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Optimization of Antidiabetic Pharmacological Treatment in Patients with Chronic Kidney Disease

Type 2 diabetes mellitus (T2DM) is the leading cause of chronic kidney disease (CKD) worldwide. In Spain, the prevalence of CKD among individuals with T2DM managed in Primary Care exceeds 27%, according to the PERCEDIME2 study (1). The presence of CKD not only increases the risk of progression to end-stage renal disease (ESRD), but also multiplies cardiovascular risk and complicates the therapeutic management of patients with diabetes (2).

CKD is defined as a structural or functional kidney abnormality lasting more than 3 months, evidenced by a reduction in estimated glomerular filtration rate (eGFR <60 mL/min/1.73 m²) and/or markers of kidney damage such as albuminuria (>30 mg/g), histologic abnormalities, or radiologic imaging alterations.

In summary, CKD means that the kidneys are damaged or do not function properly, and this condition persists over time.

In individuals with T2DM, renal involvement may precede or accompany the diagnosis, and its causes are multifactorial: sustained hyperglycemia, hypertension, chronic inflammation, endothelial dysfunction, and genetic susceptibility (3).

Optimizing antidiabetic treatment becomes a key strategy to improve clinical outcomes, prevent complications, and rationalize health care resources.

Optimization does not mean adding more drugs, but rather prioritizing those with proven cardiorenal benefit, adjusting therapy according to renal function and the patient's overall profile.

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Color / Category	Drug Class / Drug	Initiate (eGFR)	Continue Until	Clinical Notes and Dose Adjustment	Key Message
◯ • High safety and cardiorenal benefit	**Metformin**	≥45	30	Reduce dose (≤1,000 mg/day) if 30–44. Discontinue if <30 or in the setting of contrast exposure/dehydration.	First-line therapy if eGFR ≥30.
	SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin)	Empa ≥20; Dapa ≥25; Cana ≥30	Continue until dialysis if already established	Glycemic effect decreases at low eGFR, but renal and cardiac protection persists. Hold during surgery or acute illness.	Protects kidney and heart even at low eGFR.
	GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide)	No adjustment	<15: limited data	Avoid exenatide if <30 and lixisenatide if <15. Strong cardiovascular evidence. Monitor GI side effects.	Alternative or add-on therapy with cardiovascular/renal benefit.
◯ • Moderate safety / conditional use	**Tirzepatide**	No adjustment	<15 or dialysis: limited data	High glycemic and weight-loss efficacy. Possible renal benefit. Monitor GI tolerance and dehydration.	Effective; use cautiously in advanced CKD.
	DPP-4 inhibitors (linagliptin, sitagliptin, saxagliptin, alogliptin)	—	—	Linagliptin: no adjustment. Sitagliptin 50 mg (30–44) or 25 mg (<30). Saxagliptin 2.5 mg (≤50). Alogliptin 12.5 mg (30–59); 6.25 mg (<30).	Alternative if intolerance or contraindication to others.
	TZD (pioglitazone)	—	—	No renal adjustment. Monitor for fluid retention, edema, or heart failure (HF).	Useful if no HF or edema.
◯ • High risk / restricted use	**Sulfonylureas (glyburide, glipizide, gliclazide)**	—	—	Avoid glyburide. Prefer glipizide or gliclazide (dose adjustment required). High hypoglycemia risk.	Avoid or use with extreme caution.
	Glinides (repaglinide, nateglinide)	—	—	Use repaglinide cautiously; avoid nateglinide in advanced CKD.	Risk of hypoglycemia.
	Insulin	—	—	Reduce dose by 25–50% according to eGFR. Prefer basal analogs.	Adjust carefully to avoid hypoglycemia.

TABLE 1. Therapeutic traffic light for glucose-lowering drugs according to estimated glomerular filtration rate (eGFR)

SUMMARY:

● = Safe and protective → SGLT2 inhibitors, GLP-1 receptor agonists, metformin (if eGFR ≥30).

● = Use with clinical monitoring → tirzepatide, DPP-4 inhibitors, pioglitazone.

● = Caution / risk of hypoglycemia or fluid retention → sulfonylureas, glinides, high-dose insulin.

» The therapeutic approach must be holistic, considering frailty, comorbidities, polypharmacy, and patient preferences. Collaboration among Primary Care, Endocrinology, and Nephrology is essential to avoid therapeutic inertia and facilitate multidisciplinary follow-up.

The 2025 *American Diabetes Association* (ADA) *Standards of Care and the 2024 joint ADA–Kidney Disease:* Improving Global Outcomes (KDIGO) guideline recommend treatments focused on reducing renal progression, providing cardiovascular benefit, and ensuring safety (4, 5). In this context, drugs with cardiorenal protective effects take center stage, as explained in ***Table 1*** using a practical "traffic light" format for glucose-lowering agents (4, 5).

The key is to prioritize agents with proven cardiorenal benefit (SGLT2 inhibitors, GLP-1 receptor agonists) rather than focusing solely on HbA1c or glucose reduction.

NON-PHARMACOLOGICAL RECOMMENDATIONS

Finally, in patients with diabetes and CKD, individualized glycemic control and strict blood pressure management should be prioritized, along with a cardiorenal diet (low in salt and moderate in protein), adequate hydration, regular exercise, smoking cessation, and periodic monitoring of eGFR and albuminuria ***(Table 2)***. D

CHRONIC KIDNEY DISEASE MEANS THAT THE KIDNEYS ARE DAMAGED OR DO NOT FUNCTION PROPERLY, AND THIS PROBLEM PERSISTS OVER TIME

OBJECTIVE / AREA	PRACTICAL RECOMMENDATION	SUGGESTED TARGET OR FREQUENCY
GLYCEMIC CONTROL	Adjust treatment and lifestyle to maintain stable blood glucose. Avoid hypoglycemia.	HbA1c <7% (individualize according to age and comorbidities).
BLOOD PRESSURE	Monitor blood pressure at home and during clinic visits.	<130/80 mmHg.
RENAL-PROTECTIVE DIET	Reduce salt intake, moderate protein consumption, limit ultra-processed foods. Follow a Mediterranean dietary pattern.	Salt <5 g/day; protein ≈0.8 g/kg/day.
HYDRATION	Water as the main beverage. Avoid soft drinks, processed juices, and energy drinks.	1.5–2 L/day depending on renal function.
AVOID NEPHROTOXIC AGENTS	Avoid chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs); use caution with contrast agents and non-prescribed supplements.	Strict medical supervision.
WEIGHT AND EXERCISE	Maintain a healthy weight and engage in regular physical activity.	BMI 20–25; exercise ≥150 minutes/week.
SMOKING	Complete smoking cessation.	Prevention of vascular and renal damage.
MONITORING	Check serum creatinine, eGFR, and urine albumin-to-creatinine ratio.	1–2 times per year.

TABLE 2. Key Non-Pharmacological Renal Protection Measures in Diabetes Mellitus. Own elaboration

CONCLUSIONS

Optimization of antidiabetic treatment in patients with CKD is both a clinical and strategic priority. It implies a paradigm shift: from isolated glycemic control to a comprehensive approach centered on renal and cardiovascular protection, with particular attention to safety. Clinical practice guidelines facilitate decision-making in daily practice, and coordination between levels of care—together with patient empowerment—is essential.

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