfunction, creating a self-sustaining cycle of injury.

The inflammatory component of diabetic kidney disease provides a mechanistic rationale for therapies that reduce inflammatory and fibrotic signaling. Finerenone is particularly relevant in this context because mineralocorticoid receptor overactivation contributes to inflammation and fibrosis in kidney and cardiovascular tissues. The benefits observed with finerenone in large outcome trials support the clinical importance of targeting non-glycemic pathways in diabetic CKD.

Oxidative stress, mitochondrial dysfunction, and renal hypoxia

Oxidative stress is a common downstream pathway linking hyperglycemia, lipotoxicity, RAAS activation, inflammation, and hypoxia. In diabetic kidney disease, excessive reactive oxygen species production overwhelms antioxidant defenses and damages cellular structures. Mitochondria are both a source and a target of oxidative injury. In renal cells, mitochondrial dysfunction impairs energy production, increases reactive oxygen species generation, promotes apoptosis, and contributes to cellular senescence.

The kidney is highly metabolically active, and the proximal tubule requires large amounts of energy for sodium and solute reabsorption. In diabetes, increased proximal tubular sodium-glucose reabsorption raises oxygen demand. At the same time, microvascular dysfunction and capillary rarefaction reduce oxygen delivery. This mismatch creates renal hypoxia, which promotes inflammation, tubular injury, epithelial-to-mesenchymal transition-like responses, and fibrotic signaling.

Renal hypoxia may help explain why tubulointerstitial injury is strongly associated with CKD progression. As fibrosis and capillary rarefaction worsen, oxygen delivery declines further, creating a vicious cycle of hypoxia, tubular injury, and scarring. This mechanism also supports the importance of treatments that reduce tubular workload, intraglomerular pressure, albuminuria, and inflammation.

Endothelial dysfunction and microvascular injury

Endothelial dysfunction is a key feature of both diabetes and CKD. Hyperglycemia, insulin resistance, oxidative stress, advanced glycation end products, inflammation, and dyslipidemia impair endothelial nitric oxide bioavailability and promote vasoconstriction, vascular stiffness, thrombosis, and increased permeability. In the glomerulus, endothelial injury disrupts the filtration barrier and contributes to albuminuria. In the renal microcirculation, endothelial dysfunction reduces perfusion and promotes ischemic injury.

Microvascular injury also links kidney disease with cardiovascular disease. Albuminuria is often interpreted as a marker of systemic endothelial dysfunction because it reflects abnormal vascular permeability not only in the kidney but also throughout the

circulation. This helps explain why albuminuria predicts cardiovascular events, heart failure, and mortality. In patients with type 2 diabetes and CKD, kidney microvascular disease and systemic vascular disease often progress together.

Cardio-renal-metabolic interaction

The interaction among diabetes, kidney disease, and cardiovascular disease is bidirectional. Type 2 diabetes promotes kidney injury through hyperglycemia, insulin resistance, obesity, dyslipidemia, inflammation, and vascular dysfunction. CKD then worsens cardiovascular risk through sodium retention, hypertension, volume overload, anemia, uremic toxin accumulation, mineral metabolism abnormalities, vascular calcification, inflammation, and oxidative stress. Cardiovascular disease, particularly heart failure, can further accelerate kidney injury through reduced renal perfusion, venous congestion, neurohormonal activation, and repeated episodes of acute kidney injury.

This interconnected pathophysiology explains why contemporary treatment is shifting from single-risk-factor control to integrated cardio-renal-metabolic protection. SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone are clinically important because they act on multiple disease pathways rather than only lowering glucose. SGLT2 inhibitors reduce hyperfiltration, tubular workload, albuminuria, and heart failure risk. GLP-1 receptor agonists improve glycemic control, reduce weight, lower cardiovascular risk, and may reduce inflammatory and albuminuric pathways. Finerenone targets mineralocorticoid receptor-mediated inflammation and fibrosis. The FLOW trial also strengthened the evidence that semaglutide can reduce clinically important kidney outcomes and cardiovascular death in patients with type 2 diabetes and CKD [3].

Summary of pathophysiological mechanisms

In summary, diabetic kidney disease develops through a complex interaction of metabolic, hemodynamic, inflammatory, fibrotic, and vascular mechanisms. Hyperglycemia initiates biochemical injury, while glomerular hyperfiltration and RAAS activation increase intraglomerular pressure. Podocyte injury and endothelial dysfunction disrupt the filtration barrier and promote albuminuria. Tubular injury, renal hypoxia, mitochondrial dysfunction, and inflammation contribute to progressive tubulointerstitial fibrosis. These kidney-specific processes are closely linked with systemic cardiovascular and metabolic dysfunction.

Understanding these mechanisms is clinically important because it explains why modern therapy must go beyond glucose lowering. Effective management requires early detection of albuminuria and eGFR decline, reduction of intraglomerular pressure, suppression of maladaptive neurohormonal activity, attenuation of inflammation and fibrosis, cardiovascular protection, and individualized glycemic management. This pathophysiological foundation supports the current shift toward integrated cardio-renal-metabolic care in patients with type 2 diabetes and chronic kidney disease.

Diagnosis, screening, and risk stratification

Diagnostic framework of chronic kidney disease in type 2 diabetes

Chronic kidney disease in patients with type 2 diabetes mellitus is defined by abnormalities of kidney structure or function that persist for at least three months and have implications for health. In clinical practice, the most important markers used to identify CKD in patients with diabetes are estimated glomerular filtration rate and urinary albumin-to-creatinine ratio. eGFR reflects kidney filtration capacity, whereas UACR reflects albumin leakage and structural or functional damage to the glomerular filtration barrier. Because these two markers provide complementary information, current guidelines recommend that both should be used for CKD detection, staging, prognosis, and follow-up.

The diagnosis of CKD should not be made from a single abnormal laboratory result without considering clinical context. Albuminuria may be transiently increased during fever, urinary tract infection, acute hyperglycemia, uncontrolled hypertension, intense physical activity, acute heart failure, or recent acute illness. Similarly, an abrupt decline in eGFR may represent acute kidney injury rather than chronic disease. Therefore, persistent abnormalities should be confirmed by repeat testing over time, especially when the findings are unexpected or inconsistent with the patient's clinical course.

In patients with type 2 diabetes, CKD is commonly attributed to diabetic kidney disease, but kidney dysfunction may also result from hypertension, atherosclerotic renovascular disease, obesity-related kidney injury, recurrent acute kidney injury, heart failure, drug-induced nephrotoxicity, or primary glomerular disease. For this reason, the evaluation of kidney disease should include not only staging but also assessment of the likely cause. The KDIGO approach classifies CKD according to cause, GFR category, and albuminuria category, often referred to as the CGA framework. This framework is clinically useful because it connects diagnosis with prognosis and management intensity.

Screening for chronic kidney disease in type 2 diabetes

Screening for CKD should be performed systematically in all patients with type 2 diabetes because early kidney damage is frequently asymptomatic. Many patients do not experience symptoms until kidney function has already declined substantially. Relying only on symptoms or serum creatinine may delay diagnosis and reduce the opportunity for early intervention. Current diabetes and kidney disease guidelines recommend regular assessment of both eGFR and UACR in people with type 2 diabetes [4].

At minimum, patients with type 2 diabetes should undergo annual screening with serum creatinine-based eGFR and spot urine UACR. If CKD is detected, the frequency of monitoring should increase according to disease stage, albuminuria severity, rate of eGFR decline, medication changes, blood pressure control,

cardiovascular risk, and presence of complications. Patients with high-risk or very-high-risk CKD may require monitoring several times per year.

Routine screening has direct therapeutic significance. Early detection of albuminuria or eGFR decline allows clinicians to intensify blood pressure control, optimize renin–angiotensin system blockade when appropriate, initiate SGLT2 inhibitor therapy in eligible patients, consider additional kidney-protective agents, adjust glucose-lowering medications, and reduce exposure to nephrotoxic drugs. Therefore, screening is not merely diagnostic; it is the entry point for risk-based cardio-renal-metabolic management.

Estimated glomerular filtration rate

Estimated glomerular filtration rate is the standard clinical measure used to evaluate kidney filtration function. In most settings, eGFR is calculated from serum creatinine using validated equations. Creatinine-based eGFR is widely available and practical for routine clinical care, but it has limitations. Serum creatinine is influenced by age, sex, muscle mass, diet, nutritional status, acute illness, and some medications. Therefore, eGFR should be interpreted carefully in patients with frailty, reduced muscle mass, severe obesity, amputation, malnutrition, or rapidly changing kidney function.

Cystatin C-based or combined creatinine–cystatin C equations may improve accuracy in selected cases, particularly when clinical decisions depend strongly on kidney function, such as drug dosing, CKD staging, referral, or assessment before major interventions. However, creatinine-based eGFR remains the most commonly used method in routine practice.

Table 1: GFR categories used for staging chronic kidney disease

GFR category	eGFR, mL/min/1.73 m²	Interpretation
G1	≥90	Normal or high kidney filtration
G2	60–89	Mildly decreased kidney filtration
G3a	45–59	Mildly to moderately decreased kidney filtration
G3b	30–44	Moderately to severely decreased kidney filtration
G4	15–29	Severely decreased kidney filtration
G5	<15	Kidney failure

In patients with type 2 diabetes, eGFR should be interpreted as a continuous marker of risk rather than a simple threshold. A patient with mildly reduced eGFR but severe albuminuria may have a higher risk of progression than a patient with lower eGFR but no albuminuria. Therefore, eGFR should always be interpreted together with UACR, blood pressure, glycemic control, cardiovascular disease, medication exposure, and the overall clinical trajectory.

Urinary albumin-to-creatinine ratio

Urinary albumin-to-creatinine ratio is the preferred test for detecting albuminuria in routine clinical practice. A spot urine sample is usually sufficient and is more convenient than 24-hour urine collection. UACR corrects urinary albumin concentration for urine creatinine concentration, thereby reducing the effect of urine dilution or concentration.

Albuminuria is one of the earliest detectable markers of diabetic kidney injury. It reflects increased permeability of the glomerular filtration barrier and may also indicate systemic endothelial dysfunction. Clinically, albuminuria is important because it predicts kidney disease progression, cardiovascular events, heart failure, and mortality. Persistent albuminuria should therefore be considered a major risk marker, even when eGFR remains preserved.

Table 2: Albuminuria categories used for chronic kidney disease risk stratification

Albuminuria category	UACR, mg/g	UACR, mg/mmol	Interpretation
A1	<30	<3	Normal to mildly increased albuminuria
A2	30–300	3–30	Moderately increased albuminuria
A3	>300	>30	Severely increased albuminuria

Because urinary albumin excretion has biological variability, abnormal UACR should be confirmed with repeat testing. Temporary increases may occur with urinary tract infection, hematuria, fever, acute hyperglycemia, uncontrolled hypertension, vigorous exercise, acute decompensated heart failure, or recent acute illness. Persistent albuminuria is generally established when abnormal results are confirmed over time.

In clinical practice, UACR has therapeutic implications. In a patient with type 2 diabetes, persistent albuminuria supports more intensive risk reduction, including optimization of blood pressure, use of renin–angiotensin system inhibition when indicated, initiation of SGLT2 inhibitors in eligible patients, and consideration of finerenone in selected patients with persistent albuminuria despite standard therapy.

Combined eGFR–UACR risk stratification

The combination of eGFR and UACR is central to CKD risk stratification. eGFR reflects filtration capacity, while UACR reflects kidney damage and vascular risk. When interpreted together, these markers provide stronger prognostic information than either marker alone. This is particularly important in type 2 diabetes because kidney disease phenotypes are heterogeneous. Some patients have preserved eGFR with significant albuminuria, whereas others have reduced eGFR with little or no albuminuria.

The KDIGO risk classification integrates GFR and albuminuria categories to estimate the risk of kidney disease progression, cardiovascular events, and mortality. In general, risk increases as eGFR declines and albuminuria increases. Patients with preserved eGFR but severe albuminuria should not be considered low risk, while patients with mildly reduced eGFR and normal albuminuria require a different level of monitoring and treatment intensity.

This combined approach helps avoid underdiagnosis. For example, a patient with eGFR of 95 mL/min/1.73 m² but UACR above 300 mg/g has severe albuminuria and a high risk of future

kidney and cardiovascular events. Conversely, a patient with eGFR of 55 mL/min/1.73 m² but UACR below 30 mg/g has reduced filtration but a different risk profile. Thus, risk stratification should be individualized rather than based on a single laboratory threshold.

Table 3: Clinical interpretation of combined eGFR and albuminuria assessment

Clinical pattern	Possible interpretation	Clinical implication
Preserved eGFR with normal UACR	No evident CKD if no other markers of kidney damage are present	Continue routine annual screening
Preserved eGFR with increased UACR	Early albuminuric kidney injury or systemic vascular risk	Confirm albuminuria and intensify risk reduction
Reduced eGFR with normal UACR	Non-albuminuric CKD phenotype, vascular disease, aging-related decline, or other causes	Evaluate trend and consider alternative causes
Reduced eGFR with increased UACR	Higher-risk CKD with both filtration loss and kidney damage	Increase monitoring and optimize kidney-protective therapy
Rapid eGFR decline or sudden severe albuminuria	Possible acute kidney injury or non-diabetic kidney disease	Assess urgently and consider nephrology referral

Glycemic assessment in patients with chronic kidney disease

Glycemic assessment becomes more complicated as CKD progresses. HbA1c remains the most commonly used marker for long-term glycemic control, but its reliability may be reduced in advanced CKD. Anemia, shortened red blood cell lifespan, iron deficiency, erythropoiesis-stimulating agents, transfusion, inflammation, and uremia may affect HbA1c values. As a result, HbA1c may underestimate or overestimate true glycemic exposure in some patients.

Kidney dysfunction also increases the risk of hypoglycemia. The kidney contributes to insulin clearance and gluconeogenesis. When kidney function declines, insulin clearance decreases, and the glucose-lowering effects of insulin or some oral agents may be prolonged. Patients with CKD may also have poor appetite, irregular food intake, malnutrition, acute illness, or polypharmacy, all of which increase glycemic variability.

Therefore, glycemic targets should be individualized. A younger patient with early CKD, few comorbidities, and low hypoglycemia risk may benefit from tighter glycemic control. In contrast, an older patient with advanced CKD, frailty, cardiovascular disease, recurrent hypoglycemia, or limited life expectancy may require less stringent targets. In selected patients, continuous glucose monitoring or structured self-monitoring of blood glucose may help identify hypoglycemia, postprandial excursions, and discordance between HbA1c and actual glucose patterns [5].

Differentiating diabetic kidney disease from non-diabetic kidney disease

Although diabetic kidney disease is common in patients with type 2 diabetes, not all kidney disease in this population is caused by diabetes. Non-diabetic kidney disease should be considered when the presentation is atypical, because some conditions require disease-specific investigation or treatment. These may include primary glomerulonephritis, autoimmune kidney disease, obstructive nephropathy, renovascular disease, polycystic kidney disease, drug-induced kidney injury, infection-related kidney disease, or hypertensive nephrosclerosis.

Table 4: Clinical features suggesting possible non-diabetic kidney disease in patients with type 2 diabetes

Clinical feature	Reason for concern
Rapid decline in eGFR	May suggest acute kidney injury, glomerulonephritis, obstruction, or vascular disease
Sudden onset of heavy proteinuria	May indicate primary glomerular disease
Active urinary sediment	Hematuria or cellular casts may suggest inflammatory kidney disease
Short duration of diabetes with advanced CKD	Time course may be inconsistent with typical diabetic kidney disease
Absence of diabetic retinopathy in selected patients	May raise suspicion when combined with heavy proteinuria or rapid decline
Systemic symptoms	May suggest autoimmune, infectious, or malignant disease
Refractory hypertension	May suggest renovascular disease or advanced kidney disease
Unexplained electrolyte or tubular abnormalities	May indicate tubular, endocrine, or medication-related disorders

The absence of diabetic retinopathy does not completely exclude diabetic kidney disease, particularly in type 2 diabetes. However, when combined with rapid progression, active urinary sediment, or abrupt onset of severe proteinuria, it should prompt further evaluation. Kidney biopsy is not required for most patients with typical diabetic kidney disease, but it may be considered when the diagnosis is uncertain and histological confirmation would change management [6].

Monitoring disease progression

Monitoring CKD progression requires repeated evaluation of eGFR and UACR over time. A single eGFR value should not be overinterpreted because short-term changes may reflect hydration status, intercurrent illness, laboratory variation, medication effects, or hemodynamic changes. For example, initiation of a renin–angiotensin system inhibitor or SGLT2 inhibitor may cause a modest early decline in eGFR. In many cases, this early dip reflects reduced intraglomerular pressure rather than structural kidney damage and may be followed by slower long-term progression.

Progression should be assessed by the overall trajectory of kidney function and albuminuria. Important indicators include sustained eGFR decline, increasing UACR, worsening blood pressure control, recurrent acute kidney injury, persistent hyperkalemia, and development of CKD complications. Monitoring should also include medication review, because drug dosing and safety profiles change as kidney function declines.

Monitoring frequency should be individualized according to CKD stage, albuminuria category, recent changes in therapy, comorbidities, and risk of progression. Patients with early, stable CKD may require annual or semiannual follow-up, while those with high-risk CKD may need closer monitoring.

Table 5: Key parameters for monitoring patients with type 2 diabetes and chronic kidney disease

Parameter	Clinical purpose
eGFR and serum creatinine	Assess kidney filtration and progression
UACR	Assess albuminuria, kidney damage, and residual risk
Serum potassium	Monitor safety of RAS inhibitors and mineralocorticoid receptor antagonists
Blood pressure	Guide cardiovascular and kidney risk reduction
HbA1c and/or glucose profile	Assess glycemic control and hypoglycemia risk
Lipid profile	Guide cardiovascular risk management
Medication review	Adjust doses and reduce nephrotoxic exposure
Cardiovascular symptoms	Detect heart failure, ischemic disease, or volume overload
Hemoglobin and mineral parameters	Identify CKD-related complications in more advanced disease

Nephrology referral

Table 6: Common indications for nephrology referral in patients with type 2 diabetes and chronic kidney disease

Indication	Clinical rationale
Severely reduced eGFR	Requires advanced CKD management and preparation for kidney replacement planning
Rapid eGFR decline	May indicate progressive disease or superimposed acute kidney injury
Severe or increasing albuminuria	Indicates high risk of kidney progression and cardiovascular events
Resistant hypertension	May require specialized evaluation and treatment adjustment
Persistent hyperkalemia	May limit kidney-protective therapy and require specialist management
Active urinary sediment	Suggests possible non-diabetic kidney disease
Suspected glomerulonephritis or systemic kidney disease	May require serology, imaging, or kidney biopsy
Recurrent acute kidney injury	Increases risk of CKD progression
Uncertain diagnosis	Specialist assessment may clarify cause and treatment strategy
Preparation for dialysis, transplantation, or conservative kidney care	Requires timely education and shared decision-making

Nephrology referral should be considered when patients have high-risk CKD, uncertain diagnosis, rapid progression, or complications requiring specialized management. Early referral allows diagnostic clarification, optimization of kidney-protective therapy, management of complications, and preparation for advanced CKD care when necessary.

Referral should not be understood as a transfer of responsibility away from primary care or endocrinology. Patients with type 2 diabetes and CKD benefit most from coordinated multidisciplinary care involving primary care physicians, endocrinologists, nephrologists, cardiologists, pharmacists, dietitians, diabetes educators, and nurses.

Summary of diagnostic and risk stratification approach

Diagnosis and risk stratification of CKD in type 2 diabetes require a structured and repeated assessment rather than reliance on serum creatinine alone. eGFR and UACR should be used together because they capture different but complementary dimensions of kidney disease. The CGA framework allows clinicians to define the likely cause of CKD, classify the degree of kidney function impairment, quantify albuminuria, estimate prognosis, guide monitoring frequency, and select appropriate therapies.

Early identification of CKD is clinically important because effective kidney- and cardiovascular-protective therapies are now available. Patients with type 2 diabetes should therefore undergo routine screening with both eGFR and UACR, followed by individualized monitoring based on risk level. Persistent albuminuria, rapid eGFR decline, active urinary sediment, severe hypertension, hyperkalemia, or atypical features should prompt closer evaluation and possible nephrology referral. A risk-based diagnostic strategy is essential for timely intervention and long-term cardio-renal-metabolic protection.

Contemporary Management and Treatment Strategies

General principles of contemporary management

The management of type 2 diabetes mellitus complicated by chronic kidney disease has changed substantially over the past decade. Historically, treatment focused mainly on glycemic control, blood pressure reduction, lipid management, and renin–angiotensin system inhibition. Although these components remain essential, they are no longer sufficient as the sole therapeutic strategy. Contemporary management emphasizes comprehensive cardio-renal-metabolic protection, aiming not only to control blood glucose but also to slow kidney disease progression, reduce albuminuria, prevent heart failure, lower atherosclerotic cardiovascular risk, minimize hypoglycemia, and preserve quality of life.

This shift is based on the recognition that T2DM and CKD interact through multiple biological pathways. Hyperglycemia, insulin resistance, obesity, inflammation, oxidative stress, glomerular hyperfiltration, endothelial dysfunction, RAAS activation, and mineralocorticoid receptor-mediated fibrosis collectively contribute to kidney and cardiovascular injury. Therefore, treatment should target both traditional risk factors and disease-modifying pathways. In clinical practice, this means combining individualized glycemic management with kidney-protective and cardiovascular-protective therapies.

Table 7: Core therapeutic goals in type 2 diabetes mellitus complicated by chronic kidney disease

Therapeutic goal	Clinical rationale
Slow decline in eGFR	Delays progression to advanced CKD and kidney failure
Reduce albuminuria	Reflects lower glomerular injury and residual kidney risk
Prevent heart failure	Diabetes and CKD markedly increase heart failure risk
Reduce cardiovascular events	Cardiovascular disease is a leading cause of death in this population
Avoid hypoglycemia	CKD increases hypoglycemia risk through altered insulin and drug clearance
Control blood pressure	Reduces kidney disease progression and cardiovascular complications
Individualize glycemic targets	Balances microvascular benefit against treatment-related harm
Minimize medication burden	Improves adherence and long-term treatment sustainability
Preserve quality of life	Supports patient-centered chronic disease care

Current guideline-based care supports early initiation of therapies with proven organ-protective benefits in eligible patients. SGLT2 inhibitors are now considered foundational therapy for many patients with T2DM and CKD because they reduce kidney disease progression and heart failure risk. GLP-1 receptor agonists are particularly useful in patients requiring additional glycemic control, weight reduction, or cardiovascular risk reduction. Finerenone provides additional benefit in selected patients with persistent albuminuria despite optimized standard therapy. These therapies should be selected according to eGFR, albuminuria, cardiovascular disease, heart failure, potassium level, hypoglycemia risk, tolerability, cost, and patient preference [7].

Lifestyle and non-pharmacological interventions

Lifestyle intervention remains a foundational component of care, but it should be individualized rather than applied as a rigid prescription. Patients with T2DM and CKD differ widely in age, kidney function, nutritional status, cardiovascular risk, frailty, physical capacity, socioeconomic background, and cultural dietary patterns. Therefore, lifestyle management should be practical, sustainable, and aligned with the patient's clinical condition.

Dietary sodium reduction is important because excess sodium contributes to hypertension, volume overload, albuminuria, and heart failure. Patients should be advised to reduce highly processed foods, salty condiments, and excessive sodium intake. However, counseling should avoid unrealistic restrictions that reduce adherence. Protein intake should also be individualized. Excessive protein intake may increase intraglomerular pressure and kidney workload, whereas overly restrictive protein intake may worsen malnutrition, especially in older adults, frail patients, or those with advanced CKD. When available, dietary counseling should involve a renal dietitian familiar with both diabetes and kidney disease.

Weight management is clinically relevant in patients with obesity, insulin resistance, metabolic syndrome, or heart failure risk. Moderate weight reduction may improve insulin sensitivity, blood pressure, albuminuria, and cardiovascular risk. However, aggressive weight-loss strategies should be avoided in patients with frailty, sarcopenia, poor appetite, or advanced CKD. Physical activity should be encouraged according to functional capacity and cardiovascular safety. Regular exercise can improve glycemic control, body composition, blood pressure, functional status, and quality of life.

Smoking cessation is essential. Smoking accelerates kidney function decline, worsens endothelial dysfunction, increases albuminuria, and raises cardiovascular risk. Patient education should also include avoidance of unnecessary nephrotoxic medications, recognition of dehydration and acute illness, adherence to laboratory monitoring, and early medical consultation when symptoms of volume depletion, infection, or hypoglycemia occur.

Blood pressure control and renin–angiotensin system blockade

Blood pressure control is one of the most important strategies for slowing CKD progression and reducing cardiovascular events. Hypertension is highly prevalent in patients with T2DM and CKD and contributes to intraglomerular hypertension, albuminuria, arterial stiffness, left ventricular hypertrophy, stroke, heart failure, and progressive kidney injury. Blood pressure targets should be individualized according to albuminuria, CKD stage, cardiovascular disease, frailty, orthostatic symptoms, and treatment tolerability.

Renin–angiotensin system inhibitors, including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are especially important in patients with diabetes, hypertension, and albuminuria. These agents reduce efferent arteriolar constriction, lower intraglomerular pressure, reduce albuminuria, and slow kidney disease progression [8]. Their role is most clearly established in albuminuric CKD, where persistent protein leakage and glomerular hypertension are major drivers of progression.

Table 8: Practical considerations for renin–angiotensin system inhibitor therapy

Clinical consideration	Practical implication
Albuminuria	Stronger indication for ACE inhibitor or ARB therapy
Serum creatinine/eGFR	Should be checked after initiation or dose escalation
Serum potassium	Hyperkalemia risk increases as CKD progresses
Volume status	Dehydration increases risk of acute kidney injury
Blood pressure tolerance	Targets should be individualized in frail or older patients
Avoid dual ACE inhibitor–ARB therapy	Reduces risk of hyperkalemia and acute kidney injury
Medication review	NSAIDs and other nephrotoxic agents should be avoided when possible

RAS blockade requires careful monitoring. Serum creatinine and potassium should be assessed after treatment initiation or dose escalation. A modest early rise in serum creatinine may reflect a hemodynamic reduction in intraglomerular pressure and does not necessarily indicate structural kidney damage. However, marked creatinine elevation, symptomatic hypotension, volume depletion, or persistent hyperkalemia should prompt reassessment. Dual blockade with an ACE inhibitor and an ARB is generally avoided because it increases the risk of hyperkalemia, hypotension, and acute kidney injury without sufficient additional benefit.

SGLT2 inhibitors as foundational kidney-protective therapy

Sodium–glucose cotransporter 2 inhibitors have become foundational therapy for many patients with T2DM and CKD. Although they were originally developed as glucose-lowering agents, their kidney and cardiovascular benefits are partly independent of glycemic effects. Mechanistically, SGLT2 inhibitors reduce proximal tubular sodium-glucose reabsorption, increase sodium delivery to the macula densa, restore tubuloglomerular feedback, reduce intraglomerular pressure, and attenuate

hyperfiltration-mediated injury. These effects directly address one of the central hemodynamic abnormalities in diabetic kidney disease.

Beyond glomerular hemodynamics, SGLT2 inhibitors may reduce albuminuria, tubular workload, renal hypoxia, inflammation, oxidative stress, body weight, blood pressure, and heart failure risk. These mechanisms explain why their protective effects can persist even when glucose-lowering efficacy is reduced at lower eGFR levels. Clinically, this has shifted their role from purely antidiabetic drugs to disease-modifying cardio-renal therapies.

The DAPA-CKD trial demonstrated that dapagliflozin reduced the risk of sustained kidney function decline, kidney failure, or death from renal or cardiovascular causes in patients with CKD [6]. The EMPA-KIDNEY trial further showed that empagliflozin reduced the risk of kidney disease progression or cardiovascular death in a broad CKD population. These findings support the early use of SGLT2 inhibitors in eligible patients rather than reserving them for late-stage disease.

Table 9: Clinical benefits and safety considerations of SGLT2 inhibitors in type 2 diabetes mellitus with chronic kidney disease

Aspect	Clinical relevance
Kidney protection	Slows eGFR decline and reduces CKD progression
Albuminuria	Often reduces albuminuria and residual kidney risk
Heart failure	Reduces the risk of heart failure hospitalisation
Blood pressure and weight	Provides modest reductions that support cardiometabolic control
eGFR threshold	Recommended for eligible patients with eGFR ≥20 mL/min/1.73 m²
Early eGFR dip	Usually reflects hemodynamic change and may stabilise over time
Common adverse effects	Genital mycotic infection and volume depletion
Rare serious risk	Ketoacidosis, especially during acute illness or prolonged fasting
Patient education	Hydration, genital hygiene, and sick-day guidance are important

In practice, clinicians should consider SGLT2 inhibitor therapy for eligible patients with T2DM and CKD, particularly those with albuminuria or high cardiovascular risk. Current ADA recommendations support their use in people with T2DM and CKD when eGFR is at least 20 mL/min/1.73 m² to reduce CKD progression and cardiovascular events [1]. Before initiation, volume status, blood pressure, kidney function, and concomitant diuretic use should be reviewed. Patients should be educated about genital mycotic infections, symptoms of volume depletion, rare ketoacidosis risk, and temporary interruption during severe acute illness, prolonged fasting, or major surgery.

GLP-1 receptor agonists and cardio-renal-metabolic protection

Glucagon-like peptide-1 receptor agonists have an increasingly important role in the management of T2DM complicated by CKD, especially in patients with obesity, suboptimal glycemic control, established cardiovascular disease, or high cardiovascular risk. These agents improve glucose-dependent insulin secretion, suppress glucagon secretion, delay gastric emptying, reduce appetite, and promote weight loss. Because their glucose-lowering effect is glucose-dependent, they have a low intrinsic risk of hypoglycemia when not combined with insulin or sulfonylureas.

The role of GLP-1 receptor agonists has expanded beyond glucose control. Several agents in this class have demonstrated cardiovascular benefits in patients with T2DM and high cardiovascular risk. Kidney-related benefits were initially observed mainly through reductions in albuminuria and slower decline in kidney function in secondary outcomes. More recently, the FLOW trial showed that semaglutide reduced clinically important kidney outcomes and cardiovascular death in patients with T2DM and CKD. This strengthened the position of GLP-1 receptor agonists as part of a broader cardio-renal-metabolic protection strategy.

GLP-1 receptor agonists may be considered when additional glycemic control is needed after foundational therapy, when weight reduction is clinically desirable, when cardiovascular risk is high, or when SGLT2 inhibitors are not tolerated or contraindicated. In many high-risk patients, GLP-1 receptor agonists may be used together with SGLT2 inhibitors because the two classes have complementary mechanisms. SGLT2 inhibitors mainly reduce intraglomerular pressure, tubular workload, and heart failure risk, whereas GLP-1 receptor agonists improve glycemic control, reduce body weight, and lower atherosclerotic cardiovascular risk.

Table 10: Clinical role of GLP-1 receptor agonists in type 2 diabetes mellitus complicated by chronic kidney disease

Clinical role	Explanation
Glycemic control	Improves glucose levels with low intrinsic hypoglycemia risk
Weight reduction	Supports management of obesity and metabolic risk
Cardiovascular protection	Reduces major cardiovascular events in selected high-risk populations
Kidney protection	Reduces albuminuria; semaglutide has demonstrated kidney outcome benefit
Combination therapy	May complement SGLT2 inhibitors in high-risk patients
Common adverse effects	Gastrointestinal symptoms and reduced appetite
Practical consideration	Slow dose escalation and hydration counselling are important

Common adverse effects include nausea, vomiting, diarrhoea, constipation, and reduced appetite. These effects are usually dose-related and most prominent during treatment initiation or escalation. In patients with CKD, prolonged vomiting or poor oral intake may increase dehydration risk; therefore, slow dose escalation and hydration counselling are important.

Finerenone and mineralocorticoid receptor antagonism

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist that targets inflammatory and fibrotic pathways in kidney and cardiovascular tissues. Mineralocorticoid receptor overactivation contributes to oxidative stress, endothelial dysfunction, macrophage infiltration, extracellular matrix deposition, glomerulosclerosis, tubulointerstitial fibrosis, vascular remodeling, and cardiac injury. These mechanisms are highly relevant in patients with T2DM and CKD, particularly those with persistent albuminuria despite optimized standard therapy.

The FIDELIO-DKD trial demonstrated that finerenone reduced the risk of CKD progression and cardiovascular events in patients with T2DM and CKD [9]. The FIGARO-DKD trial showed that finerenone reduced cardiovascular events in a broader population of patients with T2DM and CKD [9]. Together, these trials support finerenone as an important add-on therapy in selected patients with persistent albuminuria despite maximally tolerated renin–angiotensin system inhibition.

The major safety concern with finerenone is hyperkalemia. Therefore, serum potassium and eGFR should be assessed before initiation and monitored after treatment begins. Finerenone is most appropriate for patients with persistent albuminuria, acceptable potassium levels, and access to follow-up monitoring. In patients with advanced CKD, baseline hyperkalemia, or concurrent use of medications that increase potassium, treatment requires particular caution.

Table 11: Clinical considerations for finerenone therapy in type 2 diabetes mellitus with chronic kidney disease

Clinical consideration	Practical implication
Main indication	T2DM with CKD and persistent albuminuria despite standard therapy
Mechanistic target	Mineralocorticoid receptor-mediated inflammation and fibrosis
Kidney benefit	Reduces risk of CKD progression
Cardiovascular benefit	Reduces cardiovascular events
Key safety issue	Hyperkalemia
Monitoring requirement	Serum potassium and eGFR should be checked before and after initiation
Use with RAS inhibition	Usually considered as add-on to optimised ACE inhibitor or ARB therapy
Patient selection	Best suited for patients with persistent albuminuria and feasible monitoring

Metformin and individualized glucose-lowering therapy

Metformin remains an important glucose-lowering therapy for many patients with T2DM, but its use in CKD depends on kidney function and clinical stability. Because metformin is renally cleared, declining eGFR increases concern about drug accumulation and lactic acidosis in high-risk settings. In patients with mild to moderate CKD, metformin may often be continued with appropriate dose adjustment and monitoring, but it should be reassessed during acute illness, dehydration, hypoxia, sepsis, or rapid kidney function decline [8].

Insulin remains effective across CKD stages but requires caution because insulin clearance decreases as kidney function declines. This may increase the risk of hypoglycemia, especially in older adults, patients with poor oral intake, or those with advanced CKD. Sulfonylureas should also be used carefully because some agents are associated with prolonged hypoglycemia in CKD. Agents with higher hypoglycemia risk should be avoided or replaced when safer alternatives are available.

Dipeptidyl peptidase-4 inhibitors may be useful in selected patients because they provide modest glucose-lowering effects with low intrinsic hypoglycemia risk, although several agents require renal dose adjustment. Thiazolidinediones may improve insulin sensitivity but can cause fluid retention and are often unsuitable for patients with heart failure or advanced CKD. Overall, glucose-lowering therapy should be selected not only according to HbA1c but also according to eGFR, albuminuria, cardiovascular disease, heart failure, weight, hypoglycemia risk, cost, and patient preference.

Table 12: Practical considerations for glucose-lowering therapy in type 2 diabetes mellitus with chronic kidney disease

Drug class	Potential role	Key CKD-related consideration
Metformin	Foundational glucose-lowering therapy in eligible patients	Requires eGFR-based use and reassessment during acute illness
SGLT2 inhibitors	Kidney and cardiovascular protection	Recommended in eligible patients with eGFR ≥20 mL/min/1.73 m²
GLP-1 receptor agonists	Glycemic control, weight loss, cardiovascular and kidney benefit	Gastrointestinal tolerability and cost/access should be considered
Insulin	Effective at all CKD stages	Dose may need reduction as kidney function declines
Sulfonylureas	Glucose lowering	Higher hypoglycemia risk; high-risk agents should be avoided in CKD
DPP-4 inhibitors	Modest glucose lowering with low hypoglycemia risk	Several agents require renal dose adjustment
Thiazolidinediones	Insulin sensitization	Fluid retention limits use in heart failure or advanced CKD

Lipid management and cardiovascular prevention

Cardiovascular disease is a leading cause of morbidity and mortality in patients with T2DM and CKD. Therefore, cardiovascular risk reduction is a central component of management. Lipid-lowering therapy, especially statin therapy, is generally recommended for most adults with diabetes and CKD who are not receiving dialysis, particularly when additional cardiovascular risk factors are present [10].

Lipid management should be integrated with blood pressure control, glycemic management, smoking cessation, weight management, antiplatelet decision-making, and kidney-protective therapy. Aspirin may be appropriate for secondary prevention in patients with established cardiovascular disease, but its use for primary prevention should be individualized according to bleeding risk and absolute cardiovascular risk.

Heart failure prevention deserves special attention. Patients with T2DM and CKD are at high risk of both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. SGLT2 inhibitors are especially valuable because they reduce heart failure hospitalization while also providing kidney protection. Volume status should be monitored carefully, especially in patients receiving diuretics, renin–angiotensin system inhibitors, SGLT2 inhibitors, or mineralocorticoid receptor antagonists.

Medication safety and prevention of acute kidney injury

Medication safety is critical in patients with T2DM and CKD because reduced kidney function alters drug clearance and increases susceptibility to adverse events. Regular medication

review should assess nephrotoxic exposure, dose appropriateness, hypoglycemia risk, potassium balance, blood pressure tolerance, and volume status.

Nonsteroidal anti-inflammatory drugs should generally be avoided or minimized because they can reduce renal perfusion and increase the risk of acute kidney injury, especially in patients receiving renin–angiotensin system inhibitors or diuretics. During acute illness, vomiting, diarrhea, dehydration, severe infection, prolonged fasting, or poor oral intake, selected medications may require temporary interruption to reduce the risk of acute kidney injury, hypotension, hypoglycemia, or ketoacidosis.

Patient education is essential. Patients should understand the importance of hydration, medication adherence, laboratory monitoring, avoidance of unnecessary nephrotoxic drugs, and early medical contact during acute illness. This is particularly important for patients receiving SGLT2 inhibitors, insulin, diuretics, RAS inhibitors, or finerenone, because these therapies require context-specific safety monitoring.

Table 13: Medication safety priorities in type 2 diabetes mellitus complicated by chronic kidney disease

Safety priority	Clinical importance
Avoid unnecessary NSAIDs	Reduces risk of acute kidney injury
Adjust drug doses by eGFR	Prevents drug accumulation and toxicity
Monitor serum potassium	Essential with RAS inhibitors and finerenone
Monitor volume status	Prevents hypotension and kidney hypoperfusion
Prevent hypoglycemia	Requires caution with insulin and sulfonylureas
Provide sick-day guidance	Reduces medication-related harm during acute illness
Review polypharmacy	Improves adherence and lowers adverse event risk

Multidisciplinary and patient-centered care

T2DM complicated by CKD is a complex chronic condition that often requires multidisciplinary care. Primary care physicians, endocrinologists, nephrologists, cardiologists, pharmacists, dietitians, diabetes educators, and nurses each contribute to optimal management. Coordinated care improves CKD screening, medication selection, dose adjustment, laboratory monitoring, complication prevention, and patient education.

Patient-centered care is equally important. Treatment decisions should consider patient preferences, financial constraints, health literacy, cultural dietary habits, access to laboratory monitoring, ability to tolerate injections, and capacity to manage complex medication regimens. Shared decision-making can improve adherence and align treatment intensity with patient goals, safety, and quality of life.

In real-world practice, one of the main challenges is not the absence of effective therapies but the underuse of available therapies. Many patients with albuminuria or reduced eGFR do not receive timely kidney-protective treatment. Health systems should therefore strengthen routine UACR testing, clinical decision support, multidisciplinary referral pathways, and equitable access to medications.

Summary of contemporary treatment strategy

Contemporary management of T2DM complicated by CKD is based on integrated cardio-renal-metabolic protection. Lifestyle intervention, blood pressure control, renin–angiotensin system blockade, individualized glycemic management, lipid control, and medication safety remain foundational. However, disease-modifying therapy now increasingly includes SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone in appropriately selected patients.

A practical strategy begins with early diagnosis using eGFR and UACR, followed by risk-based treatment selection. Patients with hypertension and albuminuria should receive optimized renin–angiotensin system blockade when tolerated. Eligible patients should receive SGLT2 inhibitors for kidney and cardiovascular protection. GLP-1 receptor agonists should be considered when additional glycemic control, weight reduction, cardiovascular protection, or kidney benefit is needed. Finerenone should be considered in selected patients with persistent albuminuria despite standard therapy and acceptable potassium levels. Ongoing monitoring is necessary to maintain safety, adjust therapy, and reduce long-term cardio-renal complications.

Real-World Implementation Challenges and Future Directions

Gap between evidence and clinical practice

Although the therapeutic landscape of type 2 diabetes mellitus complicated by chronic kidney disease has advanced substantially, a considerable gap remains between evidence-based recommendations and real-world clinical practice. Current guidelines emphasize routine screening with eGFR and UACR, early risk stratification, individualized glycemic targets, blood pressure control, and timely use of kidney- and cardiovascular-protective therapies [11]. However, in many healthcare settings, these recommendations are not consistently implemented.

One of the most important gaps is underdiagnosis of early CKD. Serum creatinine is commonly measured in patients with diabetes, but urinary albumin-to-creatinine ratio testing is often underused. As a result, patients with early albuminuric kidney disease may remain undetected until kidney injury has progressed. This is clinically important because albuminuria is not only a marker of glomerular damage but also an indicator of increased cardiovascular risk. Without UACR testing, clinicians may underestimate disease severity and delay initiation of kidney-protective therapy.

Another gap is therapeutic inertia. Even when CKD is identified, evidence-based therapies may not be initiated promptly. SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone have demonstrated important cardio-renal benefits, yet their use may be limited by cost, lack of access, physician uncertainty, concern about adverse effects, polypharmacy, or fragmented care. Patients may

also hesitate to start newer medications because of limited understanding of their organ-protective role, fear of side effects, or financial burden.

Table 14: Common gaps between guideline recommendations and real-world care

Recommended practice	Common real-world gap	Potential consequence
Annual eGFR and UACR screening	UACR is often underused	Delayed detection of albuminuric CKD
Risk stratification using eGFR and UACR	Risk may be judged by serum creatinine alone	Underestimation of kidney and cardiovascular risk
Early SGLT2 inhibitor initiation	Delayed or absent prescription	Missed opportunity to slow CKD progression
Individualised glycemic targets	Uniform HbA1c targets may be applied	Increased hypoglycemia or undertreatment risk
Potassium and eGFR monitoring	Laboratory follow-up may be inconsistent	Reduced safety of RAS inhibitors or finerenone
Multidisciplinary care	Care may be fragmented across specialities	Inconsistent treatment and follow-up
Patient education	Limited counselling on CKD and medication safety	Poor adherence and higher acute illness risk

Barriers to early diagnosis

Early diagnosis of CKD in patients with type 2 diabetes is limited by several factors. First, CKD is often asymptomatic in its early stages. Patients may feel clinically well despite persistent albuminuria or mild eGFR decline. Without systematic screening, kidney disease may remain hidden until more advanced stages.

Second, serum creatinine may appear normal despite early kidney damage. This is especially true in older adults, women, patients with reduced muscle mass, and those with early albuminuric disease. Relying only on serum creatinine can therefore miss clinically important CKD. The combined use of eGFR and UACR is necessary because these markers assess different dimensions of kidney health [12].

Third, UACR testing may not be routinely ordered or may not be available in some healthcare settings. Even when available, clinicians may not repeat abnormal results to confirm persistence, or patients may not return for follow-up testing. In resource-limited systems, laboratory cost, insurance coverage, transportation difficulties, and fragmented care further reduce screening completion.

Fourth, CKD risk may be underestimated when albuminuria is viewed only as a kidney marker rather than a systemic vascular risk marker. In patients with diabetes, albuminuria should prompt broader risk reduction, including blood pressure optimisation, cardiovascular prevention, and consideration of organ-protective therapies.

Barriers to optimal pharmacological treatment

The availability of effective therapies does not guarantee their use. Several barriers may prevent optimal pharmacological management in patients with type 2 diabetes and CKD. Cost and access are among the most important barriers, particularly for SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone. In many healthcare systems, these agents may be unavailable, only partially reimbursed, or unaffordable for long-term use.

Clinician uncertainty is another barrier. Some clinicians may be unfamiliar with current eGFR thresholds, sick-day guidance, safety monitoring, or the distinction between glucose-lowering effects and kidney-protective effects. For example, SGLT2 inhibitors may be underused in patients with reduced eGFR because clinicians may focus on diminished glycemic efficacy while overlooking preserved kidney and heart failure benefits.

Concern about adverse effects may also limit treatment. SGLT2 inhibitors may raise concern about genital infections, dehydration, or ketoacidosis. GLP-1 receptor agonists may be limited by gastrointestinal intolerance, injection concerns, or cost. Finerenone may be underused because of concern about hyperkalemia and the need for potassium monitoring. These concerns are clinically valid, but they should be managed through careful patient selection, education, and follow-up rather than automatic avoidance.

Table 15: Barriers to optimal use of kidney- and cardiovascular-protective therapies

Barrier	Affected therapy or process	Practical implication
High medication cost	SGLT2 inhibitors, GLP-1 receptor agonists, finerenone	Limits long-term adherence and access
Limited clinician familiarity	Newer organ-protective therapies	Delayed initiation or inappropriate avoidance
Fear of adverse effects	SGLT2 inhibitors, GLP-1 receptor agonists, finerenone	Underuse despite clear indications
Laboratory monitoring constraints	RAS inhibitors, finerenone, CKD follow-up	Reduced safety and confidence in prescribing
Polypharmacy	All chronic therapies	Poor adherence and higher interaction risk
Fragmented care	Screening, treatment, monitoring	Inconsistent implementation
Patient misunderstanding	Long-term preventive therapies	Low adherence when symptoms are absent

Polypharmacy further complicates treatment. Patients with type 2 diabetes and CKD often already take multiple medications for glucose, blood pressure, lipids, cardiovascular disease, anemia, acidosis, mineral metabolism, and fluid status. Adding new therapies may increase pill burden, monitoring needs, and patient anxiety. Therefore, treatment decisions should include medication review, deprescribing of unnecessary agents, and clear explanation of therapeutic priorities.

Challenges in glycemic management

Glycemic management in CKD is particularly challenging because kidney dysfunction changes glucose metabolism, drug clearance, and hypoglycemia risk. HbA1c remains useful, but its interpretation may be affected by anemia, altered red blood cell lifespan, iron therapy, erythropoiesis-stimulating agents, transfusion, inflammation, and uremia. Therefore, a single HbA1c value may not fully reflect true glycemic exposure in advanced CKD.

Hypoglycemia is one of the most important treatment-related risks. As kidney function declines, insulin clearance decreases, and the effects of insulin or insulin secretagogues may be prolonged. In addition, CKD is often associated with poor appetite, irregular food intake, malnutrition, acute illness, and comorbid cardiovascular disease. These factors increase glycemic variability and make overly aggressive glycemic targets potentially harmful.

Management should therefore be individualized. In patients with early CKD, long life expectancy, low hypoglycemia risk, and few comorbidities, tighter glycemic control may be appropriate. In contrast, in older adults, frail patients, those with advanced CKD, recurrent hypoglycemia, cardiovascular disease, or limited life expectancy, less stringent targets may be safer. Continuous glucose monitoring or structured self-monitoring can be useful when HbA1c is discordant with symptoms or when insulin therapy is used, although access may be limited.

The central challenge is balancing long-term microvascular benefit with immediate safety. In CKD, the safest glycemic strategy is not necessarily the most intensive one; rather, it is the one that achieves reasonable control while avoiding hypoglycemia, excessive treatment burden, and drug toxicity.

Multidisciplinary care and care coordination

Type 2 diabetes complicated by CKD is too complex to be managed effectively through isolated, disease-specific care. Patients often require input from primary care physicians, endocrinologists, nephrologists, cardiologists, pharmacists, dietitians, diabetes educators, and nurses. Each discipline addresses a different aspect of the cardio-renal-metabolic spectrum.

Table 16: Roles of multidisciplinary team members in type 2 diabetes mellitus with chronic kidney disease

Team member	Main contribution
Primary care physician	Screening, longitudinal follow-up, coordination, and preventive care
Endocrinologist	Glycemic targets, glucose-lowering therapy, and hypoglycemia prevention
Nephrologist	CKD staging, progression monitoring, electrolyte management, and referral planning
Cardiologist	Heart failure, coronary disease, arrhythmia, cardiovascular risk reduction
Pharmacist	Dose adjustment, medication safety, interaction review, adherence support
Dietitian	Sodium, protein, weight, and culturally appropriate nutrition counselling
Diabetes educator	Self-management, glucose monitoring, and hypoglycemia education
Nurse	Follow-up, patient communication, adherence reinforcement, and monitoring support

Primary care is often responsible for early screening, long-term follow-up, medication reconciliation, and coordination. Endocrinologists contribute to individualized glycemic management and selection of glucose-lowering therapies. Nephrologists assist with CKD staging, progression assessment, albuminuria management, electrolyte abnormalities, and preparation for advanced CKD care. Cardiologists are important when heart failure, coronary artery disease, arrhythmia, or high cardiovascular risk is present. Pharmacists can support dose adjustment, interaction screening, adherence counseling, and medication access. Dietitians and diabetes educators help translate medical recommendations into practical daily behaviors [13].

Care coordination is essential because fragmented treatment can lead to duplicated medications, inconsistent advice, delayed laboratory monitoring, and missed therapeutic opportunities. A shared care plan should clearly identify treatment goals, medication indications, monitoring schedule, referral triggers, and patient education priorities.

Patient education and shared decision-making

Patient education is central to long-term success. Many patients with early CKD have no symptoms and may not understand why additional medications or laboratory monitoring are necessary. Explaining CKD as a silent but modifiable complication can improve adherence and engagement. Education should focus on practical actions rather than abstract risk alone.

Patients should understand the meaning of eGFR and UACR in simple terms. eGFR can be explained as a measure of kidney filtering function, while UACR can be explained as a sign of kidney leakage or early kidney stress. Patients should also understand that some medications protect the kidneys and heart even when they do not produce immediate symptom improvement.

Shared decision-making is especially important when adding newer therapies. Clinicians should discuss expected benefits, possible adverse effects, cost, monitoring needs, and patient preferences. For example, a patient may accept an injectable GLP-1 receptor agonist if weight reduction and cardiovascular protection are clearly explained, while another may prioritize oral therapy because of injection concerns. Similarly, finerenone may be acceptable if the patient understands the need for potassium monitoring.

Education should also include sick-day guidance. Patients should know when to seek medical advice during vomiting, diarrhea, dehydration, severe infection, poor oral intake, or planned surgery. This can reduce the risk of acute kidney injury, ketoacidosis, hypoglycemia, and medication-related complications.

Health-system priorities

At the health-system level, improving outcomes requires more than publishing clinical guidelines. Systems must make guideline-based care easier to deliver. One priority is improving routine UACR testing. Electronic medical record reminders, diabetes care checklists, nurse-led screening, and bundled annual diabetes complication reviews may increase detection of early CKD.

Another priority is clinical decision support. Automated alerts can help identify patients with low eGFR, elevated UACR, persistent albuminuria, rapid eGFR decline, or missing laboratory monitoring. Decision support can also suggest appropriate medication review, dose adjustment, nephrology referral, or consideration of SGLT2 inhibitors and other protective therapies.

Medication access is also essential. If organ-protective therapies are unaffordable or unavailable, guideline

recommendations cannot be implemented equitably. Health policies should consider the long-term cost savings of preventing kidney failure, dialysis, heart failure hospitalization, and cardiovascular events. In resource-limited settings, prioritizing high-risk patients with albuminuria or reduced eGFR may be a practical first step.

Finally, quality indicators should move beyond HbA1c alone. Diabetes care performance should include CKD screening rates, UACR testing, blood pressure control, SGLT2 inhibitor use in eligible patients, statin use where indicated, nephrology referral when appropriate, and avoidance of high-risk medications in CKD.

Table 17: Health-system strategies to improve care for type 2 diabetes mellitus complicated by chronic kidney disease

Health-system strategy	Expected benefit
Routine annual eGFR and UACR screening protocols	Earlier CKD detection
Electronic reminders for missing UACR	Reduces underdiagnosis of albuminuric CKD
Risk-based treatment algorithms	Supports consistent use of protective therapies
Medication access programs	Improves equity and adherence
Multidisciplinary CKD-diabetes clinics	Reduces fragmented care
Pharmacist-led medication review	Improves drug safety and dose adjustment
Patient education materials	Enhances adherence and self-management
Quality indicators beyond HbA1c	Encourages comprehensive cardio-renal-metabolic care

Future directions

Future care for T2DM complicated by CKD is likely to move further toward precision-based, integrated cardio-renal-metabolic management. Several areas are particularly important. First, better risk prediction tools are needed to identify which patients are most likely to progress rapidly and which patients will benefit most from specific therapies. Combining eGFR, UACR, clinical factors, biomarkers, and digital health data may improve individualized risk assessment.

Second, the optimal sequencing and combination of therapies require further clarification. Many patients may benefit from combined use of SGLT2 inhibitors, GLP-1 receptor agonists, RAS inhibitors, statins, and finerenone, but real-world questions remain about timing, tolerability, cost, adherence, and monitoring. Future research should evaluate practical treatment pathways across different healthcare systems and patient populations.

Third, more evidence is needed in underrepresented groups, including older adults, frail patients, patients with advanced CKD, low-income populations, and individuals from diverse ethnic backgrounds. Clinical trial populations may not fully reflect the complexity of real-world patients, especially those with multimorbidity, polypharmacy, and limited access to care.

Fourth, digital health may play an expanding role. Remote monitoring, electronic reminders, telemedicine, continuous glucose monitoring, home blood pressure monitoring, and patient portals may improve follow-up and self-management. However, digital solutions must be designed carefully to avoid widening disparities among patients with limited health literacy, internet access, or technological familiarity [14].

Finally, implementation science should become a major priority. The central question is no longer only whether effective therapies exist, but how to ensure that patients who need them receive them safely, early, and consistently.

Summary of implementation challenges and future priorities

Despite major therapeutic advances, type 2 diabetes complicated by CKD remains difficult to manage in real-world practice. Key challenges include underuse of UACR screening, delayed CKD diagnosis, therapeutic inertia, high medication cost, polypharmacy, hypoglycemia risk, fragmented care, and limited patient understanding of silent kidney disease. These barriers reduce the impact of evidence-based therapies and contribute to preventable kidney and cardiovascular complications.

Future progress will depend on earlier detection, wider implementation of organ-protective therapies, multidisciplinary care, patient-centred education, medication access, and system-level quality improvement. A modern care model should treat T2DM with CKD as a cardio-renal-metabolic condition requiring coordinated, long-term, risk-based management rather than isolated glucose control. By closing the gap between evidence and practice, healthcare systems can reduce kidney failure, cardiovascular events, hospitalizations, and premature mortality in this high-risk population [15].

Limitations of current evidence

Although recent advances have substantially improved the management of type 2 diabetes mellitus complicated by chronic kidney disease, several limitations remain in the current evidence base. First, many landmark clinical trials were conducted in selected populations with predefined inclusion and exclusion criteria. As a result, trial participants may not fully represent the complexity of real-world patients, particularly older adults, frail individuals, patients with multiple comorbidities, advanced CKD, recurrent acute kidney injury, limited health literacy, or restricted access to long-term monitoring.

Second, although SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone have demonstrated clinically meaningful cardio-renal benefits, the optimal sequencing and combination of these therapies remain incompletely defined. In clinical practice, many patients may be eligible for more than one organ-protective therapy. However, questions remain regarding treatment prioritization, timing of initiation, long-term adherence, cumulative adverse effects, cost-effectiveness, and feasibility of monitoring in different healthcare systems. More pragmatic studies are needed to determine how best to implement combination cardio-renal-metabolic therapy in routine care.

Third, long-term data remain limited for some newer therapeutic strategies. While major trials have shown significant benefits over several years of follow-up, type 2 diabetes and CKD are lifelong conditions. More evidence is needed regarding durability of benefit, long-term safety, real-world persistence, and

outcomes in patients treated across different stages of CKD. This is especially important for patients with advanced disease, in whom competing risks, polypharmacy, malnutrition, hypoglycemia, hyperkalemia, and cardiovascular instability are common.

Fourth, evidence from low- and middle-income countries remains insufficient. Most large outcome trials are conducted in settings with structured follow-up, regular laboratory monitoring, and access to expensive medications. In contrast, many healthcare systems face limited access to UACR testing, nephrology services, continuous glucose monitoring, newer drug classes, dialysis, and transplantation. Therefore, global implementation of guideline-based care requires attention to affordability, health-system capacity, medication availability, and culturally appropriate patient education.

Finally, current diagnostic and therapeutic approaches still rely heavily on eGFR and UACR. Although these markers are clinically useful, they do not fully capture the biological heterogeneity of diabetic kidney disease. Future research should identify additional biomarkers, imaging tools, and predictive models that can distinguish disease phenotypes, predict rapid progression, and guide individualized therapy [16].

CONCLUSION

Type 2 diabetes mellitus complicated by chronic kidney disease is a high-risk cardio-renal-metabolic condition associated with progressive kidney function decline, cardiovascular events, heart failure, hospitalization, therapeutic complexity, and premature mortality. Its pathophysiology extends far beyond chronic hyperglycemia and involves interacting metabolic, hemodynamic, inflammatory, fibrotic, tubular, endothelial, and cardiovascular mechanisms. This complexity explains why management based on glucose-lowering alone is no longer sufficient.

Early detection is central to improving outcomes. Routine assessment of both eGFR and UACR allows clinicians to identify kidney damage earlier, classify disease severity, estimate prognosis, guide treatment intensity, and determine monitoring frequency. Albuminuria should be regarded as a clinically meaningful marker of kidney and systemic vascular injury, even when eGFR remains preserved. Similarly, reduced eGFR should prompt careful medication review, individualized glycemic assessment, cardiovascular risk evaluation, and monitoring for CKD-related complications.

Contemporary management has shifted toward integrated cardio-renal-metabolic protection. Lifestyle intervention, blood pressure control, renin–angiotensin system blockade, lipid management, individualized glycemic targets, and medication safety remain essential. However, disease-modifying therapies such as SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone have transformed care by providing kidney and cardiovascular benefits beyond glucose control. These therapies should be considered early in eligible patients and implemented with appropriate monitoring and patient education.

Despite strong evidence, real-world gaps remain. Underuse of UACR testing, delayed diagnosis, therapeutic inertia, medication cost, polypharmacy, fragmented care, and limited access to newer therapies reduce the impact of current advances. Addressing these barriers requires multidisciplinary care, health-system support, patient-centered education, and equitable access to evidence-based treatment. Future research should clarify optimal combination therapy, improve risk prediction, expand evidence in underrepresented populations, and support implementation in resource-limited settings.

Overall, type 2 diabetes with chronic kidney disease should be managed as a progressive but modifiable cardio-renal-metabolic disorder. Earlier screening, risk-based treatment, and coordinated long-term care offer the greatest opportunity to reduce kidney failure, cardiovascular complications, hospitalizations, and premature death.

Author's commitment statement

The author contributed to the conceptualization, literature synthesis, drafting, critical revision, and final approval of the manuscript.

Conflicts of interest

The author declares no conflicts of interest related to this manuscript.

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