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"Glomerular Disease in Focus: Distinguishing and Overlapping Mechanisms of Nephrotic Syndrome and Diabetic Nephropathy"

Manne Dinesh Kumar [1], SHOBANARAJ.M [2], ABHISHEK. V.P [3]

[1] *MSc 1 st year student Renal sciences and Dialysis Technology, Saveetha college of allied health sciences, Thandalam, Tamil Nadu, India*

[2] *Master of Renal Sciences and Dialysis Technology, Saveetha college of allied health sciences, Thandalam, Tamil Nadu, India*

Abstract

Nephrotic syndrome and diabetic nephropathy represent two of the most prevalent and clinically significant causes of chronic kidney disease worldwide. Nephrotic syndrome, defined by massive proteinuria (>3.5 g/day), hypalbuminaemia, oedema, and hyperlipidaemia, encompasses a spectrum of primary and secondary glomerulopathies. Diabetic nephropathy, the leading cause of end-stage renal disease globally, arises from complex interplay of haemodynamic, metabolic, and inflammatory mechanisms in the setting of diabetes mellitus.

This review provides a detailed examination of the pathophysiology, clinical presentation, diagnostic approach, and current evidence-based management strategies for both conditions. We discuss the key histopathological features distinguishing the two entities, their shared risk factors, and emerging therapeutic targets including SGLT2 inhibitors, endothelin receptor antagonists, and mineralocorticoid receptor antagonists. Understanding these conditions is critical for nephrologists, endocrinologists, internists, and primary care physicians to improve patient outcomes and slow progression to end-stage renal disease.

Keywords: *nephrotic syndrome; diabetic nephropathy; glomerulosclerosis; proteinuria; SGLT2 inhibitors*

1 Introduction

Kidney disease affects approximately 850 million people worldwide, representing a global public health crisis of enormous proportions. Among the many aetiologies of renal dysfunction, nephrotic syndrome and diabetic nephropathy stand out as particularly prevalent, morbid, and economically burdensome conditions. Together they account for the majority of cases progressing to end-stage renal disease (ESRD) requiring dialysis or transplantation.

Nephrotic syndrome is not a single disease but rather a clinical syndrome characterised by massive urinary protein loss exceeding 3.5 grams per day per 1.73 m^2 of body surface area. This proteinuria drives secondary abnormalities including hypoalbuminaemia, peripheral oedema, hyperlipidaemia, and lipiduria. The syndrome can arise from primary glomerular diseases such as minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN), or secondarily from systemic diseases, infections, or medications.

Diabetic nephropathy (DN), increasingly termed diabetic kidney disease (DKD) to reflect its broader pathological spectrum, is the single most common cause of ESRD in developed nations. It affects approximately 20–40% of individuals with either type 1 or type 2 diabetes mellitus and is characterised by progressive albuminuria, declining glomerular filtration rate (GFR), and cardiovascular co-morbidity. The pathological hallmark is Kimmelstiel–Wilson nodular glomerulosclerosis, alongside diffuse mesangial expansion, glomerular basement membrane thickening, and afferent/efferent arteriolar hyalinosis.

Despite their distinct aetiologies, both conditions share common pathophysiological mechanisms including podocyte injury, disruption of the glomerular filtration barrier, intraglomerular hypertension, oxidative stress, and activation of fibrogenic pathways. This review integrates current understanding of both diseases and highlights evidence-based therapeutic advances, including the transformative role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in reducing renal and cardiovascular endpoints across a broad population of CKD patients.

NEPHROTIC SYNDROME

1.1 Pathophysiology of Nephrotic Syndrome

1.1.1 The Glomerular Filtration Barrier

The glomerular filtration barrier (GFB) is a sophisticated three-layer structure consisting of the fenestrated glomerular endothelium, the glomerular basement membrane (GBM), and the podocyte foot processes connected by the slit diaphragm. Each layer contributes both size-selectivity and charge-selectivity that restrict passage of albumin and larger molecules into the filtrate.

The slit diaphragm, composed of nephrin, podocin, CD2-associated protein (CD2AP), and other structural proteins, represents the final and most critical filtration checkpoint. Disruption of any component of the GFB—through immune-mediated mechanisms, genetic mutations, toxic insults, or haemodynamic stress—results in increased permeability to albumin and other plasma proteins.

1.1.2 Podocyte Biology and Injury

Podocytes are terminally differentiated, post-mitotic epithelial cells with limited regenerative capacity. Their foot processes are anchored to the GBM via αvβ3 and α1β1 integrins, while their apical surface is protected by an anti-adhesion coat of podocalyxin. Podocyte injury—characterised by foot process effacement, loss of slit diaphragm integrity, and eventual detachment—is the unifying pathological event in most proteinuric kidney diseases.

In minimal change disease, a circulating permeability factor (possibly a cytokine such as IL-13 or hemopexin) induces reversible foot process effacement without structural glomerular damage, explaining the dramatic response to corticosteroids. In FSGS, podocyte loss is more severe and may involve genetic defects in structural proteins (NPHS1, NPHS2, TRPC6, ACTN4, INF2), circulating soluble urokinase plasminogen activator receptor (suPAR), or secondary haemodynamic injury from hyperfiltration.

1.1.3 Downstream Consequences of Massive Proteinuria

The nephrotic state is associated with profound systemic consequences. Urinary protein loss exceeding hepatic synthesis capacity leads to hypoalbuminaemia, which reduces plasma oncotic pressure and drives fluid into the interstitium, producing the characteristic oedema. Additionally, reduced oncotic pressure stimulates hepatic lipoprotein synthesis, while catabolism of VLDL is impaired due to urinary loss of lipoprotein lipase cofactors, resulting in hypercholesterolaemia and hypertriglyceridaemia.

The hypercoagulable state in nephrotic syndrome arises from urinary loss of natural anticoagulants (antithrombin III, protein S, protein C), elevated fibrinogen from compensatory hepatic synthesis, platelet hyperaggregability, and increased blood viscosity. This predisposes to both venous and arterial thromboembolism, including the characteristic renal vein thrombosis seen particularly in membranous nephropathy.

1.2 Major Causes of Nephrotic Syndrome

Table 1 summarises the primary and secondary causes of nephrotic syndrome by frequency and clinical context:

Category	Disease Entity	Typical Age Group	Key Distinguishing Feature
Primary	Minimal Change	Children; adults	Normal LM; foot process

Category	Disease Entity	Typical Age Group	Key Distinguishing Feature
(Idiopathic)	Disease (MCD)	possible	effacement on EM; steroid-responsive
Primary	Focal Segmental Glomerulosclerosis (FSGS)	Young adults; Black race ↑ risk	Segmental sclerosis; NPHS1/NPHS2/TRPC6 mutations in genetic forms
Primary	Membranous Nephropathy (MN)	Middle-aged adults	PLA2R antibody positive (~70%); subepithelial immune deposits
Primary	Membranoproliferative GN (MPGN)	Young adults	Tram-track GBM; C3 deposition
Secondary	Diabetic Nephropathy	Adults with DM	Kimmelstiel-Wilson nodules; glomerulomegaly
Secondary	Lupus Nephritis (class V)	Young women	Anti-dsDNA; full-house immunofluorescence
Secondary	Amyloidosis (AA/AL)	Older adults	Congo red positivity; apple-green birefringence
Secondary	Hepatitis B/C associated	Varies	Cryoglobulinaemia; MN pattern with HBV
Genetic	Congenital NS (Finnish type)	Neonates	NPHS1 mutation; massive proteinuria at birth
Drug-induced	NSAIDs, gold, penicillamine	Adults on offending drugs	Resolution on drug withdrawal

1.3 Clinical Presentation and Diagnosis

1.3.1 History and Physical Examination

The classic presentation of nephrotic syndrome includes periorbital oedema (often more pronounced in the morning), dependent pitting oedema, ascites, and occasionally pleural effusions or anasarca in

severe cases. Patients frequently report frothy urine due to proteinuria. Systemic symptoms such as fatigue and dyspnoea may accompany severe hypoalbuminaemia.

Physical examination may reveal anasarca, xanthelasma (from hyperlipidaemia), white nails (leukonychia), and signs of specific underlying diseases such as malar rash in lupus or peripheral neuropathy in amyloidosis. Blood pressure may be normal or elevated; in MCD it is often normal.

1.3.2 Laboratory Investigations

The following investigations are essential in evaluating a patient with suspected nephrotic syndrome:

- Urinalysis with microscopy: proteinuria (≥ 3+ on dipstick), lipiduria (oval fat bodies, fatty casts), occasional haematuria
- Spot urine albumin-to-creatinine ratio (UACR) or 24-hour urine protein: >3.5 g/day or >2200 mg/g UACR
- Serum albumin: typically, <3.0 g/dL
- Serum lipid panel: elevated total cholesterol, LDL, triglycerides
- Serum creatinine and eGFR: may be normal or reduced depending on severity
- Complement levels (C3, C4): low in lupus nephritis, MPGN; normal in MN, MCD, FSGS
- Immunological: ANA, anti-dsDNA, ANCA, serum protein electrophoresis, free light chains
- Serological: hepatitis B and C, HIV, anti-PLA2R antibodies (membranous nephropathy)
- Coagulation studies: PT/APTT, antithrombin III levels in hypercoagulable state assessment

1.3.3 Renal Biopsy

Kidney biopsy with light microscopy, immunofluorescence, and electron microscopy remains the gold standard for establishing a definitive diagnosis in adult nephrotic syndrome. In children, empirical corticosteroid treatment for presumed MCD is appropriate as the first step given its high prevalence and steroid-responsiveness in that age group. Biopsy is reserved for children with atypical features, steroid resistance, or frequent relapses.

Histopathological findings guide prognosis and therapy. The Oxford classification (MEST-C) is used for IgA nephropathy, while the Columbia classification stratifies FSGS lesions into tip, cellular, perihilar, collapsing (most severe), and not-otherwise-specified variants.

1.4 Management of Nephrotic Syndrome

1.4.1 General Measures

General measures applicable to all nephrotic patients include sodium restriction (<2 g/day) and judicious fluid management to address oedema. Loop diuretics (furosemide) are the mainstay of oedema management; combination with thiazide-type diuretics may be required in resistant cases. Intravenous albumin infusion followed by diuretics may benefit patients with severe hypoalbuminaemia and refractory oedema, though its routine use is debated.

Renin-angiotensin-aldosterone system (RAAS) blockade with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) reduces proteinuria and slows CKD progression and should be used unless contraindicated. Statins are recommended for hyperlipidaemia given the heightened cardiovascular risk. Anticoagulation with warfarin or low molecular weight heparin is indicated when serum albumin falls below 2.0–2.5 g/dL or when membranous nephropathy is the underlying diagnosis due to high thrombosis risk.

1.4.2 Disease-Specific Immunosuppressive Therapy

Therapy is tailored to the underlying cause:

Minimal Change Disease: Prednisolone at 1 mg/kg/day (maximum 80 mg/day) for 4–8 weeks achieves complete remission in >90% of adults. Frequent relapsers or steroid-dependent patients require alkylating agents (cyclophosphamide), calcineurin inhibitors (cyclosporine, tacrolimus), or rituximab (anti-CD20). Recent evidence strongly supports rituximab as a steroid-sparing agent in relapsing MCD.

Focal Segmental Glomerulosclerosis: Primary FSGS is treated with high-dose corticosteroids, though response rates are lower than in MCD (30–50% complete remission). Calcineurin inhibitors are used in steroid-resistant disease. Sparsentan, a dual endothelin-angiotensin receptor antagonist, received FDA approval in 2023 for IgA nephropathy and is under investigation for FSGS.

Membranous Nephropathy: The KDIGO 2021 guidelines recommend an initial 6-month period of conservative management (RAAS blockade, anti-PLA2R monitoring) before initiating immunosuppression. Rituximab has emerged as the preferred first-line immunosuppressive agent based on the MENTOR trial, demonstrating superiority over cyclosporine in achieving complete remission. Cyclophosphamide with alternating corticosteroids (Ponticelli regimen) remains an alternative.

DIABETIC NEPHROPATHY

1.5 Epidemiology and Natural History

Diabetic kidney disease (DKD) is the leading cause of ESRD globally, accounting for approximately 44% of new dialysis cases in the United States. The prevalence of DKD correlates with diabetes duration, glycaemic control, hypertension, dyslipidaemia, and genetic susceptibility. While the classic presentation follows the Mogensen staging system of normoalbuminuric → microalbuminuria → macroalbuminuria → declining GFR, a substantial proportion of patients with DKD exhibit GFR decline without preceding albuminuria—a non-proteinuric phenotype increasingly recognised in type 2 diabetes.

Type 1 diabetes is associated with a more predictable progression through albuminuric stages. In type 2 diabetes, the natural history is more heterogeneous, partly due to the concurrent presence of other renal comorbidities such as hypertensive nephrosclerosis and obesity-related glomerulopathy. Cardiovascular disease is a major competing risk, particularly in type 2 DM where cardiovascular mortality often precedes ESRD.

1.6 Pathophysiology of Diabetic Nephropathy

1.6.1 Haemodynamic Mechanisms

Hyperglycaemia induces afferent arteriolar vasodilation (mediated by nitric oxide and prostaglandins) with relative efferent arteriolar vasoconstriction (mediated by angiotensin II), producing intraglomerular hypertension and hyperfiltration. This haemodynamic stress damages the GFB, podocytes, and mesangial cells. The RAAS plays a central role: angiotensin II promotes mesangial cell contraction, TGF-β production, and extracellular matrix accumulation, driving glomerulosclerosis and tubulointerstitial fibrosis.

The tubuloglomerular feedback (TGF) mechanism is also perturbed in diabetes. Proximal tubular sodium-glucose cotransport (SGLT2) activity is upregulated in hyperglycaemia, leading to enhanced tubular sodium reabsorption, reduced distal NaCl delivery to the macula densa, and consequent afferent arteriolar vasodilation and intraglomerular hypertension. SGLT2 inhibitors correct this aberrant feedback, reducing intraglomerular pressure and offering renoprotection independent of their glucose-lowering effects.

1.6.2 Metabolic Mechanisms

Advanced glycation end-products (AGEs) accumulate in the glomerular basement membrane and mesangium, inducing crosslinking, reduced elasticity, and receptor-mediated (RAGE) inflammatory signalling. Activation of protein kinase C (PKC) by diacylglycerol (DAG) in hyperglycaemia promotes vascular endothelial dysfunction, increased permeability, extracellular matrix production, and TGF-β upregulation.

The polyol pathway converts excess glucose to sorbitol via aldose reductase, consuming NADPH and depleting glutathione, thereby reducing cellular antioxidant defences. The hexosamine pathway generates O-GlcNAc modifications on nuclear and cytoplasmic proteins, altering their function and contributing to insulin resistance and gene expression changes relevant to DKD pathogenesis.

1.6.3 Inflammatory and Fibrogenic Pathways

Chronic low-grade inflammation, characterised by infiltration of monocytes/macrophages and elevated circulating cytokines (IL-1β, IL-6, TNF-α), contributes to glomerular and tubulointerstitial injury in DKD. Podocyte injury leads to foot process effacement, podocyte detachment, and depletion, which is now recognised as a key driver of FSGS-like lesions in advanced DKD.

TGF-β signalling activates downstream SMAD2/3 pathways promoting myofibroblast differentiation, tubular epithelial-mesenchymal transition (EMT), and matrix metalloproteinase dysregulation, collectively driving the fibrotic remodelling of the tubulointerstitium characteristic of advanced DKD. Mineralocorticoid receptor (MR) activation in kidney cells amplifies inflammation and fibrosis, providing the rationale for MR antagonism as a therapeutic target.

1.7 Histopathology of Diabetic Nephropathy

Renal biopsy in DKD reveals a spectrum of changes that evolve with disease duration. Early changes include glomerular hypertrophy and GBM thickening (detectable within 2–3 years of diabetes onset). Mesangial expansion follows, initially diffuse and later forming the pathognomonic Kimmelstiel–Wilson (KW) nodules—ovoid, laminated, PAS-positive nodular deposits of matrix material in the periphery of the mesangium.

Afferent and efferent arteriolar hyalinosis (the latter more specific to DKD), "capsular drop" lesions (accumulation of plasma proteins between parietal epithelium and Bowman’s capsule), and "fibrin cap" lesions (eosinophilic deposits overlying peripheral capillary loops) are additional histological features. Tubulointerstitial fibrosis and tubular atrophy correlate most strongly with GFR decline. Interestingly, Armanni–Ebstein lesions (glycogen accumulation in tubular epithelial cells) are a transient feature of uncontrolled hyperglycaemia.

1.8 Diagnosis and Staging of Diabetic Nephropathy

The diagnosis of DKD is primarily clinical in the appropriate context (diabetes mellitus plus albuminuria and/or reduced eGFR, with exclusion of other causes). Biopsy is reserved for atypical presentations: absence of diabetic retinopathy (which correlates with DKD in type 1 DM), acute kidney injury, heavy haematuria, short diabetes duration, or rapid GFR decline.

Table 2 summarises the KDIGO CKD staging as applied to diabetic nephropathy:

Albuminuria Category	UACR (mg/g)	CKD Stage (eGFR)	Clinical Significance
A1 - Normal/Mildly increased	<30	G1: ≥90 mL/min	Normoalbuminuric; screen annually
A2 - Moderately increased	30–300	G2: 60–89 mL/min	Microalbuminuria; initiate RAAS blockade
A3 - Severely increased	>300	G3a: 45–59 mL/min	Macroalbuminuria; optimise all risk factors
A3 - Severely increased	>300	G3b: 30–44 mL/min	High risk; add SGLT2i/finerenone if eligible
A3 - Severely increased	>300	G4: 15–29 mL/min	Prepare for renal replacement therapy
A3 - Severely increased	>300	G5: <15 mL/min	ESRD; dialysis or transplantation

1.9 Management of Diabetic Nephropathy

1.9.1 Glycaemic Control

Intensive glycaemic control (HbA1c <7%) reduces the risk of developing microalbuminuria and slows progression in early DKD. The DCCT/EDIC trial in type 1 DM and the UKPDS in type 2 DM established the renal benefits of early glycaemic optimisation. However, in advanced CKD (eGFR <30 mL/min), many glucose-lowering agents require dose adjustment or cessation. Metformin is contraindicated below eGFR 30 mL/min. Individualization of HbA1c targets (7–8%) is recommended in patients with advanced DKD given hypoglycaemia risk.

1.9.2 Blood Pressure Management and RAAS Blockade

The KDIGO 2022 guidelines recommend a blood pressure target of <120/80 mmHg in patients with DKD and proteinuria, based on the SPRINT trial. ACEi or ARBs are first-line antihypertensives in DKD due to their additional renoprotective effects beyond blood pressure reduction, including reduction of intraglomerular pressure and proteinuria. Dual RAAS blockade (ACEi + ARB) is not recommended due to excess risk of hyperkalaemia and acute kidney injury (ONTARGET trial).

1.9.3 SGLT2 Inhibitors: A Paradigm Shift

Sodium-glucose cotransporter 2 inhibitors have transformed the management of DKD in the past decade. The CREDENCE trial (canagliflozin), DAPA-CKD trial (dapagliflozin), and EMPA-KIDNEY trial (empagliflozin) each demonstrated significant reductions in composite renal endpoints, including a 30–40% reduction in ESRD, doubling of serum creatinine, or renal death. Notably, DAPA-CKD and EMPA-KIDNEY included non-diabetic CKD patients, confirming that benefits extend beyond glucose control.

The mechanisms of renoprotection include: (1) restoration of tubuloglomerular feedback with consequent reduction in intraglomerular hypertension; (2) reduction in sodium and fluid retention; (3) anti-inflammatory and anti-fibrotic effects; (4) metabolic switch toward ketone oxidation and improved mitochondrial efficiency; and (5) weight reduction with consequent lowering of glomerular hyperfiltration from obesity-related mechanisms. SGLT2 inhibitors are now recommended in DKD patients with eGFR ≥20 mL/min and UACR ≥30 mg/g by both KDIGO and ADA/EASD guidelines.

1.9.4 Finerenone: Selective Mineralocorticoid Receptor Antagonist

Finerenone, a non-steroidal, selective mineralocorticoid receptor antagonist (MRA), demonstrated renal and cardiovascular benefits in the FIDELIO-DKD and FIGARO-DKD trials. Unlike spironolactone and eplerenone, finerenone has higher receptor selectivity and tissue distribution favouring kidney and heart over vasculature, with a lower risk of hyperkalaemia and no androgenic side effects. The combined FIDELITY analysis showed a 23% reduction in composite renal outcomes.

Finerenone is indicated in patients with type 2 DM, eGFR ≥25 mL/min, and UACR ≥30 mg/g on maximal ACEi/ARB therapy, provided serum potassium ≤5.0 mmol/L at initiation. It is now incorporated into the KDIGO 2022 guidelines as a complementary agent alongside SGLT2 inhibitors.

GLP-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (liraglutide, semaglutide, dulaglutide) have demonstrated cardiorenal benefits in cardiovascular outcomes trials. The FLOW trial (semaglutide) specifically designed to assess renal outcomes in DKD, demonstrated a 24% reduction in the primary composite renal endpoint. GLP-1 RAs reduce albuminuria, promote weight loss, lower blood pressure, and have anti-inflammatory effects that may directly benefit the kidney. They are recommended in patients with type 2 DM and DKD, particularly those with cardiovascular disease or high cardiovascular risk.

1.9.5 Dietary and Lifestyle Measures

Dietary protein restriction to 0.8 g/kg/day is recommended in advanced DKD to reduce glomerular hyperfiltration and uraemic substrate generation. Sodium restriction (<2.3 g/day) enhances the

efficacy of RAAS blockade and reduces fluid retention. Smoking cessation is strongly recommended as tobacco use accelerates DKD progression. Regular aerobic exercise, weight reduction in obese patients, and management of anaemia (with erythropoiesis-stimulating agents and iron replacement) complete the multidisciplinary approach.

COMPARISION, OVERLAP, AND EMERGING THERAPIES

1.10 Distinguishing Nephrotic Syndrome from Diabetic Nephropathy

While massive proteinuria is the cardinal feature of both nephrotic syndrome and advanced DKD, several clinical, laboratory, and histopathological features aid in their distinction:

Feature	Primary Nephrotic Syndrome	Diabetic Nephropathy
Setting	Any age; no metabolic disease required	Established diabetes mellitus (typically >5–10 years)
Haematuria	May be present (MPGN, lupus)	Absent (haematuria prompts biopsy)
Hypertension	Variable; often mild in MCD	Usually present and often severe
Diabetic Retinopathy	Absent	Usually present in type 1 DM (strong correlation)
Complement Levels	Low in MPGN, lupus; normal in MCD, FSGS, MN	Normal
Anti-PLA2R Antibody	Positive in ~70% of primary MN	Negative
eGFR at Presentation	Often preserved in MCD; variable in FSGS/MN	Progressive decline over years
Histology	Disease-specific (e.g. foot process effacement, KW nodules absent)	KW nodules, GBM thickening, arteriolar hyalinosis
Response to Steroids	Excellent in MCD; variable in FSGS	No role for immunosuppression
Thrombosis Risk	Very high (especially MN, serum albumin <2 g/dL)	Elevated but lower than nephrotic syndrome

1.11 Shared Pathophysiology and Therapeutic Synergies

Despite distinct primary aetiologies, nephrotic syndrome and DKD share several pathophysiological nodes: podocyte injury, disruption of the slit diaphragm, activation of the RAAS, intraglomerular hypertension, and progression through common fibrogenic pathways involving TGF-β and NF-κB. These shared mechanisms explain why RAAS blockade benefits both conditions and why SGLT2 inhibitors demonstrate renoprotection even in non-diabetic proteinuric kidney diseases.

The DAPA-CKD trial included patients with IgA nephropathy, FSGS, and other proteinuric non-diabetic CKDs, demonstrating that the renal benefits of dapagliflozin were consistent across subgroups. This broadens the therapeutic scope of SGLT2 inhibitors considerably. Similarly, sparsentan's dual endothelin-angiotensin receptor antagonism shows promise in proteinuric glomerular diseases regardless of cause.

1.12 Emerging Therapeutic Targets

The therapeutic landscape for both nephrotic syndrome and DKD continues to evolve rapidly:

Endothelin Receptor Antagonists: Sparsentan (dual AT1/ETA receptor antagonist) demonstrated significant proteinuria reduction in the DUPLEX trial in IgA nephropathy and is under evaluation in FSGS. Endothelin-1 promotes mesangial contraction, podocyte injury, and tubulointerstitial fibrosis, making ET-1 blockade an attractive target.

Complement Inhibition: C3 glomerulopathy and certain forms of MPGN with complement dysregulation are increasingly targeted with complement inhibitors (avacopan, pegcetacoplan, iptacopan). Iptacopan, a factor B inhibitor, received FDA approval for paroxysmal nocturnal haemoglobinuria and is under investigation in complement-mediated GN.

Rituximab and B-cell Depletion: Rituximab has become standard of care for frequently relapsing or steroid-dependent MCD and primary MN, with evidence from multiple randomised controlled trials including GEMRITUX, MENTOR, and RI-CYCLO.

JAK Inhibition: Baricitinib and other JAK inhibitors are being evaluated in lupus nephritis and other immune-mediated glomerular diseases, targeting the JAK-STAT signalling pathway central to cytokine-driven inflammation.

Aldosterone Synthase Inhibition: Baxdrostat, an aldosterone synthase (CYP11B2) inhibitor, is under evaluation for treatment-resistant hypertension with CKD, potentially offering RAAS blockade benefits with fewer side effects than MR antagonists.

Atrasentan: This selective ETA receptor antagonist demonstrated significant proteinuria reduction in the SONAR trial and is being re-evaluated in combination with SGLT2 inhibitors for DKD.

1.13 Monitoring and Follow-Up

Both conditions require systematic long-term monitoring. For nephrotic syndrome, follow-up should assess proteinuria (UACR or 24-hour urine), serum albumin, eGFR, lipid profile, blood pressure, oedema status, and treatment toxicity at 1–3 monthly intervals during active disease. Immunological markers (anti-PLA2R titres in MN, complement levels in MPGN) guide treatment decisions.

For DKD, KDIGO recommends at minimum annual monitoring of UACR and eGFR in all diabetic patients. Patients with UACR >30 mg/g or eGFR <60 mL/min should be monitored every 3–6 months. Serum potassium must be monitored closely when using RAAS blockers and finerenone. Haemoglobin, calcium-phosphate metabolism, and parathyroid hormone should be tracked in CKD G3b and beyond.

1.14 Special Populations

1.14.1 Paediatric Nephrotic Syndrome

In children, nephrotic syndrome is predominantly MCD (~90% of cases in children under 10). The first episode is treated empirically with corticosteroids without biopsy. Steroid-responsive patients have an excellent long-term renal prognosis. Genetic causes should be considered in children with steroid-resistant nephrotic syndrome, particularly under 1 year of age.

1.14.2 Nephrotic Syndrome in Pregnancy

Pre-eclampsia is the most common cause of nephrotic-range proteinuria in pregnancy and must be differentiated from primary glomerular disease. Management involves close blood pressure control, timing of delivery, and cautious use of anticoagulation given thrombosis risk.

1.14.3 Elderly Patients with DKD

Older adults with DKD have a higher burden of polypharmacy, falls risk, hypoglycaemia, and frailty. HbA1c targets are relaxed to 7.5–8.5% in frail elderly patients. SGLT2 inhibitors should be used with caution given the risk of volume depletion and urinary tract infections; genital mycotic infections are also more common in the elderly.

1.15 Transition to End-Stage Renal Disease

Both nephrotic syndrome (particularly FSGS and secondary causes) and DKD carry significant risk of progression to ESRD. Preparation for renal replacement therapy should begin when eGFR falls to 20–25 mL/min. Options include haemodialysis, peritoneal dialysis, and kidney transplantation. Pre-

emptive transplantation, when eGFR falls to 15–20 mL/min, is associated with the best outcomes. Living donor transplantation offers superior graft survival compared to deceased donor transplantation.

In patients with DKD and type 2 DM who are transplant candidates, simultaneous pancreas-kidney (SPK) transplantation may be considered in carefully selected patients. Recurrence of primary FSGS post-transplantation occurs in up to 30–40% of cases and is mediated by the same circulating permeability factor implicated in primary disease; rituximab and plasma exchange are used prophylactically and therapeutically.

2 Conclusion

Nephrotic syndrome and diabetic nephropathy are distinct but overlapping clinical entities that together represent the leading causes of chronic kidney disease and ESRD globally. A thorough understanding of their pathophysiology, accurate diagnostic evaluation—including the judicious use of renal biopsy—and application of evidence-based, targeted therapies are essential for optimising patient outcomes.

The past decade has witnessed transformative advances in treatment, particularly the emergence of SGLT2 inhibitors and finerenone as renoprotective agents with benefits extending beyond glucose control to encompass broad anti-inflammatory, anti-fibrotic, and haemodynamic mechanisms. Rituximab has become standard of care in immune-mediated nephrotic syndrome. Further progress in precision medicine, including genetic testing for podocytopathies, biomarker-guided therapy in membranous nephropathy, and complement pathway targeting in specific glomerulopathies, holds great promise for the future.

Multidisciplinary collaboration among nephrologists, endocrinologists, cardiologists, dietitians, and primary care providers remains the cornerstone of comprehensive CKD care in both nephrotic syndrome and diabetic nephropathy. Ongoing clinical trials will continue to refine the therapeutic armamentarium and improve the prospects of patients living with these challenging conditions.

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Conflict of Interest

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