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Nephrotic syndrome: Management of dyslipidemia, pathophysiological insights, and therapeutic perspectives

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Abstract. *Dyslipidemia is a characteristic feature of nephrotic syndrome (NS), which significantly increases the risk of cardiovascular complications and progression of chronic kidney disease. This review analyzes current understanding of the complex pathophysiological mechanisms of lipid metabolism disorders in NS. Particular attention is paid to the impact of proteinuria on the synthesis of lipoproteins by the liver and impaired clearance. The article systematizes current therapeutic strategies. Therapeutic prospects aimed at correcting the lipid profile as a means of nephroprotection are considered. The review emphasizes the need for a personalized approach to the management of dyslipidemia, taking into account the etiology of NS and the functional state of the kidneys.*

Keywords: *nephrotic syndrome, dyslipidemia, hypoalbuminemia, glomerulosclerosis, chronic kidney disease, oxidative stress, atherosclerosis, chronic heart failure, hypolipidemic drugs.*

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Нефротичний синдром: лікування дисліпідемії, патофізіологічні аспекти та терапевтичні перспективи

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Резюме. *Дисліпідемія є характерною ознакою нефротичного синдрому, яка значно підвищує ризик серцево-судинних ускладнень та прогресування хронічної хвороби нирок. У цьому огляді аналізується сучасне розуміння складних патофізіологічних механізмів порушень ліпідного обміну у пацієнтів з нефротичним синдромом. Особлива увага приділяється впливу протеїнурії на синтез ліпопротеїнів печінкою та порушення їх кліренсу. У статті систематизовано сучасні терапевтичні стратегії. Розглянуто терапевтичні перспективи, спрямовані на корекцію ліпідного профілю як засобу нефропротекції. В огляді наголошується на необхідності персоналізованого підходу до лікування дисліпідемії з урахуванням етіології нефротичного синдрому та функціонального стану нирок.*

Ключові слова: *нефротичний синдром, дисліпідемія, гіпоальбумінемія, гломерулосклероз, хронічна хвороба нирок, оксидативний стрес, атеросклероз, хронічна серцева недостатність, гіполіпідемічні препарати.*

Introduction. NS is a clinical and laboratory symptom complex characterized by massive proteinuria (more than 3.5 g/day), hypoalbuminemia, peripheral edema, and severe hyperlipidemia [**1**]. While correction of fluid and electrolyte imbalances and immunosuppressive therapy for the underlying disease have traditionally been the focus of clinical attention, dyslipidemia in NS is often underestimated.

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The abnormal lipid profile in NS typically manifests as elevated levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and lipoprotein(a) (Lp(a)). These abnormalities result from a complex cascade of pathophysiological changes, including excessive hepatic synthesis of lipoproteins and defects in their plasma clearance. Long-term hyperlipidemia in NS is a powerful cardiovascular risk factor and has a direct nephrotoxic effect, contributing to tubulointerstitial fibrosis and glomerulosclerosis [**1, 2**].

Despite the existence of generally accepted clinical guidelines for the treatment of cardiovascular diseases (CVD), the management of dyslipidemia specifically in NS remains a subject of debate. Statins remain first-line treatments, but their efficacy and safety may vary depending on the severity of proteinuria and renal func-

tion. Furthermore, the emergence of new therapeutic agents, such as proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, opens new horizons in the treatment of refractory forms of lipid metabolism disorders. This review aims to systematize current data on the pathogenesis of nephrotic dyslipidemia, critically evaluate the effectiveness of existing pharmacotherapy methods, and consider promising therapeutic strategies aimed at reducing cardiovascular risk and slowing the progression of renal failure.

Materials and methods. An analysis of data from literary sources and medical articles indexed in the PubMed database was conducted to clarify the influence of nephrotic syndrome (NS) on the development and progression of dyslipidemia. A systematic literature search was performed using the PubMed database. The following keywords and Medical Subject Headings (MeSH) were used in various combinations: "nephrotic syndrome," "dyslipidemia," "hyperlipidemia," "lipid metabolism," "pathophysiology," and "management." Boolean operators (AND, OR) were applied to refine the search strategy.

The inclusion criteria were as follows: peer-reviewed articles published in English; review articles, systematic reviews, meta-analyses, randomized controlled trials, and observational studies (cohort, case-control, and cross-sectional studies); studies investigating the pathophysiological mechanisms, clinical features, or therapeutic management of dyslipidemia in patients with nephrotic syndrome, and studies involving adult and pediatric populations.

The exclusion criteria included: case reports, conference abstracts, editorials, and letters to the editor; studies not directly addressing lipid metabolism or dyslipidemia in nephrotic syndrome; articles with insufficient methodological quality or incomplete data.

The time frame for the literature search covered publications from 2000 to 2025, allowing inclusion of both foundational studies and the most recent advances in understanding the molecular mechanisms and therapeutic approaches to dyslipidemia in nephrotic syndrome. Relevant articles were initially screened based on titles and abstracts, followed by full-text evaluation for eligibility. Data were extracted and qualitatively synthesized to identify key mechanisms linking nephrotic syndrome and dyslipidemia, as well as current and emerging therapeutic perspectives.

Pathophysiology of dyslipidemia in nephrotic syndrome. Nephrotic dyslipidemia, due to hypoalbuminemia and urinary loss of lipid regulators, is characterized by elevated plasma levels of lipoprotein(a), apolipoprotein B-containing lipoprotein, and apolipoprotein A-III [1]. This is due to a combination of increased production, impaired catabolism/clearance of LDL and apoB-100 [2, 3] and is accompanied by significant increases in apoA-I, apoA-IV, apoB, apoC, and apoE levels, as well as the ratio of apoC-III to apoC-II. These changes are involved in the biosynthesis, transport, remodeling, and catabolism of lipids and lipoproteins.

Lipoprotein lipase (LPL) is the rate-limiting enzyme for chylomicron and very low-density lipoprotein (VLDL) lipolysis [4, 5]. Endothelium-derived glycosylphosphatidylinositol-anchored binding protein 1 (GPIHBP1) plays a central role in the fate and function of LPL by anchoring LPL to the endothelium and serving as a ligand for chylomicrons [6].

Downregulation of LPL and GPIHBP1 is enhanced by decreased apoE and apoCII levels and increased apoCIII to apoCII ratios in VLDL and chylomicrons. Impairment of LPL-mediated lipolysis of triglyceride-rich lipoproteins occurs through a decrease in apoE (the main ligand for binding of VLDL and chylomicrons to the endothelium) and a decrease in the ratio of apoCII (an LPL activator) to apoCIII (an LPL inhibitor) [7]. The acquisition of apoE and apoC from HDL in exchange for apoA is essential for endothelium-binding and LPL-mediated lipolysis of VLDL and chylomicrons. The lack of HDL-2, which is rich in cholesteryl esters, plays an important role in the dysregulation of triglyceride-rich lipoprotein metabolism.

Hepatic lipase is involved in HDL metabolism, mediating the unloading of its triglyceride load in the liver. NS leads to hepatic lipase deficiency, which contributes to hypertriglyceridemia, accumulation of atherogenic immediate-density lipoprotein (IDL), and TG enrichment of LDL and HDL. Regulation of hepatic LDL expression occurs through the proprotein convertase subtilisin/kexin type 9 (PCSK9). In patients with NS, LDL degradation is increased with increased intrahepatic expression of PCSK9. Thus, LDL clearance is impaired and LDL uptake by hepatocytes is reduced [8]. In addition, with increased glomerular basement membrane permeability and decreased LPL activators, LPL activity is reduced and IDL and LDL levels are increased.

Through the esterification of free cholesterol, acyl-CoA: cholesterol acyltransferase (ACAT) plays an important role in the packaging of cholesterol into apoB-100 in the liver for release into the circulation. The processes of increasing cholesterol biosynthesis and decreasing cholesterol catabolism are controlled by 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) and cholesterol-7 alpha-hydroxylase. Despite hypercholesterolemia, both are regulated by the intracellular concentration of free cholesterol, which is not increased in NS. This discrepancy may be explained in part by impaired hepatic cholesterol uptake due to acquired deficiency of the LDL receptor, as well as by upregulation of the activity of hepatic acyl-coenzyme A (CoA): cholesterol ACAT (which catalyzes cholesterol esterification).

Increased cholesterol esterification and decreased intracellular free cholesterol occur in association with increased expression and activity of liver acetyl-CoA acetyltransferase 2 (ACAT2), downregulation of genes encoding proteins involved in fatty acid catabolism in the liver [9]. Increased HMG-CoA reductase activity and cholesterol production have been observed in the liver of patients with NS.

In NS, HDL levels are normal or slightly reduced, but the HDL to total cholesterol ratio is low compared with healthy individuals. The maturation of cholesterol ester-poor HDL particles to cholesterol ester-rich HDL particles is also altered [10], suggesting that impaired reverse cholesterol transport may be a key component of NS and contribute to its associated vascular complications.

Clinical profile and consequences of dyslipidemia in NS. *Typical lipid abnormalities*. Dyslipidemia in NS is almost universal and typically severe. The classic pattern includes elevated TC, LDL-C, VLDL, IDL, TG, apoB-containing particles, and often lp(a), with normal or slightly reduced HDL that is functionally impaired. Mechanistically, heavy proteinuria and hypoalbuminemia stimulate hepatic overproduction of lipoproteins (VLDL, lp (a), apoB) and cholesterol, while urinary loss of key regulators (e.g., LCAT, CETP) and downregulation of lipoprotein lipase, hepatic lipase and LDL receptors reduce lipoprotein clearance. This combination leads to accumulation of cholesterol-rich, TG-rich and small dense LDL particles with high atherogenic potential [4]. In prolonged NS, this profile often meets criteria for combined hyperlipidemia and resembles familial forms in severity.

Differences between nephrotic syndrome types. Recent work has started to dissect lipid phenotypes across primary NS entities. In a 409-patient cohort of primary membranous nephropathy, minimal change disease and focal segmental glomerulosclerosis, Alqudsi et al. showed that after adjustment for proteinuria and hypoalbuminemia, TC and TG were comparable across groups, but LDL-C was highest in focal segmental glomerulosclerosis whereas HDL-C was significantly higher in minimal change disease than in membranous nephropathy or focal segmental glomerulosclerosis [11]. These data suggest that the underlying glomerulopathy modulates qualitative aspects of dyslipidemia beyond nephrotic severity. In patients, steroid-resistant or frequently relapsing NS is associated with more persistent and pronounced dyslipidemia than steroid-sensitive forms, reflecting longer exposure to nephrotic-range proteinuria, cumulative glucocorticoid therapy and greater chronic kidney damage. Such differences are clinically relevant, as focal segmental glomerulosclerosis and steroid-resistant phenotypes may carry a more atherogenic lipid burden and higher long-term cardiovascular and renal risk [4, 12].

CVD risk and endothelial dysfunction. The nephrotic dyslipidemic milieu contributes to premature atherosclerosis and subclinical cardiovascular damage. In both adults and children with NS, elevated LDL-C, non-HDL-C and TG correlate with increased carotid intima–media thickness and impaired flow-mediated dilation, indicating early endothelial dysfunction and arterial stiffening [13-15]. Recent data show that patients with NS in remission still exhibit impaired endothelial function compared with healthy controls, and that abnormalities are more pronounced in frequently relapsing or steroid-dependent forms [16]. These findings support the concept that dyslipidemia, together with persistent low-grade inflammation, oxidative stress, and a prothrombotic state, positions NS patients at elevated risk for cardiovascular events throughout life, even if overt clinical events occur decades later.

Contribution to glomerular injury and CKD progression ("lipid nephrotoxicity"). Beyond systemic atherosclerosis, renal "lipid nephrotoxicity" is now recognized as a key amplifier of glomerular injury in NS. Elegant experimental and clinical studies summarized by Vaziri demonstrated that NS is associated with increased renal uptake and intrarenal accumulation of cholesterol, triglycerides and oxidized lipoproteins, leading to mesangial proliferation, podocyte injury, and expansion of glomerulosclerosis [2]. Lipids and their oxidized derivatives induce reactive oxygen species generation, ER stress, and pro-inflammatory and pro-fibrotic signaling in glomerular and tubular cells, thereby accelerating nephron loss. The broader CKD literature further supports a causal link between lipid surplus and kidney function decline, with observational data showing that higher atherogenic lipid indices predict faster CKD progression and experimental models demonstrating that reducing renal lipid accumulation ameliorates structural damage [17, 18]. Dyslipidemia has been shown to exacerbate oxidative stress and inflammatory responses, with increased reactive oxygen species production and pro-inflammatory pathway activation directly linked to adverse vascular changes [19]. In NS, this creates a vicious circle: proteinuria and hypoalbuminemia drive dyslipidemia, dyslipidemia promotes glomerular and tubulointerstitial injury, which in turn, worsens proteinuria and further exacerbates the dyslipidemic state. Recognizing this bidirectional relationship is central to justifying early and aggressive management of dyslipidemia as part of a reno-cardiovascular protective strategy in nephrotic patients.

Therapeutic goals and guideline recommendations. *Overview of current guideline recommendations*. The management of dyslipidemia in NS has two goals: achieving remission of the underlying glomerular disease and lipid control. Dedicated NS-specific recommendations remain limited, so clinicians rely largely on general dyslipidemia guidelines from major cardiovascular and nephrology societies. The ESC/EAS 2019 and 2025 guidelines use a risk-stratified, treat-to-target approach, classifying moderate CKD as high risk and severe CKD as very-high risk [20, 21]. In contrast, the AHA/ACC 2018 guidelines use an intensity-based strategy, considering CKD and persistent albuminuria as risk-enhancing factors that favor statin initiation in borderline- or intermediate-risk adults. In contrast, KDIGO emphasizes a 'fire-and-forget' approach, recommending statins for most adults with CKD irrespective of LDL-C level [22, 23]. This strategy is based on evidence that statins reduce cardiovascular risk in CKD populations, even when intensive lipid monitoring is not performed.

These recommendations are particularly relevant in NS, where proteinuria per se contributes to atherogenesis [24, 25]. During active NS, LDL-C frequently exceeds 4.9 mmol/L (190 mg/dL), meeting criteria for severe hypercholesterolemia independent of calculated cardiovascular risk. In patients with glomerular disease, including NS, KDIGO advises lipid-lowering therapy for persistent dyslipidemia, especially when additional cardiovascular risk factors are present such as hypertension, diabetes mellitus, or established ASCVD. Therefore, for patients with nephrotic syndrome, the choice between these approaches should be individualized. In conditions with a high likelihood of remission, such as minimal change disease, a KDIGO-based approach with moderate-intensity statin therapy and reassessment after remission may be sufficient, as lipid abnormalities frequently resolve. However, in patients with persistent proteinuria, advanced CKD, or established cardiovascular disease, a treat-to-target strategy is more appropriate due to sustained dyslipidemia and high cardiovascular risk.

Target lipid levels and treatment thresholds. Proposed treatment targets are presented in Table 1. In brief, patients with NS but without CKD or major comorbidities (e.g., minimal change disease with anticipated remission) are pragmatically considered to be at moderate cardiovascular risk, while the presence of nephrotic syndrome is associated with increased risk but is not in itself a criterion for classifying a patient as very high risk. In line with the ESC/EAS framework, targeted lipid management is primarily aimed at lowering LDL-C, with secondary targets including non-HDL-C and apolipoprotein B. For all risk categories, triglycerides should be maintained <5.6 mmol/L (<500 mg/dL) to minimize pancreatitis risk.

Considerations for primary vs. secondary prevention. For secondary prevention in patients with documented atherosclerotic cardiovascular disease (ASCVD), high-intensity statin therapy remains first-line, with dose adjustment based on eGFR and concurrent medications. Primary prevention strategies must account for the dynamic nature of NS. In minimal change disease with anticipated remission, moderate-intensity statin therapy may suffice during the acute phase, with reassessment following proteinuria resolution. Dyslipidemia typically normalizes within weeks to months after achieving complete remission, potentially allowing therapy de-escalation. Conversely, patients with focal segmental glomerulosclerosis or membranous nephropathy, where proteinuria often persists despite immunosuppressive therapy, are indicated for more aggressive primary prevention approaching secondary prevention intensity [26].

Special consideration applies to children. While KDIGO suggests deferring statins in children with NS unless experiencing persistent, severe hyperlipidemia despite optimal disease management, emerging evidence supports that earlier intervention may be appropriate in patients with steroid-resistant disease or progressive genetic forms [27].

Tables 1

Treatment targets for dyslipidemia in NS according to CVD risk categories

Risk Category	Clinical Criteria	Primary goals	Secondary goals
Moderate risk	NS without CKD, expected remission; no additional major cardiovascular risk factors	LDL-C <2.6 mmol/L (<100 mg/dL)	Non-HDL-C <3.4 mmol/L (<130 mg/dL); ApoB <100 mg/dL
High risk	Moderate CKD (30–59 mL/min/1.73 m^2); DM without target organ damage; persistent proteinuria with ≥1 risk factor	LDL-C <1.8 mmol/L (<70 mg/dL) and ≥50% reduction	Non-HDL-C <2.6 mmol/L (<100 mg/dL); ApoB <80 mg/dL
Very-high risk	Severe CKD (eGFR <30 mL/min/1.73 m^2); DM and target organ damage; documented ASCVD	LDL-C <1.4 mmol/L (<55 mg/dL) and ≥50% reduction	Non-HDL-C <2.2 mmol/L (<85 mg/dL); ApoB <65 mg/dL

Abbreviations: Apolipoprotein B (ApoB); Atherosclerotic cardiovascular disease (ASCVD); Chronic kidney disease (CKD); Diabetes mellitus (DM); Estimated glomerular filtration rate (eGFR); High-density lipoprotein cholesterol (HDL-C); Low-density lipoprotein cholesterol (LDL-C); Nephrotic syndrome (NS).

Non-pharmacological management. The non-pharmacological management of dyslipidemia in NS represents a crucial adjunct to pharmacotherapy. A multifaceted approach, integrating lifestyle modification, dietary optimization, and control of the underlying glomerular disorder, functions not merely as supportive care but as a key determinant of metabolic stability. By modulating nutritional status, energy balance, and renal function, these interventions collectively improve lipid homeostasis, reduce proteinuria, and mitigate the elevated cardiovascular risk inherent to nephrotic states.

Dietary Interventions. Nutritional modification remains a cornerstone in addressing nephrotic dyslipidemia. Restriction of saturated fats and dietary cholesterol, alongside increased intake of mono- and polyunsaturated fatty acids, has been shown to reduce total and LDL cholesterol [10, 28]. Incorporation of omega-3 fatty acids from marine or plant-based sources provides additional triglyceride-lowering and anti-inflammatory effects [29, 30].

Protein intake should be carefully individualized: adequate protein prevents malnutrition, but excessive consumption may exacerbate glomerular hyperfiltration and proteinuria. A moderate intake of 0.8-1.0 g/kg/day, tailored to renal function, is generally advisable [31]. Sodium restriction (<2.3 g/day) aids in controlling edema and hypertension, indirectly supporting lipid regulation. High dietary fiber from whole grains, legumes, fruits, and vegetables enhances bile acid excretion, contributing to LDL reduction [32].

Control of underlying disease and proteinuria. Amelioration of the primary renal pathology and reduction of proteinuria are central to improving dyslipidemia. Effective management of glomerular diseases - through immunosuppressive therapy in minimal change disease or membranous nephropathy – often normalizes lipid abnormalities [33]. Optimization of blood pressure with renin–angiotensin–aldosterone system (RAAS) blockade reduces proteinuria and may favorably affect lipid metabolism [34]. In diabetic nephropathy, strict glycaemic control is associated with improved metabolic and renal outcomes, although evidence for direct correction of dyslipidemia is limited [35-37]. Supportive measures, including avoidance of nephrotoxins and maintenance of adequate hydration, further support renal and metabolic stability [38].

Weight management and physical activity. Obesity and sedentary behavior exacerbate dyslipidemia and proteinuria. Structured weight reduction through caloric moderation and regular physical activity improves lipid metabolism and insulin sensitivity [39]. Aerobic exercise – ideally ≥150 minutes per week at moderate intensity – is associated with lower triglyceride levels and higher HDL cholesterol in healthy populations; in nephrotic patients, programs should be tailored to individual tolerance, particularly in the presence of edema or renal impairment, favoring low-impact activities such as walking, cycling, or aquatic exercise [40, 41].

Lifestyle counselling should also emphasize smoking cessation and moderation of alcohol intake, both of which contribute to improved cardiovascular outcomes [1, 42].

Pharmacological management. Pharmacological management of dyslipidemia in NS pursues three interrelated objectives. First, the urgent prevention of pancreatitis in cases of marked hypertriglyceridemia (TGs >5.6 mmol/L, or >10 mmol/L for emergency correction).

Second, the long-term reduction of ASCVD risk, which is critical given the substantially elevated CVD associated with proteinuria and nephrotic-range dyslipidemia, as emphasized in KDIGO and ESC/EAS guidance.

Third, the prevention of lipid-mediated renal injury is an essential nephroprotective component of therapy that addresses the direct pathogenic role of lipotoxicity in progressive kidney damage. First-line lipid-lowering therapy in patients with NS involves the early initiation of statins. Treatment intensification is achieved by adding ezetimibe when LDL-C targets are not met. In individuals at very high CVD risk or with severe dyslipidemia, an upfront combination strategy may be considered. Current ESC/EAS and KDIGO guidance supports starting therapy as early as possible, irrespective of baseline LDL-C levels, with a preference for agents and combinations supported by robust evidence of renal safety [43, 44].

The main classes of hypolipidemic drugs. Statins. Statins (atorvastatin, rosuvastatin, simvastatin, pitavastatin, pravastatin) are the first-line agents for the management of dyslipidemia. They act by inhibiting HMG-CoA reductase, thereby reducing hepatic cholesterol synthesis and increasing LDL receptor expression. This class typically lowers LDL-C by approximately 30-60 percent. The principal adverse effects include myalgias and elevations in ALT/AST, with rhabdomyolysis occurring rarely. Safety monitoring requires assessment of ALT/AST prior to treatment initiation and as clinically indicated, as well as measurement of creatine kinase if muscle symptoms develop [26].

Ezetimibe. Ezetimibe acts by inhibiting intestinal cholesterol absorption through blockade of the NPC1L1 transporter. It provides an additional 18-25 percent reduction in LDL-C and is used at a fixed dose of 10 mg daily, most often in combination with statins. Adverse effects include dyspepsia and transient elevations in transaminases. Safety monitoring is generally limited to assessing ALT/AST when ezetimibe is used as part of combination therapy with a statin [44].

PCSK9 inhibitors (Proprotein Convertase Subtilisin/Kexin Type 9). This class includes the monoclonal antibodies evolocumab and alirocumab. Their mechanism of action involves binding circulating PCSK9, thereby preventing the degradation of hepatic LDL receptors and producing a 50-60 percent reduction in LDL-C. The agents are administered subcutaneously: evolocumab 140 mg every two weeks or 420 mg monthly; alirocumab 75-150 mg every two weeks. Adverse effects include injection-site reactions, arthralgias, and influenza-like symptoms. Lipid profile monitoring is recommended every 3-6 months.

Clinical trials have demonstrated that PCSK9 inhibitors are highly effective and well tolerated as intensive lipid-lowering therapy, with preserved efficacy and no excess safety concerns even in patients with severe renal impairment [45].

Inclisiran. Inclisiran is an innovative small-interfering RNA (siRNA) agent. Its mechanism of action involves the suppression of hepatic PCSK9 synthesis, which, similar to monoclonal PCSK9 inhibitors, increases LDL receptor expression. Mean LDL-C reduction is approximately 50 percent. Adverse effects are largely limited to injection-site reactions, occurring in about 1-5 percent of patients. Lipid monitoring is recommended at 3 months and then every 6-12 months.

Data from the ORION-7 and ORION-1 studies demonstrated that the pharmacodynamic effects of inclisiran (reductions in circulating PCSK9 and LDL-C)

and its safety profile are comparable in patients with normal and impaired renal function, including those with severe chronic kidney disease. Although systemic exposure increases modestly with declining kidney function, inclisiran is rapidly cleared and becomes undetectable in plasma within 48 hours, and no dose adjustment is required in individuals with renal impairment [46].

Bempedoic acid. Bempedoic acid acts by inhibiting ATP-citrate lyase, reducing cholesterol synthesis at a step upstream of HMG-CoA reductase. As monotherapy, it lowers LDL-C by approximately 17-20 percent, and up to 35 percent when combined with ezetimibe, at a standard dose of 180 mg daily. The principal adverse effects include hyperuricemia and tendinopathy. Safety monitoring requires periodic assessment of serum uric acid and clinical vigilance for symptoms suggestive of gout [47].

Fibrates. The principal agent in this class is fenofibrate, a PPAR-α agonist that enhances lipoprotein lipase activity and effectively lowers triglyceride levels by 30-50 percent. Fibrates are used primarily to manage marked hypertriglyceridemia (TGs>5.6 mmol/L). Adverse effects include dyspepsia, increases in serum creatinine, and a higher risk of myopathy when combined with a statin. Safety monitoring should include creatinine, ALT, and CK when fibrates are used in combination therapy.

The clinical utility of fenofibrate in patients with type 2 diabetes and impaired kidney function (eGFR >30 mL/min/1.73 m^2) is supported by the FIELD and ACCORD Lipid trials. These studies demonstrated that although fenofibrate causes an early, reversible rise in serum creatinine, long-term therapy slows the overall decline in eGFR and reduces albuminuria, thereby contributing to renal preservation in diabetic nephropathy.

In the later stages of CKD, the risk of side effects is increased, so there is a need for an individual assessment of the benefits and risks of using this group of drugs.

Omega-3 polyunsaturated fatty acids (PUFAs). Formulations containing eicosapentaenoic acid (EPA) reduce triglyceride secretion and very-low-density lipoprotein synthesis, producing a 20-45 percent reduction in TG levels. Adverse effects include dyspepsia and a prolongation of bleeding time. Coagulation monitoring is advisable when EPA is used concomitantly with anticoagulant therapy.

The REDUCE-IT trial demonstrated that icosapent ethyl significantly lowers the incidence of cardiovascular events regardless of baseline kidney function, supporting its broad clinical utility even in patients with mild to moderate renal impairment [48].

Bile acid sequestrants (resins). This class includes cholestyramine and colesevelam. They act locally by binding bile acids in the intestine, which in turn stimulates upregulation of hepatic LDL receptors. These agents lower LDL-C by approximately 15-25 percent (for example, colesevelam 3.75 g daily). Their use is limited by gastrointestinal adverse effects such as constipation and bloating, as well as the risk of increasing triglyceride levels. They are contraindicated in patients with TG levels above 4.5 mmol/L. Colesevelam and related agents are safe across all stages of chronic kidney disease because they are not systemically absorbed. Their dual activity – lipid lowering and potential phosphate binding – makes them a useful option for patients with advanced CKD and concomitant dyslipidemia [49].

Niacin. Niacin may be considered a second-line adjunctive therapy in NS, as it effectively lowers TG by 20-50 percent and raises HDL-C. Its use is substantially limited by a high risk of hepatotoxicity, hyperuricemia, and worsening glycemic control, particularly in patients with diabetic nephropathy. Because there is no evidence of cardiovascular outcome benefit when niacin is added to statin therapy, it is reserved for severe, refractory hypertriglyceridemia and requires careful monitoring of relevant laboratory parameters. Choice of lipid-lowering therapy and its intensity in NS are determined not only by LDL-C targets and CVD risk stratification, but also by renal functional status.

The need to account for estimated glomerular filtration rate (eGFR) stems from the increased risk of dose-dependent statin-associated myotoxicity as kidney function declines (particularly at eGFR<30 mL/min/1.73 m^2). This necessitates careful dose titration and preferential selection of agents with predominantly non-renal routes of elimination [50].

Given the dual influence of kidney function-both on CVD risk and on the pharmacokinetics of lipid-lowering agents-therapeutic approaches in patients with NS require individualized stratification (Table 2). It is therefore reasonable to distinguish treatment strategies according to eGFR. This allows for maximally intensive therapy to achieve aggressive LDL-C targets while minimizing the risk of dose-dependent statin toxicity in the setting of reduced renal clearance [51].

Table 2

Therapeutic strategy for lipid-lowering agents based on eGFR

CKD stage (eGFR mL/min/1.73 m^2)	Recommended therapy	Intensification (2nd line)	Restrictions
G1–G2 (>60)	Statins at standard doses (first-line)	Add ezetimibe if LDL-C targets unmet or risk is high	Fibrates only if TG >5.6 mmol/L; avoid with high-dose statins
G3a–G3b (30–59)	Statins (standard or reduced dose; atorvastatin preferred)	Ezetimibe is the safest add-on in CKD	Fibrates discouraged; avoid combination with statins due to myotoxicity risk

Continuation of Table 2

CKD stage (eGFR mL/min/1.73 m²)	Recommended therapy	Intensification (2nd line)	Restrictions
G4 (15–29)	Statins at reduced doses (baseline therapy)	Best intensification: statin + ezetimibe	Fibrates contraindicated (risk of rhabdomyolysis and nephrotoxicity)
G5 / G5D (<15 or on dialysis)	Continue statin only if previously used; do not start a statin de novo	Ezetimibe allowed; PCSK9 inhibitors may be used for additional LDL-C lowering	Fibrates contraindicated. · Evidence: starting statins in dialysis patients showed no benefit [4, 12]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglycerides.

Pharmacokinetic considerations of lipid-lowering therapy in the setting of hypoalbuminemia and proteinuria.

Beyond the limitations imposed by reduced renal clearance at low eGFR, patients with significant proteinuria and resultant hypoalbuminemia face an additional pharmacokinetic concern. Lower serum albumin increases the unbound fraction of highly protein-bound statins in the circulation. This elevation in the active free fraction – independent of total drug concentration – may heighten the risk of myotoxicity, necessitating vigilant monitoring and cautious dose titration. Consequently, when selecting statin therapy, particularly in the presence of reduced eGFR, preference is often given to agents with minimal renal elimination, such as atorvastatin, to optimize both efficacy and safety [52].

Monitoring the efficacy and safety of lipid-lowering therapy

Lipid profiles should be reassessed 4-6 weeks after treatment initiation and subsequently every 6-12 months. Biochemical parameters (ALT, AST, CK) are evaluated prior to therapy and thereafter as clinically indicated. When adverse reactions are detected, dose adjustment or substitution of the agent is required.

Emerging classes of lipid-lowering agents

Ongoing development of novel lipid-lowering therapies has demonstrated substantial efficacy in achieving aggressive LDL-C targets. Given that NS automatically places patients in the category of very high cardiovascular risk, these innovative therapeutic options represent an essential component of treatment intensification. Their use is justified when the standard combination of a statin with ezetimibe fails to achieve established LDL-C goals (Table 3).

Table 3

New hypolipidemic agents and active research frontiers

Name of agent	Mechanism of action	Primary targetKey findings	Status
Enlicitide (MK-0616)	oral PCSK9 inhibitor;	↓LDL-C 47–60%	Phase III (CORAL Reef Lipids)
Lepodisiran	siRNA targeting Lp(a)	↓Lp(a) ~94%	Phase III [58]
CRISPR/Cas9 gene editing	durable modification	↓LDL-C/TG ~50%	Phase I/Ia (first-in-human)
Evinacumab, Vupanorsen	ANGPTL3 inhibitors	↓ANGPTL3; ↓LDL-C/TG; evaluated for familial hypercholesterolemia	Phase II/III [52]
Olezarsen	ApoC-III inhibitor	↓ApoC-III; ↓TG; for severe hypertriglyceridemia and FCS;	Phase III (BALANCE) [53]
Obicetrapib	CETP inhibitor	↓CETP; ↓LDL-C 45%, ↑HDL-C 130%	Phase III (BROADWAY) [54]

Abbreviations: ANGPTL3 – angiopoietin-like protein 3; ApoC-III – apolipoprotein C-III; CETP – cholesteryl ester transfer protein; CRISPR/Cas9 – clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9; FCS – familial chylomicronemia syndrome; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; Lp(a) – lipoprotein(a); PCSK9 – proprotein convertase subtilisin/kexin type 9; siRNA – small interfering RNA; TG – triglycerides.

Monitoring the efficacy and safety of ongoing lipid-lowering therapy. Lipid profiles should be reassessed 4-6 weeks after treatment initiation and subsequently every 6-12 months. Biochemical parameters (ALT, AST, CK) are evaluated before starting therapy and thereafter as clinically indicated. If adverse reactions occur, dose adjustment or replacement of the agent is required [56].

Emerging and investigational therapies. Emerging and investigational therapies for dyslipidemia in NS are rapidly evolving, aimed at addressing both the unique pathophysiological mechanisms and the persistent lipid abnormalities seen in this population. Traditional therapies, such as statins, ezetimibe, and fibrates, often provide incomplete lipid control, especially in patients with refractory or severe dyslipidemia. As a result, innovative agents targeting novel pathways are being actively investigated.

Monoclonal antibodies against proprotein convertase subtilisin/kexin type-9 (PCSK9), including alirocumab and evolocumab, and the small interfering RNA (siRNA) inclisiran, have shown significant reductions in LDL-C, and early evidence suggests they are safe and well-tolerated in nephrotic patients, even those intolerant to statins. LDL apheresis continues to be an effective intervention in drug-resistant cases, rapidly improving lipid profiles and offering benefits especially in those with focal segmental glomerulosclerosis (FSGS). Furthermore, antisense oligonucleotides and siRNAs such as pelacarsen, olpasiran, zerlasiran, and lepodisiran are under investigation for the reduction of lipoprotein(a), a particularly atherogenic lipoprotein elevated in NS; pelacarsen and olpasiran are in phase 3 trials with promising early results [53, 57].

The emergence of oral inhibitors such as obicetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, represents another significant advancement. Obicetrapib has demonstrated positive lipid-lowering effects in early and ongoing late-stage trials, with the potential to become a first-in-class oral CETP inhibitor for clinical use. Additional novel targets, including angiopoietin-like protein-3 (inhibited by evinacumab and zodasiran) and apolipoprotein C-III (ARO-APOC3, volanesorsen, olezarsen), are in various phases of clinical testing and hold promise for more comprehensive lipid management in NS [1].

These advances, particularly those leveraging monoclonal antibodies and RNA-targeted therapies, are poised to transform the therapeutic landscape for dyslipidemia in NS by offering individualized and mechanistically targeted approaches [58].

Challenges, gaps, and future directions. The management of dyslipidemia in NS faces considerable challenges, with persistent gaps in understanding and treatment limiting optimal outcomes for many patients. One major challenge is the inconsistent relationship between lipid abnormalities and disease severity, as lipid dysregulation does not always correlate with the degree of proteinuria or serum albumin, leading to difficulties in risk stratification and personalized therapy [12].

Current treatment options, including statins, fibrates, and ezetimibe, are hampered by inconsistent efficacy within the nephrotic population and potential adverse effects, such as nephrotoxicity and rhabdomyolysis. LDL apheresis offers benefits for refractory cases but is limited by accessibility and cost, restricting its broad application. The high relapse rate and steroid resistance observed in adults further compound management difficulties, leaving a significant proportion of patients at risk of cardiovascular complications and progressive kidney disease [4].

Important knowledge gaps remain regarding the long-term impact of chronic dyslipidemia on renal and cardiovascular outcomes, as well as the effects of emerging therapies in specific patient subgroups. There is also limited guidance on integrating novel agents such as PCSK9 inhibitors, CETP inhibitors, and RNA-targeted therapies into existing treatment protocols.

Future directions include elucidating the molecular drivers of dyslipidemia in NS, developing safe and effective therapies tailored to individual risk profiles, and refining monitoring strategies. Greater efforts are needed for collaborative, multi-center trials to establish evidence-based guidelines and identify optimal long-term management pathways. Such advances, together with the integration of novel biomarkers and personalized approaches, hold promise for improving patient outcomes.

Conclusions. Dyslipidemia in NS is a complex metabolic disorder caused by profound dysregulation of key enzymes and lipoprotein receptors, resulting in a highly atherogenic lipid profile. This condition is associated with a substantially increased risk of cardiovascular complications and may contribute to progressive neuronal dysfunction through lipid-mediated nephrotoxicity. Management of nephrotic dyslipidemia should be comprehensive and risk-oriented. In patients with severe or persistent nephrotic dyslipidemia, statin monotherapy is frequently insufficient to achieve recommended lipid targets. In such cases, early treatment intensification is recommended, including the addition of ezetimibe or the use of PCSK9 inhibitors, particularly in patients with refractory hypercholesterolemia or high cardiovascular risk. Effective correction of lipid abnormalities may facilitate remission of the underlying renal disease, reduce proteinuria, and improve long-term renal and cardiovascular outcomes.

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