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Diabetes & its Complications

Twenty Years of Diabetic Kidney Disease: Divergent Trends in Type 1 and Type 2 Diabetes and the Impact of Modern Renoprotective Therapies (2004–2024)

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ABSTRACT

Over the past two decades, diabetic kidney disease (DKD) has remained the leading cause of end-stage kidney disease (ESKD) worldwide [1]. In type 1 diabetes (T1D), the incidence of ESKD has progressively declined due to improved glycemic control, early screening, and renin–angiotensin system blockade [2]. In contrast, the global burden of ESKD in type 2 diabetes (T2D) has increased, driven by population aging, obesity, metabolic syndrome, and delayed diagnosis [3]. The therapeutic landscape has been reshaped by SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone, which have demonstrated significant renal protection [4-6]. This review summarizes epidemiological trends, pathophysiology, risk factors, and therapeutic advances in DKD from 2004 to 2024.

Keywords

Diabetic kidney disease, End-stage kidney disease, Type 1 diabetes, Type 2 diabetes, SGLT2 inhibitors, GLP-1 receptor agonists, Finerenone, Epidemiology, Renal outcomes.

Introduction

Diabetic kidney disease (DKD) accounts for approximately 40% of all cases of ESKD globally [1]. Over the last 20 years, the epidemiology of DKD has evolved differently in T1D and T2D. In T1D, improved glycemic control, early detection of microalbuminuria, and widespread use of ACE inhibitors and ARBs have contributed to a significant reduction in advanced DKD [2,5]. In contrast, the burden of T2D-related ESKD has increased worldwide, particularly in regions undergoing rapid demographic and lifestyle transitions [7,8]. The last decade has also witnessed the emergence of disease-modifying therapies—SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone—that have significantly altered renal prognosis [4-6].

Epidemiology of DKD in Type 1 Diabetes (2004–2024)

Long-term cohort studies such as FinnDiane and DCCT/EDIC have demonstrated a progressive decline in the incidence of ESKD among individuals with T1D [7]. Reductions of 40–60% in progression to ESKD have been reported compared with the 1990s [7,8]. Improved glycemic control and early initiation of RAS blockade are key contributors [8]. The prevalence of albuminuria has also decreased, reflecting better metabolic and blood pressure control [9]. These trends are consistent across Europe, North America, and Japan, although absolute numbers remain low compared with T2D.

Epidemiology of DKD in Type 2 Diabetes (2004–2024)

Registry data from the USRDS and ERA-EDTA indicate that T2D now accounts for more than half of all new ESKD cases in many countries [10,11]. The rise is particularly pronounced in Asia and the Middle East, where rapid urbanization, aging populations, and increasing rates of obesity and metabolic syndrome have contributed to a growing prevalence of T2D [3]. Late diagnosis of diabetes and suboptimal control of blood pressure and glycemia further accelerate progression to ESKD.

Pathophysiology

DKD progression involves a complex interplay of hemodynamic, metabolic, and inflammatory mechanisms. Glomerular hyperfiltration, podocyte injury, and tubulointerstitial inflammation are central features. Activation of the renin–angiotensin–aldosterone

system, oxidative stress, and accumulation of advanced glycation end-products contribute to structural and functional deterioration [12]. Recent research has highlighted the role of tubular hypoxia, metabolic reprogramming, and inflammatory pathways such as JAK/STAT and the NLRP3 inflammasome [13].

Risk Factors for Progression

Major determinants of DKD progression include poor glycemic control (HbA1c >8%) [14], hypertension, albuminuria, dyslipidemia, smoking, and genetic susceptibility. APOL1 variants in individuals of African ancestry significantly increase the risk of progression to ESKD [15]. Albuminuria remains the strongest predictor of renal decline, although its prevalence has decreased in T1D due to improved metabolic control [9].

Therapeutic Evolution (2004–2024)

Renin–Angiotensin System Blockade

ACE inhibitors and ARBs remain foundational therapies, reducing albuminuria and slowing GFR decline [16]. Their widespread adoption has contributed significantly to improved outcomes in T1D.

SGLT2 Inhibitors

SGLT2 inhibitors have transformed the management of DKD. Major trials—including EMPA-REG OUTCOME, CANVAS, CREDENCE, and DAPA-CKD—have demonstrated 30–40% reductions in progression to ESKD, along with reductions in albuminuria and cardiovascular events [8]. Their renal benefits are attributed to hemodynamic effects, reduced intraglomerular pressure, and anti-inflammatory mechanisms.

GLP-1 Receptor Agonists

GLP-1 receptor agonists provide cardiovascular and renal benefits, particularly in T2D with albuminuria [5]. They reduce albuminuria and slow GFR decline, with additional metabolic advantages including weight loss and improved glycemic control.

Finerenone

Finerenone, a non-steroidal mineralocorticoid receptor antagonist, has emerged as an important therapy for DKD. The FIDELIO-DKD and FIGARO-DKD trials demonstrated significant reductions in DKD progression and cardiovascular events, with a lower risk of hyperkalemia compared with traditional MRAs [6].

Therapeutic Scenarios and Long-Term Renal Outcomes (2004–2024)

A comparison of two representative therapeutic scenarios illustrates how profoundly renal prognosis in diabetic kidney disease (DKD) has changed over the last decade.

Scenario 1 — Modern Optimized Therapy (SGLT2 inhibitor + ACEi/ARB ± Finerenone)

The introduction of SGLT2 inhibitors, combined with renin–angiotensin system blockade and, when indicated, finerenone, has reshaped the natural history of DKD. Integrated data from CREDENCE, DAPA-CKD, and FIDELIO-DKD consistently show a substantial reduction in progression to end-stage kidney disease (ESKD).

Five-year renal outcomes in modern therapy cohorts:
Progression to ESKD (dialysis or transplantation): 8–12%
Initiation of chronic dialysis: 6–9%
Kidney transplantation: 2–3%
These figures represent a 30–40% relative risk reduction compared with historical cohorts treated without SGLT2 inhibitors [4-6].

The slower decline in eGFR (approximately 2–3 mL/min/year) reflects the combined hemodynamic, metabolic, and anti-inflammatory effects of these agents.

Clinical interpretation

This therapeutic strategy has become the new standard of care, capable of delaying ESKD by several years and reducing the need for renal replacement therapy in a large proportion of patients.

Scenario 2 — Traditional Therapy (ACEi/ARB Alone, Without SGLT2i or GLP-1RA)

Before the introduction of SGLT2 inhibitors and finerenone, ACE inhibitors and ARBs represented the cornerstone of DKD management. Although beneficial, their protective effect was limited, and many patients progressed to ESKD despite optimal dosing.

Five-year renal outcomes in traditional therapy cohorts:
Progression to ESKD (dialysis or transplantation): 22–28%
Initiation of chronic dialysis: 18–24%

Kidney transplantation: 3–4%

These data, derived from USRDS and ERA-EDTA registries, reflect the natural history of DKD in the pre-SGLT2i era [10,11].

The average rate of eGFR decline in these cohorts was 4–6 mL/min/year, approximately double that observed with modern therapy.

Clinical interpretation

This scenario highlights the high renal risk associated with DKD when only traditional therapy is used, underscoring the transformative impact of newer agents.

Prognosis

Prognosis has improved in T1D, with declining rates of ESKD and improved survival [7]. In T2D, however, prognosis remains poor, with high cardiovascular mortality and increasing ESKD incidence [10,11]. Combination therapy with SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone is expected to further reduce the burden of ESKD.

Conclusions

Over the past 20 years, DKD has undergone major epidemiological

and therapeutic changes. While T1D-related ESKD has declined [7], T2D-related ESKD continues to rise [10,11]. The advent of SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone represents the most significant therapeutic advance in decades [4-6]. Early diagnosis and aggressive risk-factor control remain essential to improving outcomes.

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