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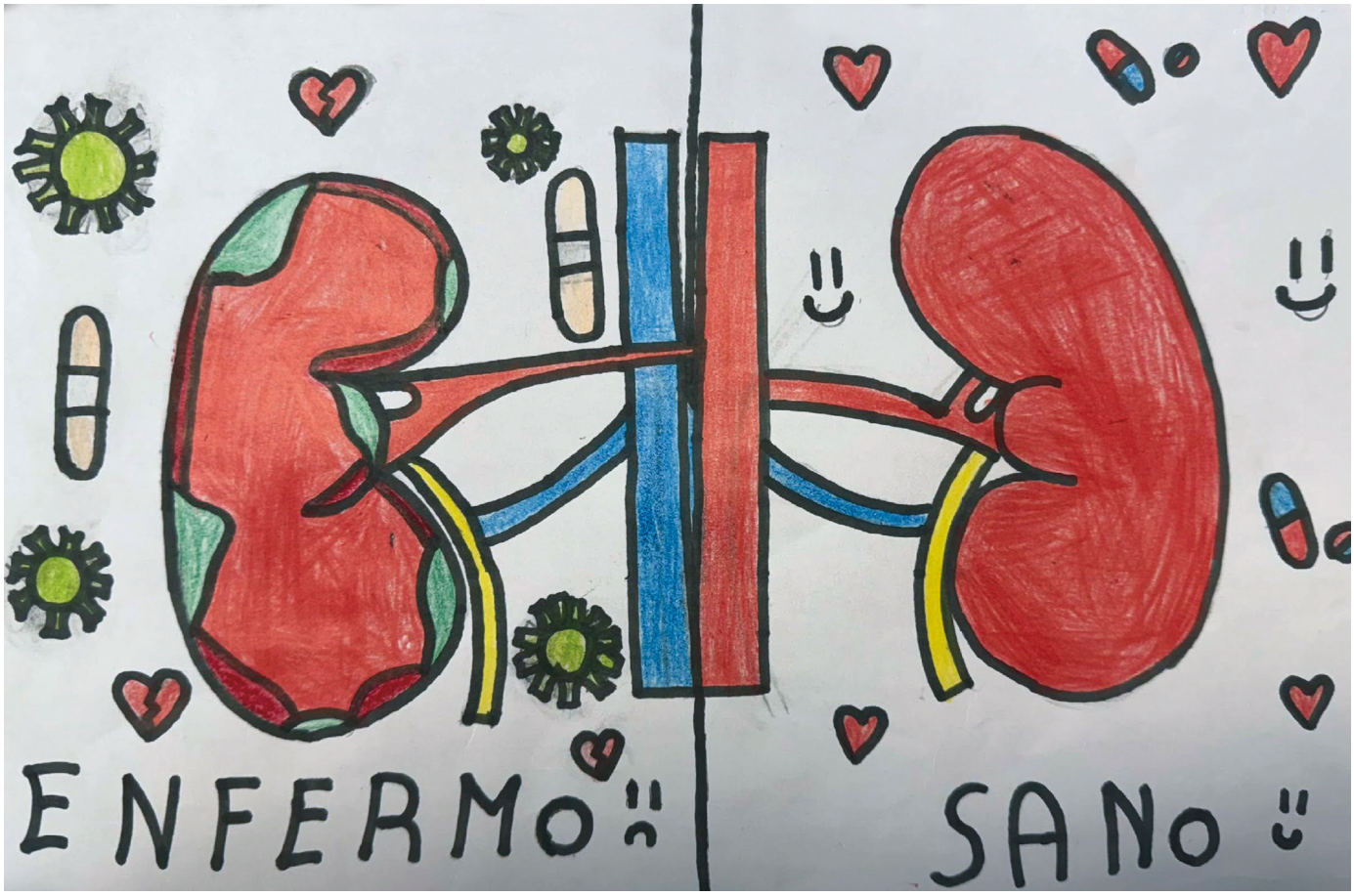

Renal disease in pediatric patients with diabetes:

early detection and comprehensive management

Diabetes mellitus is one of the most prevalent chronic diseases in childhood and adolescence. In Spain, the incidence of type 1 diabetes (T1DM) in children under 14 years is approximately 18–20 cases per 100,000 inhabitants/year, with an increasing trend. Although T1DM remains the predominant form in pediatrics, the rise in childhood obesity has led to a significant increase in type 2 diabetes (T2DM), which already accounts for 6% of new diagnoses (1).

1. PEDIATRIC DIABETES AND RENAL DISEASE: A SILENT COMPLICATION

Renal involvement, or diabetic kidney disease, is a major complication of diabetes, constituting a predisposing factor for adverse cardiovascular outcomes and significantly increasing morbidity and mortality (1, 8, 9, 10). Although advanced kidney disease usually manifests in adulthood, early signs of renal damage may appear in pediatric patients, generally **asymptomatic**, making early detection essential (1).

2. TYPES OF DIABETES IN PEDIATRIC PATIENTS

T1DM accounts for approximately 85% of pediatric cases. It is characterized by autoimmune destruction of pancreatic β cells, absolute insulin deficiency, and chronic hyperglycemia. The most frequent age at diagnosis is between 10 and 14 years, and up to 44% of children present with **diabetic ketoacidosis** (DKA) at onset (4, 5, 6, 8, 9).

T2DM is less frequent but increasing due to its association with obesity and insulin resistance, both increasingly prevalent. It typically presents with an insidious onset but rapid pancreatic β-cell dysfunction (4, 8, 9).

Monogenic diabetes represents 1%–5% of pediatric cases and is caused by mutations in a single gene. Its main subtypes include neonatal diabetes, maturity-onset diabetes of the young (MODY), and syndromic forms with extrapancreatic signs (4).

Other less frequent forms include diabetes secondary to pancreatic diseases (cystic fibrosis, pancreatitis) or drug-induced diabetes (corticosteroids, immunosuppressants).

3. PATHOPHYSIOLOGY OF RENAL DAMAGE IN PEDIATRIC PATIENTS WITH DIABETES

Chronic hyperglycemia induces a persistent inflammatory state that alters the structure and function of blood vessels, promoting micro- (nephropathy, retinopathy, neuropathy) and macrovascular complications (cardiovascular disease) (9).

Each kidney is composed of thousands of nephrons, functional units responsible for filtering blood and producing urine. Each nephron consists of the glomerulus and renal tubule. In diabetic kidney disease, chronic hyperglycemia progressively affects all nephron components through four main mechanisms: glomerular vascular damage, tubular damage, inflammation, and oxidative stress[9]. This process may begin silently years before clinical sign (1, 8, 9).

In addition to chronic kidney damage, children with diabetes may experience acute kidney injury during episodes of DKA, which represents the initial presentation in one-third of patients with T1DM (6). Acute kidney injury is defined by increased serum creatinine or decreased urine output (5). In DKA, dehydration and volume depletion lead to reduced renal perfusion, causing prerenal failure that may progres to established kidney injury if untreated (6). Acute kidney injury increases the risk of chronic kidney disease and its progression, especially with recurrent or severe episodes (8, 3, 5).

4. EARLY DETECTION: MARKERS OF RENAL DAMAGE AND SCREENING STRATEGIES IN PEDIATRICS

Early detection of renal damage in children and adolescents with diabetes is essential to prevent progression to renal failure. The following **markers are used:**

- **Estimated glomerular filtration rate (eGFR):** an indirect measure of kidney function calculated from serum creatinine using pediatric-specific equations. Early stages of diabetic kidney disease are characterized by hyperfiltration, with decline occurring in later stages (8, 9, 5).
- **Albuminuria:** classically considered the earliest marker, as it usually precedes the decline in glomerular filtration rate, although not always (8). Albumin is a blood protein that normally crosses the glomerular barrier only in small amounts; therefore, its presence in higher quantties constitutes a marker of glomerular renal damage. It is defined as microalbuminuria when excretion is between 30–300 mg day and macroalbuminuria when it exceeds 300 mg/day, the latter indicating more advanced glomerular damage (5-10).
- **Other emerging markers:** the search for new, more reliable markers capable »

RENAL INVOLVEMENT, OR DIABETIC KIDNEY DISEASE, IS A MAJOR COMPLICATION OF DIABETES, CONSTITUTING A PREDISPOSING FACTOR FOR ADVERSE CARDIOVASCULAR OUTCOMES AND SIGNIFICANTLY INCREASING MORBIDITY AND MORTALITY

of detecting renal involvement at an earlier stage is crucial. Some under investigation include tumor necrosis factor receptors (TNFR), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and liver-type fatty acid–binding protein (LFABP). However, results are inconsistent, and none are currently used in pediatric or adult clinical practice (8, 9).

Screening strategies for diabetic kidney disease in pediatrics are as follows (4, 8, 10):

- **T1DM:** screening for albuminuria using the urine albumin-to-creatinine ratio after 5 years of disease duration or from 10 years of age, whichever occurs first, and eGFR from the time of diagnosis.
- **T2DM:** initiate screening for albuminuria and eGFR at diagnosis.

Screening should be repeated annually if results are normal and every 3–6 months if persistent microalbuminuria or additional risk factors are present, such as hypertension, obesity, or poor glycemic control (4).

5. PROGRESSION OF DIABETIC KIDNEY DISEASE IN PEDIATRICS AND CHARACTERISTICS OF RENAL DISEASE ACCORDING TO THE TYPE OF DIABETES

Five evolutionary stages have been described ***(Table 1)*** (5, 10).

STAGE	ESTIMATED PERIOD	MAIN CHARACTERISTICS	ESTIMATED GLOMERULAR FILTRATION RATE (EGFR)	BLOOD PRESSURE	ALBUMINURIA
1: Hyperfiltration phase	0–5 years after onset	Hyperfiltration and glomerular hypertrophy. 20% increase in kidney size. No structural abnormalities	Normal or increased	Normal	Normoalbuminuria (<30 mg/g)
2: Silent phase	—	Mild thickening of the glomerular basement membrane and interstitial expansion	Normal	Normal	Normoalbuminuria (<30 mg/g)
3: Incipient phase	5–10 years after onset	More significant structural changes; variable focal mesangial sclerosis	Normal or slightly decreased	Possible hypertension	Microalbuminuria (30–300 mg/g)
4: Established kidney disease	10–15 years after onset	Marked thickening of the glomerular basement membrane and pronounced focal mesangial sclerosis	Decreased (<60 mL/min/1.73 m^2)	Increased	Macroalbuminuria (>300 mg/g)
5: End-stage kidney disease	Final stage	Diffuse glomerulosclerosis and end-stage kidney disease	Severely decreased (<15 mL/min/1.73 m^2)	Increased	Decreasing albuminuria (loss of renal function)

TABLE 1. Evolutionary stages of diabetic kidney disease.

CHARACTERISTICS	T1DM	T2DM	MONOGENIC DIABETES
Onset of CKD	Microalbuminuria after years of disease duration.	May be present at diagnosis.	Depends on subtype.
Progression	Slow, with persistent albuminuria preceding eGFR decline.	Rapid and aggressive.	Variable depending on subtype.
Associated risk factors	- Poor glycemic control. - Long disease duration. - Acute kidney injury at onse with diabetic ketoacidosis.	- Obesity. - Hypertension.	Structural renal abnormalities in MODY 5.
Risk of end-stage renal disease	High in the long term	Higher and earlier	High in MODY 5

TABLE 2. Types of diabetes and characteristics of renal involvement
abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; DKA, diabetic ketoacidosis; MODY, maturity-onset diabetes of the young.

THE TRANSITION FROM PEDIATRIC TO ADULT CARE IN ADOLESCENTS WITH DIABETES REPRESENTS A CRITICAL PERIOD ASSOCIATED WITH AN INCREASED RISK OF DETERIORATION IN GLYCEMIC CONTROL AND THE DEVELOPMENT OF COMPLICATIONS

6. TREATMENT AND PREVENTION STRATEGIES

Early identification of renal damage using the markers described allows the initiation of a comprehensive management strategy that combines nonpharmacological and pharmacological measures to prevent renal damage, slow its progression, and reduce cardiovascular risk (5, 7, 8, 9, 10).

- **Optimal glycemic control**
  Intensive glycemic control is the cornerstone of prevention of diabetic kidney disease. ADA 2026 guidelines recommend a glycated hemoglobin (HbA1c) target of <7.5% for most children and adolescents, individualized according to hypoglycemia risk, comorbidities, and clinical circumstances (4, 8). If the risk of hypoglycemia is low, a stricter target such as HbA1c <6.5% may be considered. The use of continuous glucose monitoring systems and closed-loop systems facilitates achieving these targets.

- **Blood pressure control**
  Hypertension is a well-known factor associated with diabetic kidney disease and accelerates its progression. If blood pressure values are above the 90th percentile for sex and age (≥p90), lifestyle changes should be initiated. If values reach those established for hypertension (≥p95 or ≥130/80 mmHg in individuals ≥13 years), pharmacological treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be started.

- **Renin-angiotensin system blockade**
  Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are the drugs of choice for renal protection in patients with persistent albuminuria, particularly when albuminuria is >300 mg/24 hours, when estimated glomerular filtration rate is <60 mL/min/m², or when hypertension is present.

- **Lifestyle changes**
  It is crucial for patients with diabetes to maintain an adequate body weight, engage in regular physical activity, follow a healthy diet, and avoid harmful habits such as smoking.

- **New drugs**
  Sodium-glucose cotransporter 2 inhibitors have demonstrated in adults a reduction in the progression of chronic kidney disease, the risk of end-stage renal disease, and cardiovascular mortality[4]. In pediatrics, they are approved by the US Food and Drug Administration for T2DM in patients ≥10 years, with efficacy in glycemic control and safety similar to adults. Ongoing clinical trials will evaluate their renal efficacy in children, although current evidence is limited.

  Glucagon-like peptide-1 receptor agonists reduce albuminuria and slow renal deterioration in adults. In pediatrics, they are approved for T2DM and obesity in patients ≥10–12 years, but not specifically for chronic kidney disease, and data on direct renal benefits are scarce (4).

KDIGO 2024 guidelines emphasize the urgent need for pediatric-specific studies, as diabetic kidney disease in children differs from that in adults, limiting extrapolation of data (7).

IMPORTANCE OF TRANSITION IN PEDIATRICS

The transition from pediatric to adult care in adolescents with diabetes represents a critical period associated with an increased risk of deterioration in glycemic control and the development of complications. This process requires early preparation, development of self-care skills, gradual transfer of responsibilities, and coordination between pediatric and adult care teams to ensure continuity and quality of care (4, 8, 10). D

CONCLUSIONS

- Renal damage in pediatric patients with diabetes is often initially silent, making early detection essential, primarily through screening for albuminuria and estimated glomerular filtration rate.

- Strict glycemic and blood pressure control, together with lifestyle interventions, constitute the main strategy to prevent progression to chronic kidney disease.

- Although pharmacological and technological advances offer promising perspectives, prevention and comprehensive management remain the fundamental pillars of renal protection in children and adolescents with diabetes.

- Appropriate transition of care in adolescent patients is crucial to avoid loss to follow-up and the development of complications.

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