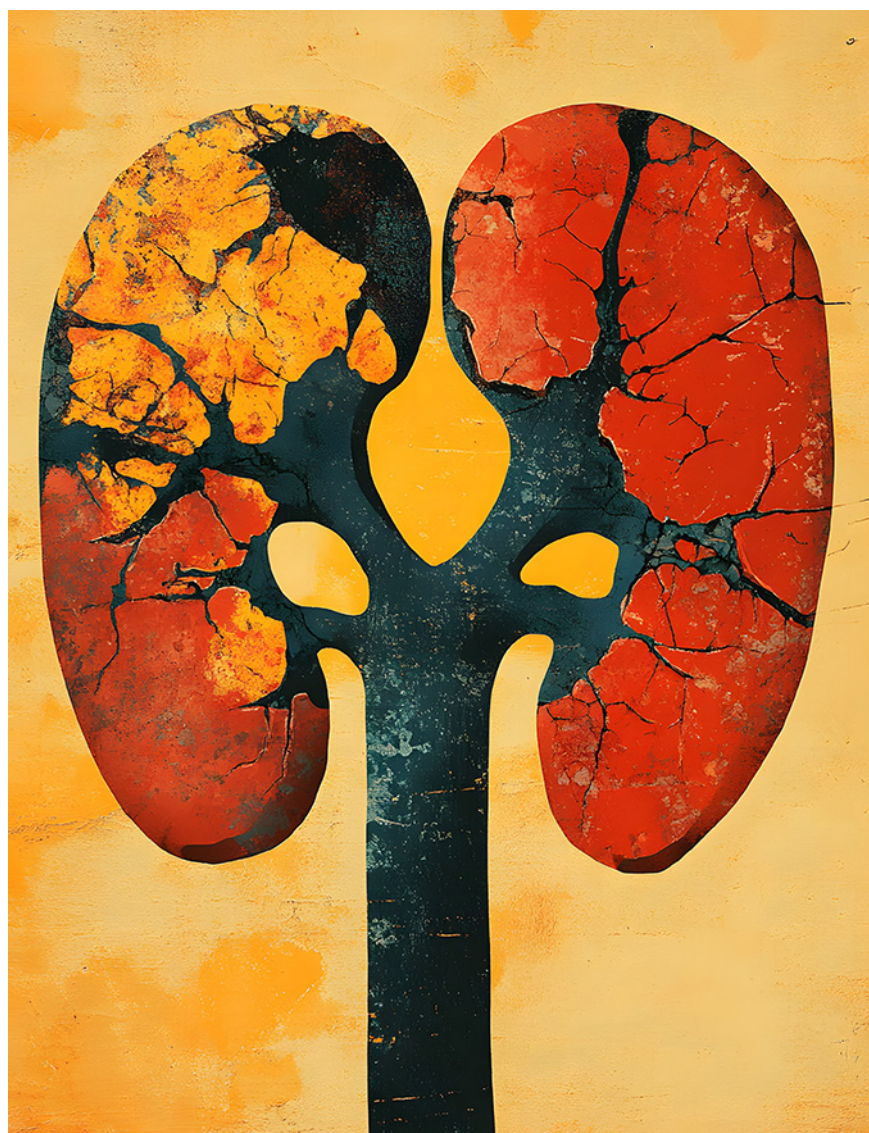


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New Horizons in the Treatment of Chronic Kidney Disease and Diabetes



Diabetes mellitus (DM) is a global pandemic. Currently, 589 million people are affected by DM, and it is estimated that by 2050 this figure will rise to 853 million (1). According to data from the National Health Survey, in 2023 the prevalence of DM in the general population was 7.1%. Likewise, in 2024, DM per se was the 11th leading cause of mortality. However, the first cause of death was ischemic heart disease, for which one of the cardiovascular risk factors increasing the likelihood of occurrence is DM, along with hypertension, dyslipidemia, and obesity. The importance of DM lies in its cardiovascular complications, such as ischemic heart disease, stroke, and chronic kidney disease (CKD) (2). CKD may occur in up to one-third of cases, often progressing to end-stage CKD requiring renal replacement therapy, either dialysis or kidney transplantation. In Catalonia, during 2023, DM was the leading known cause of CKD in incident dialysis patients (3).

Thus, DM is a disease with a profound impact on health and quality of life. For this reason, early diagnosis and appropriate treatment are fundamental. However, DM is a silent disease, as elevated blood glucose levels usually do not cause symptoms (except at very high values). A person with DM who maintains elevated blood glucose levels without treatment may, over the years, develop the associated complications previously mentioned. Therefore, to achieve early diagnosis, population health strategies focused on active detection of undiag- »

» nosed DM are essential. In this regard, the role of primary care physicians is crucial. In patients diagnosed with T2DM, from the moment of diagnosis, an annual blood test is recommended to estimate renal function with the calculation of glomerular filtration rate (GFR) using the CKD-EPI formula, along with urine testing for protein loss (albuminuria) via the albumin-to-creatinine ratio (ACR) (4). A patient with DM will be considered to have CKD if GFR is <60 mL/min/1.73 m² and/or ACR ≥ 30 mg/g for 6 months. According to CKD stage, defined by GFR and albuminuria (**Figure 1**), patients can be classified into different categories, each associated with a different level of cardiovascular risk. Primary care physicians may consider referral to nephrology in patients with DM and CKD when albuminuria >300 mg/g and/or GFR <30 mL/min. Referral may also be considered in other situations, such as resistant hypertension requiring more than three drugs, unexplained hematuria, rapid decline in renal function, acid-base disorders, and electrolyte imbalances. Individualized, multidisciplinary evaluation between primary care teams and nephrology specialists is essential (5).

The goal of managing patients with DM and CKD is to achieve metabolic control of DM by reducing blood glucose levels and glycated hemoglobin (HbA1c). In general, the HbA1c

target should be $<7\%$. In younger patients with longer life expectancy, few comorbidities, and low hypoglycemia risk, a stricter target of 6.5% may be appropriate. In older patients, with higher comorbidity and high hypoglycemia risk, a less strict goal ($<8\%$) is recommended (6, 7).

To achieve metabolic control, lifestyle interventions are fundamental. These include a healthy diet with reduced sodium and processed foods, regular physical activity, weight management, and smoking cessation (Figure 2). Nonetheless, most patients with DM and CKD will require pharmacologic treatment. Fortunately, clinicians treating CKD in patients with DM now have new therapeutic options. For decades, available drugs were scarce. Currently, sodium-glucose cotransporter 2 inhibitors (SGLT2i: empagliflozin, dapagliflozin, canagliflozin) are recommended as first-line therapy. Their hypoglycemic effect is mediated by urinary glucose excretion via inhibition of renal tubular SGLT2, responsible for 90% of glucose reabsorption. Importantly, SGLT2 inhibitors have demonstrated reduction in the onset and progression of cardiovascular and renal events in patients with type 2 DM, independent of glycemic control. Thus, European and American guidelines, as well as the Spanish Society of Nephrology consensus, recommend their use as first-line therapy »

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KD Stage	eGFR (mL/min/1.73 m ²)	Degree of albuminuria		
		A1 <30 mg/gr	A2 30-300 mg/gr	A3 > 300 mg/gr
1	>90			
2	60-89			
3A	45-59			
3B	30-44			
4	15-29			
5	<15			

	Follow-up in primary care
	Follow-up in primary care with increased frequency (every 3–4 months)
	Referral to nephrology

FIGURE 1. Shared care of patients with CKD between Primary Care and Nephrology. Adapted from García-Maset et al. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

» together with metformin. SGLT2i can be initiated in patients with GFR >20 mL/min/1.73 m² and continued until end-stage renal disease. Glucagon-like peptide-1 receptor agonists (GLP-1a: liraglutide, semaglutide, dulaglutide) are recommended as add-on therapy because of their cardiovascular and renal benefits in type 2 DM. These analogues induce weight loss, increase satiety, and slow gastric emptying. Renally, they reduce inflammation and oxidative stress, offering nephroprotection. For this reason, US guidelines recommend them as first-line agents alongside SGLT2i and metformin in CKD patients with high cardiovascular risk. Dipeptidyl peptidase-4 inhibitors (DPP-4i) may be used in frail patients because of their low risk of hypoglycemia or when GLP-1 analogues are contraindicated. They should not, however, be combined with GLP-1 analogues. High-dose thiazolidinediones (glitazones) should be used with caution in CKD. Insulin doses should be reduced in CKD because insulin clearance is renal; accumulation increases its effect compared with patients with preserved renal function (4).

Management of DM and CKD must be holistic and not based solely on glycemic control. Blood pressure targets should be <130 mmHg systolic if tolerated, otherwise <140 mmHg. Renin-angiotensin-aldosterone system (RAAS) blockers are first-line agents in hypertension for their nephroprotective effect, particularly in albuminuric CKD. Nonsteroidal mineralocorticoid receptor antagonists (MRA), such as finerenone, are additional resources for nephroprotection. Finerenone improves renal outcomes and slows CKD progression. It should be used in persistent albuminuria despite optimized therapy, provided GFR

>20 mL/min and potassium levels are controlled. Thus, the four fundamental pillars of therapy for DM and CKD are: RAAS blockers, SGLT2 inhibitors, GLP-1 receptor agonists, and Nonsteroidal MRAs. Clinicians should routinely assess whether each patient has an indication for these therapies, and if not prescribed, document the reason (6, 7).

At present, we have a broad therapeutic arsenal for an integrated and individualized approach. However, the future is even more promising, with ongoing clinical trials of new drugs for DM and CKD (Figure 3). Tirzepatide, a dual GLP-1/GIP receptor agonist, is currently the most effective agent for glycemic control and weight loss in type 2 DM.⁸ Retatrutide, a triple GLP-1/GIP/glucagon receptor agonist, is in phase 3 trials for CKD.⁹ Other investigational agents include endothelin receptor antagonists (zibotentan), guanylate cyclase activators (avciguat), and aldosterone synthase inhibitors (vicadrostad).^{10–12} Beyond drugs, mesenchymal stem cell therapy is under study in early-phase clinical trials for patients with DM and CKD, with promising results.

Importantly, these advances are not limited to T2DM. Trials are also underway to evaluate SGLT2i, GLP-1a, guanylate cyclase inhibitors, endothelin antagonists, and finerenone in type 1 DM. Positive results could soon extend these therapies to that population as well. **D**

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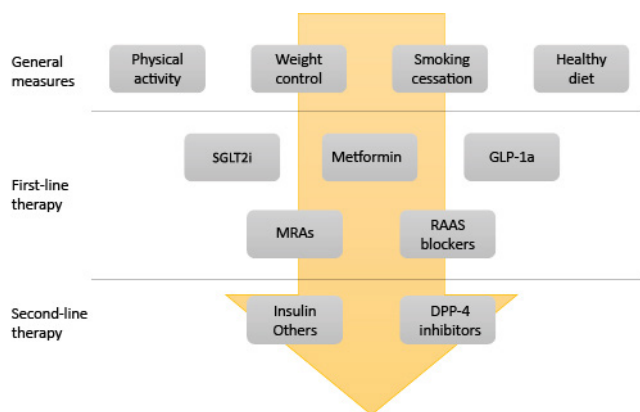


FIGURE 2. General treatment of DM and CKD according to KDIGO 2022, ADA 2025, and Spanish Society of Nephrology 2025 consensus guidelines.

SGLT2i, sodium-glucose cotransporter 2 inhibitors; GLP-1a, glucagon-like peptide 1 receptor agonists; RAAS, renin-angiotensin-aldosterone system blockers; MRA, mineralocorticoid receptor antagonists; DPP-4i, dipeptidyl peptidase-4 inhibitors.

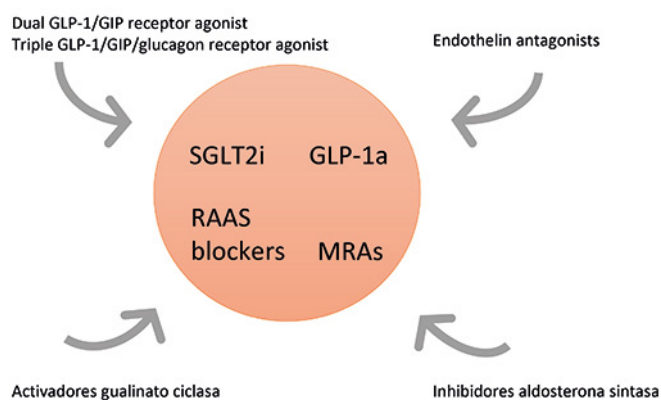


FIGURE 3. Families of nephroprotective drugs currently approved and marketed, and investigational agents under clinical trial.

SGLT2i, sodium-glucose cotransporter 2 inhibitors; GLP-1a, glucagon-like peptide 1 receptor agonists; RAAS, renin-angiotensin-aldosterone system blockers; MRA, mineralocorticoid receptor antagonists; DPP-4i, dipeptidyl peptidase-4 inhibitors.



CONCLUSIONS

DM is a major global health problem, and CKD is a frequent complication with high morbidity and mortality. Early screening in primary care and strong coordination with nephrology are essential. We are living a golden era in the treatment of DM and CKD, with an unprecedented wave of new drugs that alter the natural history of disease. Clinical guidelines have been forced to adapt rapidly—some updated within only 2 years, an extraordinary occurrence in this field. The near future is even more promising, with ongoing clinical trials of new pharmacologic agents that will likely further benefit patients with DM and CKD.

BIBLIOGRAFÍA

1. International Diabetes Federation. IDF Atlas Report. 2025;
2. Ministerio de Sanidad. Encuesta de Salud de España – ESdE 2023. 2025;
3. Organització Catalana de Trasplantaments (OCATT). Informe estadístic del Registre de malalts Renals de Catalunya Organització Catalana de Trasplantaments. 2023; Available from: <http://trasplantaments.gencat.cat>
4. Montero N, Oliveras L, Martínez-Castelao A, Gorriiz JL, Soler MJ, Fernández-Fernández B, et al. Guía de práctica clínica sobre detección y manejo de la enfermedad renal diabética: documento de consenso de la Sociedad Española de Nefrología. Nefrología. 2025;45(S 1):1–26.
5. García-Maset R, Bover J, Segura de la Morena J, Goicoechea Diezhandino M, Cebollada del Hoyo J, Escalada San Martín J, et al. Documento de información y consenso para la detección y manejo de la enfermedad renal crónica. Nefrología [Internet]. 2022 May;42(3):233–64. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0211699521001612>
6. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022;102(5):S1–127.
7. ADA. Standards of Care in Diabetes 2025: TOC. Am Diabetes Assoc [Internet]. 2023;46(January):64–64. Available from: <https://diabetesjournals.org/care>
8. Heerspink HJL, Sattar N, Pavo I, Haupt A, Duffin KL, Yang Z, et al. Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. Lancet Diabetes Endocrinol [Internet]. 2022 Nov;10(11):774–85. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S2213858722002431>
9. Lilly Trials. The Effect of Retatrutide Once Weekly on Cardiovascular Outcomes and Kidney Outcomes in Adults (TRIUMPH-Outcomes). Clin GOV TRIALS [Internet]. Available from: <https://trials.lilly.com/en-US/trial/479798>
10. Heerspink HJL, Greasley PJ, Ahlström C, Althage M, Dwyer JP, Law G, et al. Efficacy and safety of zibotentan and dapagliflozin in patients with chronic kidney disease: study design and baseline characteristics of the ZENITH-CKD trial. Nephrol Dial Transplant. 2024;39(3):414–25.
11. Heerspink HJL, Cherney D, Gafor AHA, Górriz JL, Pergola PE, Tang SCW, et al. Effect of Avenciguat on Albuminuria in Patients with CKD. J Am Soc Nephrol [Internet]. 2024 Sep;35(9):1227–39. Available from: <https://journals.lww.com/10.1681/ASN.0000000000000418>
12. Tuttle KR, Hauske SJ, Canziani ME, Caramori ML, Cherney D, Cronin L, et al. Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial. Lancet [Internet]. 2024 Jan;403(10424):379–90. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S014067362302408X>