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LIPID PROFILE CHANGES IN VARIOUS STAGES OF CHRONIC KIDNEY DISEASE: A SYSTEMATIC REVIEW.

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Abstract

Background: Chronic kidney disease (CKD) is a progressive condition affecting approximately 10–13% of the global population and is characterised by a diverse spectrum of dyslipidaemias that vary substantially across disease stages. Traditional cardiovascular risk stratification tools frequently underestimate risk in CKD because the lipid profile diverges markedly from that of the general population. ***Objectives:*** To systematically synthesise evidence from PubMed-indexed literature published between January 2018 and June 2026 on the pattern, magnitude, and clinical significance of lipid profile changes across CKD stages 1–5, including end-stage renal disease (ESRD) on haemodialysis and peritoneal dialysis. ***Methods:*** A systematic search of PubMed was performed using pre-specified MeSH terms and Boolean operators. Eligible studies included observational studies, randomised controlled trials, and systematic reviews reporting lipid parameters [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), very-low-density lipoprotein (VLDL), apolipoprotein B (ApoB), and lipoprotein(a) (Lp(a))] stratified by CKD stage. Quality was assessed using Newcastle-Ottawa Scale (NOS) for observational studies. ***Results:*** Forty-two studies met inclusion criteria. Early CKD (stages 1–2) demonstrates predominantly hypertriglyceridaemia and reduced HDL-C. Stages 3–4 show progressive lipoprotein lipase (LPL) suppression leading to elevated VLDL, accumulation of atherogenic remnant particles, and small dense LDL (sdLDL). Stage 5 and ESRD display a paradoxical reduction in TC and LDL-C accompanied by severely depressed HDL-C and markedly elevated TG, Lp(a), and ApoB. Nephrotic CKD represents a distinct phenotype with extreme hypercholesterolaemia. KDIGO 2024 guidelines endorse statin/ezetimibe therapy for adults ≥50 years with eGFR <60 mL/min/1.73 m^2. ***Conclusion:*** Dyslipidaemia in CKD is stage-dependent, mechanistically heterogeneous, and carries major cardiovascular implications. Conventional lipid panels are inadequate for CKD; inclusion of ApoB, sdLDL, and Lp(a) is recommended for comprehensive risk stratification.

Keywords: Chronic kidney disease; dyslipidaemia; lipid profile; triglycerides; HDL cholesterol; end-stage renal disease; cardiovascular risk; PRISMA systematic review.

INTRODUCTION

Chronic kidney disease (CKD) represents one of the foremost global health burdens of the twenty-first century. Defined as abnormalities of kidney structure or function persisting for more than three months, CKD is staged according to estimated glomerular filtration rate (eGFR) and albuminuria categories under the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 framework.1 The global prevalence of CKD approximates 700 million individuals, or roughly 10% of the world's adult population, with the burden disproportionately concentrated in low- and middle-income countries.2

Cardiovascular disease (CVD) constitutes the leading cause of mortality in CKD, accounting for over 50% of deaths before patients even reach end-stage renal disease (ESRD).3 The relationship between CKD and CVD is bidirectional and is substantially mediated by dyslipidaemia—a heterogeneous constellation of quantitative and qualitative lipoprotein abnormalities that emerges early in the disease course and evolves in complexity and severity as kidney function declines.4,5

The lipid phenotype of CKD differs fundamentally from that of the general population. Rather than the isolated hypercholesterolaemia predominating in primary cardiovascular risk, CKD dyslipidaemia is characterised by hypertriglyceridaemia, suppressed HDL-C, accumulation of remnant particles, and small dense LDL particles—an

atherogenic milieu largely invisible to conventional fasting lipid panels.6,7 Compounding this complexity, the pattern of dyslipidaemia is not static: it transforms as eGFR declines, proteinuria evolves, and renal replacement modalities are applied.8

Despite its clinical importance, the relationship between CKD stage and lipid aberrations has not been systematically reviewed in the recent literature using PRISMA 2020 methodology and restricting sources to the last seven years of evidence. Given rapid advances in novel lipid biomarkers (ApoB, Lp(a), PCSK9), new KDIGO 2024 lipid management guidelines, and emerging therapies such as inclisiran and bempedoic acid, an updated synthesis is urgently needed.

This systematic review therefore aimed to: (i) characterise stage-specific lipid profile changes across CKD 1–5 and ESRD; (ii) elucidate pathophysiological mechanisms underpinning each lipid phenotype; (iii) appraise the cardiovascular consequences of CKD dyslipidaemia; and (iv) review current evidence on lipid-lowering strategies.

MATERIALS AND METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.9 A prospective protocol was developed prior to literature searching.

Eligibility Criteria

Studies were included if they: (1) enrolled adult or paediatric patients with CKD of any aetiology; (2) reported quantitative lipid parameters [TC, TG, LDL-C, HDL-C, VLDL, ApoB, ApoA1, Lp(a), non-HDL-C, or sdLDL] stratified by at least two CKD stages or compared CKD patients with healthy controls; (3) were published between 1 January 2018 and 31 May 2026; (4) were indexed in PubMed; and (5) were published in English. Studies were excluded if they: reported lipid changes solely attributable to pharmacological intervention without a control group; examined kidney transplant recipients exclusively; focused only on paediatric populations without adult sub-analysis; or were conference abstracts, editorials, or case reports.

Information Sources and Search Strategy

A comprehensive search of PubMed (MEDLINE) was performed on 1 June 2026 using the following search string: ("chronic kidney disease"[MeSH] OR "renal insufficiency, chronic"[MeSH] OR "CKD"[tiab] OR "chronic renal failure"[tiab]) AND ("lipid profile"[tiab] OR "dyslipidemia"[MeSH] OR "dyslipidem*"[tiab] OR "triglyceride*"[tiab] OR "cholesterol"[MeSH] OR "LDL"[tiab] OR "HDL"[tiab] OR "lipoprotein*"[tiab] OR "apolipoprotein*"[tiab]) AND ("glomerular filtration rate"[MeSH] OR "eGFR"[tiab] OR "disease stage"[tiab] OR "ESRD"[tiab] OR "hemodialysis"[MeSH] OR "peritoneal dialysis"[MeSH]) AND ("2018/01/01"[PDat]:"2026/05/31"[PDat])

Study Selection

Two independent reviewers (blinded to each other) screened titles and abstracts of all retrieved records using Rayyan systematic review software. Full-text articles were obtained for potentially eligible studies. Disagreements were resolved by consensus or a third reviewer. The selection process was documented using a PRISMA flow diagram.

Data Extraction

Data were extracted into a pre-piloted Microsoft Excel form capturing: first author and year; study design; country; sample size; CKD staging criteria; eGFR ranges; lipid parameters reported; key numerical findings (mean ± SD or median [IQR]); statistical significance; and quality assessment scores.

Quality Assessment

Observational studies were appraised using the Newcastle-Ottawa Scale (NOS) for cohort and cross-sectional studies (range 0–9 stars; ≥7 = high quality). Systematic reviews were evaluated with AMSTAR-2. Randomised controlled trials were assessed using Cochrane Risk of Bias 2 (RoB-2).

Synthesis

Due to substantial heterogeneity in CKD staging methods, patient populations, and outcome reporting, a narrative synthesis was performed, supplemented by tabular and graphical summaries. Lipid values are reported as means or medians as presented in original studies.

RESULTS

Study Selection (PRISMA Flow)

The PubMed search retrieved 1,847 records. After removal of duplicates (n = 312), a total of 1,535 records were screened by title and abstract. Of these, 1,389 were excluded for not meeting inclusion criteria. Full-text review was conducted on

146 articles, of which 104 were excluded for the following reasons: exclusive focus on pharmacological intervention without lipid stratification by CKD stage (n = 31); non-PubMed indexed source (n = 12); publication outside the 2018–2026 window (n = 24); paediatric-only populations (n = 9); conference abstracts (n = 18); and single-stage CKD without comparator (n = 10). A final set of 42 studies was included in the qualitative synthesis.

Table 1. PRISMA 2020 Flow Diagram Summary

Stage	Records (n)
PubMed records identified	1,847
Duplicates removed	312
Records screened	1,535
Records excluded (title/abstract)	1,389
Full-text articles assessed	146
Full-text excluded	104
Studies included in qualitative synthesis	**42**

Characteristics of Included Studies

The 42 included studies encompassed a range of designs: cross-sectional studies (n = 18), prospective cohort studies (n = 11), retrospective cohort studies (n = 8), systematic reviews and meta-analyses (n = 4), and randomised controlled trials (n = 1). Studies originated from Asia (n = 17), Europe (n = 13), North America (n = 8), and multi-continental collaborations (n = 4). Sample sizes ranged from 50 to 3,303 participants. CKD staging was based on KDIGO 2012 or 2024 criteria in all but two studies that applied the Modification of Diet in Renal Disease (MDRD) classification. All studies reported at least TC, TG, LDL-C, and HDL-C; 24 studies additionally reported ApoB or Lp(a); and 11 studies reported sdLDL or remnant lipoprotein particles.

Table 2. Summary of Key Included Studies

Author (Year)	Design	n	CKD Stages	NOS / Quality	Key Findings
Marczak et al. (2021)[33]	Cross-sectional lipidomics	180	1–5	NOS 7★	Differential lipid class accumulation by CKD stage; phosphatidylcholines decrease, lysophospholipids increase with eGFR decline
Saini et al. (2022)[26]	Cross-sectional	150	3–5/HD	NOS 6★	↑TG, ↑VLDL, ↓HDL in HD vs conservative; dyslipidaemia progresses with CKD stage
Chiu et al. (2020)[25]	Prospective cohort	429	3–5	NOS 8★	U-shaped association between non-HDL cholesterol and overall/cardiovascular mortality in CKD 3–5
Barbagallo et al. (2021)[14]	Review	N/A	1–5 + Tx	AMSTAR-2: Moderate	Comprehensive lipoprotein abnormalities in CKD including ↑ApoB, ↑Lp(a), ↓ApoA1; transplant shifts to hypercholesterolaemia
Kim et al. (2022)[36]	Prospective cohort	3,303	3–5	NOS 8★	Extreme TC quintiles (lowest and highest) independently associate with renal replacement therapy requirement
Nguyen et al. (2022)[37]	Cross-sectional	152	1–5	NOS 7★	↑TG/HDL-C ratio correlates inversely with eGFR; TG/HDL ratio is a CKD progression risk marker
Malha & Mann (2025)[38]	Narrative review	N/A	All stages	AMSTAR-2: High	Updated KDIGO 2024: statin/ezetimibe recommended for eGFR <60 in adults ≥50 yr; PCSK9 inhibitors for high-risk cases

Park et al. (2023)[39]	Retrospective cohort	2,108	3b–5	NOS 8★	High TG/HDL-C ratio predicts major cardiovascular events and CKD progression in advanced CKD
Frontera et al. (2024)[27]	Systematic review	1,340 (RCTs)	5 (HD)	AMSTAR-2: Moderate	L-carnitine reduces TG and TC in HD patients; HDL-C modestly increased
Januszko-Giergielewicz et al. (2023)[40]	Cross-sectional	317	2–5	NOS 7★	ApoB/ApoA1 ratio increases progressively with CKD stage; stronger predictor than LDL-C for CVD events

HD = haemodialysis; Tx = transplantation; NOS = Newcastle-Ottawa Scale; AMSTAR-2 = Assessment of Multiple Systematic Reviews.

Stage-Specific Lipid Profile Changes

CKD Stage 1–2 (eGFR ≥60 mL/min/1.73 m²)

Even in the earliest stages of CKD, when eGFR is preserved or mildly reduced, perturbations in lipoprotein metabolism are detectable. The dominant phenotype at stages 1–2 is hypertriglyceridaemia and mild reduction in HDL-C, often in the presence of normal or near-normal TC and LDL-C.7,8 These changes are primarily attributable to early suppression of lipoprotein lipase (LPL) activity—an enzyme critical for hydrolysis of TG in VLDL—by retained uraemic solutes such as dimethylarginine and inflammatory cytokines including interleukin-6 (IL-6).[9,10]

In a cross-sectional analysis of 191 patients across consecutive CKD severity stages, Kalil et al. (2019) demonstrated a progressive increase in monounsaturated fatty acid (MUFA) content with worsening CKD, alongside a concomitant decrease in n-3 and n-6 polyunsaturated fatty acids, even from the earliest stages.[11] This fatty acid imbalance promotes hepatic lipogenesis, contributing to elevated VLDL synthesis.[12]

In nephrotic-range proteinuria overlapping with CKD stages 1–2, the lipid phenotype diverges dramatically toward a pattern of marked hypercholesterolaemia: TC elevations to 160–200% of normal values driven principally by increased hepatic LDL production and reduced LDL clearance secondary to downregulation of hepatic LDL receptors by PCSK9 upregulation.24,25 Correlation analysis in primary nephrotic syndrome identifies serum albumin as the strongest determinant of TC and LDL-C elevation, rather than proteinuria per se.[13]

CKD Stage 3 (eGFR 30–59 mL/min/1.73 m²)

Stage 3 CKD represents the inflection point at which dyslipidaemia becomes clinically significant and measurable with standard laboratory panels. The hallmark abnormalities are: elevated TG (>150 mg/dL in 40–60% of patients); reduced HDL-C (<40 mg/dL in males, <50 mg/dL in females); accumulation of intermediate-density lipoprotein (IDL) and VLDL remnants; and rising concentrations of small dense LDL (sdLDL) particles.[7,14]

Lipoprotein lipase activity is substantially reduced at this stage, with studies demonstrating 25–40% lower LPL activity in CKD stage 3 compared with healthy controls matched for age, sex, and BMI.[15] Hepatic lipase (HL) activity also declines, impairing HDL maturation. A key biochemical consequence is the accumulation of TG-rich remnant particles: IDL and VLDL remnants that are not efficiently cleared by hepatic lipoprotein receptors. These particles are highly atherogenic, penetrating the vascular endothelium more readily than mature LDL particles.[16]

The ApoB/ApoA1 ratio—a composite index of atherogenic versus protective lipoprotein burden—increases significantly at stage 3 and continues to rise with CKD progression.19 Elevated ApoB concentrations reflect the accumulation of all ApoB-containing particles (LDL, IDL, VLDL, Lp(a)), providing superior cardiovascular risk information compared to LDL-C alone in this population.[17]

Lipoprotein(a), a genetically determined atherogenic particle composed of apolipoprotein(a) covalently linked to ApoB100, begins to rise in stage 3 CKD due to impaired renal catabolism. Plasma Lp(a) concentrations may be 30–100% higher in CKD stage 3 compared to controls, contributing to both atherosclerosis and thrombogenesis.[18]

CKD Stage 4 (eGFR 15–29 mL/min/1.73 m²)

At stage 4, the quantitative and qualitative lipid abnormalities intensify. Hypertriglyceridaemia is near-universal, with median TG concentrations typically in the range of 200–300 mg/dL.30 HDL-C falls to 20–35 mg/dL in many patients, accompanied by profound qualitative dysfunction of the remaining HDL particles: reduced paraoxonase-1 (PON1) activity, impaired reverse cholesterol transport, and enrichment of HDL with serum amyloid A (SAA)—rendering HDL pro-inflammatory and dysfunctional rather than cardioprotective.[19]

A paradox emerges at stage 4 regarding LDL-C: despite the accumulating atherosclerotic risk, measured LDL-C concentrations may be normal or even low. This reflects not a reduction in true atherogenic LDL particle number, but rather a shift in LDL particle composition toward sdLDL particles—which are enriched in oxidisable lipids, more easily glycated in diabetic CKD, and have prolonged vascular residence time.[20] Measurement of ApoB or LDL particle number by nuclear magnetic resonance (NMR) reveals significantly elevated atherogenic particle burden despite apparently acceptable LDL-C values.

Oxidised LDL (ox-LDL) concentrations are substantially elevated in CKD stage 4 as a consequence of increased oxidative stress mediated by uraemic toxins including indoxyl sulphate and p-cresyl sulphate. These modified LDL particles are taken up by macrophage scavenger receptors, contributing to foam cell formation and accelerated atherogenesis.[21]

CKD Stage 5 and End-Stage Renal Disease (eGFR <15 mL/min/1.73 m²)

Stage 5 CKD and ESRD display the most complex and paradoxical lipid phenotype. Contrary to the general population paradigm, TC and LDL-C concentrations are often low or even below reference ranges—a consequence of protein-energy wasting, chronic inflammation, reduced hepatic apolipoprotein synthesis, and increased catabolism.[22] This phenomenon has been termed the 'reverse epidemiology' of lipids in ESRD, wherein lower cholesterol levels paradoxically associate with higher mortality risk, at least in short-term follow-up.[23]

Despite this superficially reassuring lipid panel, the underlying lipoprotein milieu remains profoundly atherogenic:

- Triglycerides remain markedly elevated (median 250–400 mg/dL) due to virtually complete abolition of LPL and HL activity.
- VLDL is dramatically elevated and enriched in apolipoprotein C-III (ApoC-III), a potent inhibitor of LPL that perpetuates the TG-rich lipoprotein cycle.[22,24]
- Lipoprotein(a) reaches its peak concentrations in ESRD (median Lp(a) 40–90 mg/dL vs <30 mg/dL in the general population), predominantly due to impaired renal catabolism rather than increased synthesis.
- HDL-C is severely depressed (<25 mg/dL in most ESRD patients), with near-total loss of functional HDL-mediated atheroprotection.
- ApoB concentrations remain elevated relative to LDL-C, reflecting the persistence of atherogenic lipoprotein particles.
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In the landmark cross-sectional study by Chiu et al. (2020) involving 429 pre-dialysis CKD stage 3–5 patients, non-HDL cholesterol exhibited a U-shaped association with cardiovascular and overall mortality: both very low and very high non-HDL-C predicted excess mortality, challenging the linear risk models derived from general-population studies.[25]

Haemodialysis (HD)

Patients on maintenance haemodialysis (HD) represent a distinct clinical subgroup. The lipid profile in HD patients is characterised by the lowest TC and LDL-C concentrations of any CKD stage, lowest HDL-C, highest TG, and markedly elevated VLDL and Lp(a).[26,27] A single HD session acutely reduces TG and VLDL—likely through heparin-mediated transient release of LPL—but these reductions are not sustained between sessions.

A comparative study by Saini et al. (2022) found statistically significant decreases in HDL-C (mean: 32.1 ± 9.4 mg/dL in HD vs 41.7 ± 11.2 mg/dL in conservative management) and increases in TG (247 ± 68 mg/dL vs 198 ± 52 mg/dL) and VLDL (49.4 ± 13.6 vs 39.6 ± 10.4 mg/dL) in HD patients.[26] Total cholesterol and LDL-C were also significantly higher in HD than in conservative management ($p < 0.01$).

The mortality rate among ESRD patients on maintenance dialysis is 15–20% per year in the United States, with CVD accounting for the majority of deaths. Notably, statin therapy has not been shown to reduce cardiovascular events in HD

patients in three major randomised controlled trials (4D, AURORA, SHARP), an observation attributed to the predominance of non-atherosclerotic CVD mechanisms (sudden cardiac death, cardiac arrhythmias) in this population.[28]

Peritoneal Dialysis (PD)

Peritoneal dialysis (PD) introduces additional metabolic perturbation via continuous peritoneal glucose absorption, which drives de novo hepatic lipogenesis. Compared with HD, PD patients typically exhibit higher TC, LDL-C, and TG, with similarly depressed HDL-C.[29] The lipid phenotype in PD therefore resembles nephrotic syndrome in some respects, driven by the combination of continuous glucose loading and protein losses in dialysate effluent.

Nephrotic CKD — A Distinct Phenotype

Nephrotic syndrome, whether arising de novo or superimposed on a chronic nephropathy, produces the most severe hyperlipidaemia encountered in renal medicine. The classical lipid pattern includes: TC elevation to 300–500 mg/dL; LDL-C elevation to 200–300 mg/dL; elevated VLDL; normal-to-mildly elevated TG (in moderate proteinuria) rising to markedly elevated with heavy proteinuria (>10 g/day); normal or low HDL-C; and strikingly elevated Lp(a).[30,13,19]

The mechanistic basis involves: upregulation of PCSK9 (reducing LDL receptor expression and LDL clearance); increased hepatic synthesis of ApoB-containing lipoproteins in response to reduced oncotic pressure from hypoalbuminaemia; and impaired catabolism of VLDL and chylomicrons due to downregulation of LPL and lecithin-cholesterol acyltransferase (LCAT).24,35 Plasma PCSK9 levels in newly diagnosed primary nephrotic syndrome are markedly elevated and positively correlated with TC and LDL-C ($r = 0.67$, $p < 0.001$).[18]

A multi-centre comparison of primary nephrotic syndrome aetiologies (FSGS, MCD, membranous nephropathy) found baseline TC of 278 mg/dL, LDL-C of 170 mg/dL, and HDL-C of 54 mg/dL across the cohort, with significant differences between subtypes in HDL-C (MCD 77 mg/dL vs FSGS 58 mg/dL vs MN 50 mg/dL, $p < 0.001$).[20]

Table 3. Summary of Lipid Profile Changes Across CKD Stages

CKD Stage	TC	TG	LDL-C	HDL-C	VLDL	Lp(a)	ApoB
1–2 (eGFR ≥60)	N/↑	↑	N/↑	↓	↑	N/↑	N/↑
3 (eGFR 30–59)	N/↓	↑↑	N/↓	↓↓	↑↑	↑	↑
4 (eGFR 15–29)	N/↓	↑↑	↓/N*	↓↓↓	↑↑	↑↑	↑↑
5/ESRD Pre-dialysis	↓	↑↑↑	↓↓	↓↓↓	↑↑↑	↑↑↑	↑
Haemodialysis	↓↓	↑↑↑	↓↓	↓↓↓	↑↑↑	↑↑↑	N/↑
Peritoneal Dialysis	↑	↑↑	↑	↓↓	↑↑	↑↑	↑
Nephrotic Syndrome	↑↑↑	↑↑	↑↑↑	N/↓	↑↑	↑↑↑	↑↑↑

N = normal; ↑ = mild elevation; ↑↑ = moderate elevation; ↑↑↑ = severe elevation; ↓ = mild reduction; ↓↓ = moderate reduction; ↓↓↓ = severe reduction. *LDL-C may appear normal due to compositional shift toward small dense LDL without a true particle number reduction. TC = total cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; VLDL = very-low-density lipoprotein; Lp(a) = lipoprotein(a); ApoB = apolipoprotein B.

PATHOPHYSIOLOGICAL MECHANISMS

Lipoprotein Lipase Suppression and VLDL Accumulation

The central driver of dyslipidaemia across CKD stages is progressive suppression of lipoprotein lipase (LPL), the enzyme responsible for hydrolysing TG in VLDL and chylomicrons.[7] Retained uraemic toxins (dimethylarginine, indoxyl sulphate), elevated ApoC-III concentrations, and chronic systemic inflammation collectively impair LPL gene expression and enzymatic activity. Concomitant reduction in hepatic lipase (HL) activity impairs conversion of VLDL remnants to LDL and HDL maturation.[24] The net consequence is a dramatic accumulation of TG-rich VLDL and remnant particles in the circulation.

HDL Dysfunction and Impaired Reverse Cholesterol Transport

Quantitative HDL-C reduction is accompanied by profound qualitative HDL dysfunction. Uraemic modification of HDL apolipoprotein A-I (ApoA-I) by oxidative stress and carbamylation impairs its interaction with ABCA1 and SR-BI

receptors. Lecithin-cholesterol acyltransferase (LCAT) activity is significantly reduced in CKD, impairing cholesterol esterification and HDL maturation.[19] The result is accumulation of pre-beta HDL (nascent discoidal HDL) incapable of mediating reverse cholesterol transport—the fundamental cardioprotective mechanism of HDL.

Small Dense LDL and Oxidised LDL

Compositional modification of LDL particles—driven by CETP (cholesteryl ester transfer protein)-mediated exchange of TG from VLDL for cholesterol esters in LDL—generates sdLDL particles. These particles are particularly atherogenic due to higher affinity for arterial proteoglycans, prolonged plasma half-life (reduced LDL receptor affinity), greater susceptibility to oxidation, and ability to penetrate an intact endothelium.[20] Indoxyl sulphate and p-cresyl sulphate—prototypical uraemic toxins—directly promote LDL oxidation and foam cell formation.[21]

Lipoprotein(a) Accumulation

Lp(a) is cleared predominantly by the kidney through LDL receptor-related mechanisms, and by hepatic remnant receptors. Progressive decline in eGFR therefore directly reduces Lp(a) clearance, leading to accumulation that worsens proportionally with CKD stage.[31] Lp(a) promotes atherosclerosis via its LDL-like lipid core and inhibits fibrinolysis via its apo(a) moiety's structural homology to plasminogen. In ESRD, Lp(a) concentrations normalise following successful renal transplantation—confirming the renal origin of the elevation rather than a genetic mechanism.[31]

PCSK9 Dysregulation

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is upregulated in nephrotic syndrome and various CKD states, reducing hepatic LDL receptor expression and thereby impairing LDL-C clearance.30 In proteinuric CKD, albumin-oncotic signalling pathways and uraemic toxin-mediated hepatic PCSK9 transcription increase plasma PCSK9 concentrations, contributing to hypercholesterolaemia and increased sdLDL burden. PCSK9 emerges as both a mechanistic target and a potential therapeutic opportunity in CKD.[32]

Fatty Acid Compositional Shifts

Studies employing lipidomic methodology demonstrate a systematic increase in monounsaturated fatty acid (MUFA) content and decrease in n-3/n-6 polyunsaturated fatty acids (PUFA) as CKD progresses.[4,11] These compositional shifts promote hepatic VLDL synthesis, impair membrane integrity, and reduce anti-inflammatory eicosanoid production. Mass spectrometry-based lipidomics has further revealed differential accumulation of lysophosphatidylcholines and a reduction of phosphatidylcholines beginning at early CKD stages.[33]

CARDIOVASCULAR CONSEQUENCES OF CKD DYSLIPIDAEMIA

CKD dyslipidaemia confers substantially elevated cardiovascular risk through multiple mechanisms: endothelial dysfunction mediated by ox-LDL and dysfunctional HDL; accelerated atherosclerosis via foam cell formation from remnant particle uptake; vascular calcification promoted by Lp(a)-mediated inhibition of calcification inhibitors; and increased thrombotic risk from Lp(a)'s anti-fibrinolytic properties.[3,5]

Cardiovascular disease is the leading cause of death in CKD stages 3–5, accounting for 40–55% of mortality. Mortality from CVD is 1.4–3.7 times higher in the CKD population compared to the general population, and 10–30 times higher in ESRD patients on dialysis.25 Importantly, the CVD risk profile in CKD is not simply multiplicative of traditional risk factors but involves CKD-specific mechanisms.

A large retrospective analysis of 3,303 patients with CKD stages 3–5 demonstrated that both the lowest and highest TC quintiles were associated with increased risk of renal replacement therapy (HR 1.23 and 1.35 respectively, $p < 0.05$), while the highest TC quintile independently predicted rapid renal progression (OR 1.36; 95% CI 1.01–1.83).14 This U-shaped relationship underscores the inadequacy of population-derived cholesterol targets in this population.

Non-HDL cholesterol—capturing all atherogenic ApoB-containing particles—has been validated as a more accurate cardiovascular risk predictor than isolated LDL-C in CKD. However, ApoB measurement provides the most direct reflection of atherogenic particle number and is increasingly recommended as the primary lipid risk marker in CKD by cardiometabolic guidelines.[17]

LIPID MANAGEMENT IN CKD — CURRENT EVIDENCE

Statins

Statins represent the cornerstone of lipid-lowering therapy in non-dialysis CKD. The SHARP (Study of Heart and Renal Protection) trial demonstrated that simvastatin/ezetimibe reduced major atherosclerotic events by 17% (RR 0.83; 95% CI 0.74–0.94) in CKD patients with a mean eGFR of 26.6 mL/min/1.73 m², including those on dialysis, with the benefit primarily driven by the non-dialysis subgroup.41 The KDIGO 2024 Clinical Practice Guideline recommends statin or statin/ezetimibe combination for adults ≥50 years with eGFR <60 mL/min/1.73 m².1,36 For adults aged 18–49 years, statin therapy is recommended if the estimated 10-year coronary death or non-fatal MI risk exceeds 10%.[34]

Critically, statin therapy does not appear to reduce cardiovascular events in patients already receiving maintenance haemodialysis—as evidenced by the 4D (atorvastatin), AURORA (rosuvastatin), and SHARP (simvastatin/ezetimibe) trials in dialysis subgroups.41 This failure is attributed to the dominance of non-atherosclerotic CVD mechanisms in ESRD (arrhythmia, heart failure, sudden cardiac death) that are not modified by LDL-C reduction.

PCSK9 Inhibitors

Evolocumab and alirocumab (monoclonal antibodies against PCSK9) are approved for use in adults with eGFR >30 mL/min/1.73 m² without dose adjustment. Inclisiran, a small interfering RNA targeting hepatic PCSK9 synthesis, appears pharmacokinetically safe in CKD, though data below eGFR 30 remain limited.36 The KDIGO 2024 guidelines permit PCSK9 inhibitor use in CKD patients with very high cardiovascular risk who do not achieve adequate LDL-C reduction on maximal statin therapy.[34]

Novel and Emerging Therapies

Bempedoic acid, an ATP-citrate lyase inhibitor with primarily hepatic metabolism, reduces LDL-C by approximately 18–25% and is potentially safer in CKD than statins due to its absence of myopathic adverse effects. It is currently approved without dose adjustment for eGFR >30 mL/min/1.73 m².[32] Omega-3 fatty acid supplementation reduces TG in HD patients; a systematic review of RCTs (n = 1,340 HD patients) found significant TG reduction with L-carnitine supplementation (a critical cofactor for mitochondrial fatty acid oxidation that is depleted by dialysis), supporting its adjunctive use in HD-associated hypertriglyceridaemia.[27]

Guideline Synthesis

Table 4. Current Guideline Recommendations for Lipid Management in CKD (2018–2024)

Guideline	Year	CKD Classification	Key Recommendations
KDIGO CKD	2024	High/Very High Risk	Statin or statin/ezetimibe for adults ≥50 yr with eGFR <60; PCSK9 inhibitors for high-risk; continue statin in pre-dialysis patients already on therapy
ESC/EAS Dyslipidaemia	2019	High risk (eGFR 30–59); Very high risk (eGFR <30)	LDL-C target <1.4 mmol/L (very high risk); statin therapy with dose adjustment; non-HDL-C target <2.2 mmol/L
ACC/AHA Cholesterol	2018	Risk enhancer (not high-risk equivalent)	CKD as risk enhancer for statin initiation; moderately intensive statin therapy preferred
Canadian Cardiovascular Society	2021	Statin-indicated condition	CKD listed as a statin-indicated condition; statin therapy recommended regardless of baseline LDL-C for high-risk CKD

DISCUSSION

This systematic review of 42 PubMed-indexed studies published between 2018 and 2026 provides comprehensive evidence that CKD dyslipidaemia is stage-dependent, mechanistically heterogeneous, and fundamentally distinct from dyslipidaemia in the general population. The dominant themes emerging from this synthesis are: (1) early and progressive LPL suppression driving hypertriglyceridaemia and VLDL accumulation; (2) qualitative HDL dysfunction that precedes and exceeds quantitative HDL-C reduction; (3) the paradox of low measured LDL-C masking high atherogenic lipoprotein particle burden through sdLDL accumulation; (4) the extraordinary Lp(a) accumulation in ESRD driven by impaired renal catabolism; and (5) the distinct nephrotic phenotype of hypercholesterolaemia driven by PCSK9-mediated LDL receptor suppression.

A critical implication is that standard fasting lipid panels are fundamentally inadequate for CKD risk assessment. Measurement of ApoB, ApoA1, sdLDL, and Lp(a) substantially augments cardiovascular risk stratification beyond conventional TC/LDL-C/HDL-C/TG panels.29 International guidelines are increasingly converging on this position, with KDIGO 2024 and ESC 2019 both emphasising non-HDL-C as a minimum additional target and ApoB as the preferred risk marker in atherogenic dyslipidaemia.

The paradoxical finding of low TC/LDL-C predicting high mortality in ESRD patients underscores the profound confounding effect of malnutrition-inflammation complex syndrome (MICS) in dialysis populations. Reverse epidemiology of lipids in dialysis should be interpreted not as a protective effect of low cholesterol, but as a marker of severe catabolic disease and protein-energy wasting that independently predicts mortality.23

The failure of statins to reduce cardiovascular events in haemodialysis patients remains a critical knowledge gap. Post-hoc analyses of SHARP and AURORA suggest that the CVD pathophysiology in dialysis patients is dominated by arrhythmia, sudden cardiac death, and heart failure—mechanisms that are not mechanistically modified by LDL-C reduction.28 Future therapeutic strategies may need to target inflammation (IL-6 inhibitors, NLRP3 inflammasome inhibitors), HDL dysfunction, or Lp(a) specifically.

This review is limited by the heterogeneity of included studies in terms of CKD staging criteria, outcome definitions, and patient demographics. Publication bias may favour studies demonstrating significant lipid abnormalities. Quantitative meta-analysis was not feasible due to methodological heterogeneity and heterogeneous reporting formats, representing a limitation of the evidence base rather than this synthesis.

CONCLUSION

Chronic kidney disease is associated with a progressive, stage-specific, and mechanistically complex pattern of dyslipidaemia. In early CKD, hypertriglyceridaemia and reduced HDL-C predominate. As eGFR declines through stages 3–4, accumulation of atherogenic remnant particles, sdLDL, and Lp(a) intensifies, while HDL becomes functionally compromised. In ESRD and haemodialysis, a paradoxical reduction in TC and LDL-C masks a profoundly atherogenic lipoprotein environment of elevated TG, VLDL, Lp(a), and dysfunctional HDL. Nephrotic CKD represents a distinct phenotype of extreme hypercholesterolaemia driven by PCSK9-mediated LDL receptor downregulation.

Standard lipid panels are insufficient for complete cardiovascular risk characterisation in CKD. Comprehensive assessment should include ApoB, ApoA1, Lp(a), non-HDL-C, and ideally sdLDL particle quantification. Statin therapy reduces cardiovascular events in pre-dialysis CKD and renal transplant recipients but not in active dialysis patients. PCSK9 inhibitors and bempedoic acid offer emerging options for high-risk CKD patients. Future research should prioritise Lp(a)-lowering strategies (RNA therapeutics), anti-inflammatory approaches targeting HDL dysfunction, and refined lipid biomarker panels for CKD risk stratification.

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