Review Article

Current perspectives on lipid management in diabetic kidney disease: Can fibrates offer advantages over statins for renal outcomes?

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Diabetic kidney disease (DKD) affects 30%–40% of patients with diabetes mellitus (DM). Dyslipidemia is a key modifiable risk factor for the development and progression of DKD. Statins remain the mainstay of lipid management in DM, but concerns exist about their renal effects and limited impact on high-density lipoprotein (HDL) and triglycerides. Fibrates, which primarily target HDL elevation and triglyceride reduction, have shown promise in addressing the lipid profile most relevant to DKD; however, they initially raise serum creatinine levels. This review aims to compare the effects of statins and fibrates on the development and progression of DKD, examining their mechanisms of action, clinical evidence, and limitations of current research. A comprehensive search of PubMed, Scopus, and Web of Science identified clinical studies published from 2000 onward, evaluating the renal effects of statins and/or fibrates in patients with DM, focusing on kidney function, damage markers, and disease progression. According to our findings, statins offer modest, short-term kidney protection; however, their long-term renal effects, and their limited impact on the specific dyslipidemia pattern associated with DKD, are a concern. Fibrates, which more effectively target triglycerides and HDL, show promise in preserving kidney function, though their use may be limited in advanced kidney disease. While some evidence suggests fibrates may be superior, especially in patients with low HDL and high triglycerides, more long-term studies are needed to confirm their definitive advantage over statins. Future research should focus on long-term studies with comprehensive assessments of kidney function.

Key words: Diabetes mellitus, diabetic kidney disease, diabetic nephropathies, dyslipidemia, fibrates, statins

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INTRODUCTION

Diabetes mellitus (DM) is a major global health challenge,[1] affecting 285 million people in 2010 and projected to reach 552 million by 2030. By 2040, one in ten adults will likely have DM, increasing mortality and morbidity due to micro- and macrovascular complications.[2] Diabetic kidney disease (DKD), a common microvascular complication, affects 20%–40% of DM patients and can lead to end-stage renal disease (ESRD),[3,4] raising cardiovascular disease (CVD) risk and being a primary cause of cardiovascular mortality in DM.[5] Despite treatments like strict glycemic control and blood pressure management, DKD remains prevalent, especially in DM patients with dyslipidemia.[6,7]

Dyslipidemia significantly contributes to DKD, and its molecular mechanisms of kidney damage have been extensively studied.[8] Dyslipidemia is common in DM, especially in type 2 DM (T2DM), exhibiting a distinct pattern compared to non-DM patients.[9] Therefore, effectively managing dyslipidemia in patients with DM can significantly reduce their risk of developing DKD.[10]

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Fibrates and statins are the two main medication classes used to treat dyslipidemia.[11] Statins have demonstrated remarkable efficacy in reducing CVD risk in patients with DM, establishing them as a cornerstone and first-line medical treatment for dyslipidemia management in this population.[12] In addition to their cardiovascular benefits, statins have indicated renoprotective effects, mitigating the development and progression of DKD.[13-15] This dual benefit has led to the hypothesis that statin therapy may offer comprehensive protection against the detrimental renal effects of dyslipidemia in patients with DM. However, it remains unclear whether statins are the optimal pharmacological treatment for dyslipidemia in patients with DM to prevent and manage DKD. Moreover, recent evidence has raised concerns that long-term statin therapy may have detrimental effects on DKD.[16-21] Conversely, while fibrates have shown promising effects in lipid regulation, their use in patients with DKD and chronic kidney disease (CKD) is limited due to concerns over efficacy and possible serum creatinine elevation.[22] Given these uncertainties, the present study aims to review and compare the renal outcomes of statin and fibrate treatment in individuals with DM, and their impact on the development and progression of DKD. This analysis draws upon mechanistic insights and preclinical and clinical evidence.

METHODS

Search strategy

To inform this narrative review, a comprehensive literature search was conducted in PubMed, Scopus, and Web of Science databases to identify studies published since 2000 that examined the renal effects of statins and/or fibrates on patients or animal models with DM. The search was limited to publications in English, type, or species.

We employed a systematic search strategy to identify relevant studies utilizing Medical Subject Headings (MeSH) and keyword combinations across titles and abstracts. The specific search terms and queries are detailed in Supplementary Table 1. All the terms and queries were strategically combined to locate the relevant studies.

Study selection and data extraction

For the section "Statins and Fibrates in DM: Renal Outcomes and DKD – Clinical Evidence and Controversies," we aimed to review the clinical studies (observational or interventional) that examined the renal effects of fibrates and/or statins in patients with DM. Renal outcomes were assessed using a variety of indicators, including measures of kidney function like blood urea nitrogen (BUN) or urea, serum creatinine, cystatin C, and GFR, markers of kidney damage like micro-albuminuria, proteinuria, urinary albumin to creatinine ratio, and clinical events such as acute kidney injury (AKI), DN or DKD, CKD, end-stage kidney disease (ESKD), and the need for dialysis. The discussion sections of these studies and relevant review articles were investigated to identify additional pertinent literature. To provide a comprehensive overview of the pathophysiology and mechanisms involved (not the outcome), we investigated both animal studies and review articles to evaluate the interaction of statins and fibrates with the pathophysiology of DKD.

Lipid abnormalities in diabetes mellitus, and related modifiable risk factors of diabetic kidney disease

Lipid abnormalities in diabetes mellitus

DM is a chronic, systemic disease involving complex interactions across multiple physiological systems, from the gut microbiome to lipid metabolism.[23-25] Dyslipidemia is characterized by high levels of triglycerides (TG), low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol, along with low levels of high-density lipoprotein (HDL) cholesterol. In patients with DM, dyslipidemia typically appears in a mixed pattern.[24,26] Additionally, patients with DM often exhibit a range of lipid abnormalities, such as smaller and denser LDL and HDL particles, elevated TG content in VLDL and intermediate-density lipoproteins (IDL), and oxidized LDL and free fatty acids (FFA).[27-29]

Lipids' exact role in DKD is unclear. However, they may contribute through increased insulin resistance, lipotoxicity, inflammation, oxidative stress, podocyte and endothelial dysfunction, and mesangial cell proliferation, leading to kidney scarring and fibrosis.[30-33] Emerging evidence suggests that HDL and TG levels are more strongly associated with DKD than LDL. Thus, managing HDL and TG may be more important than LDL for DKD prevention and progression.[34]

It has been observed that patients with DM tend to have higher albumin-to-creatinine ratios (ACR) and lower estimated glomerular filtration rate (eGFR) when their levels of apolipoprotein B (apoB), VLDL, IDL, and FFA are elevated, along with abnormal HDL and TG levels.[35] This finding is also evident when the LDL and HDL particles are smaller and denser and VLDL and IDL TG contents are higher.[36]

In conclusion, lipid abnormalities, particularly in HDL and TG, seem to worsen DKD-related metabolic imbalances, accelerating kidney decline. Therefore, lipid management, particularly focusing on TG and HDL, appears to be critical for improving renal outcomes in patients with DM.

Other modifiable risk factors of diabetic kidney disease interacted with lipid abnormalities

DM is characterized by hyperglycemia, the primary cause of its complications, including DKD. While some studies suggest hyperglycemia's role in DKD progression may weaken in advanced DM, large observational studies still highlight it as a key predictor of progressive kidney disease. Dyslipidemia and hyperglycemia often co-occur, and their relationship is two-sided.[37] Thus, treatments for dyslipidemia may indirectly affect DKD by improving hyperglycemia.

In addition to hyperglycemia, clinical studies have shown that insulin resistance is an independent risk factor for DKD.[38] Among patients with T2DM, those with albuminuria have lower glucose disposal rates than those without albuminuria. In addition, a strong association exists between baseline hyperinsulinemia in patients with T2DM and normoalbuminuria and the development of albuminuria after 5 years.[37] Studies have shown that certain factors, such as dyslipidemia, are closely linked to insulin resistance.[39] Therefore, treatments for dyslipidemia may indirectly affect DKD by affecting insulin resistance.

In conclusion, although hyperglycemia is the primary contributor to DKD, dyslipidemia, secondary hyperglycemia, and insulin resistance are also contributors. Therefore, managing dyslipidemia may improve DKD outcomes by improving hyperglycemia and insulin sensitivity, and combining dyslipidemia treatment with glycemic control may optimize DKD risk reduction.

Statins versus fibrates in managing the risk factors of diabetic kidney disease

Abnormalities in lipids

Statins are primarily used to lower LDL levels and reduce the risk of CVD in patients with DM. Meanwhile, fibrates primarily improve TG and HDL levels.[11]

Statins inhibit HMG-CoA reductase, blocking cholesterol synthesis in the liver, increasing LDL uptake, positively regulating LDL receptors. However, they have limited effects on hypertriglyceridemia and HDL levels, as they primarily target LDL. Since statins minimally improve HDL or TG, key risk factors for DKD, their impact on DKD via dyslipidemia modification may be minimal.[40-43]

Fibrates primarily work by activating proliferator-activated receptor (PPAR), which enhances lipoprotein lipolysis, hepatic fatty acid uptake, and HDL production while reducing hepatic TG and VLDL secretion. This mechanism boosts VLDL clearance, lowers plasma TG-rich lipoproteins, and increases HDL levels. Unlike statins, fibrates promote LDL particle removal and reduce VLDL production by stimulating fatty acid breakdown.[44,45] As mentioned, TG, VLDL, and HDL exert key roles in the development and advancement of DKD.

Although studies have demonstrated that fibrates have a modest effect on overall LDL levels, they significantly impact small-dense LDL (sdLDL), which is crucial in diabetic nephropathy (DN). Fibrate's mechanism of action on sdLDL is mediated by the drug's effect on TG. Their effect on reducing sdLDL is comparable to statins.[36,46]

Both statins and fibrates can reduce serum VLDL levels, with fibrates having a slightly more significant effect. Fibrates have also been shown to impact VLDL TG content and VLDL TG significantly: apoB ratio more than statins by approximately 14% and 30%, respectively.[47] No studies have directly compared the effects of fibrates and statins on oxidized LDL and FFA. However, both classes of drugs appear to have a beneficial effect on these parameters.[45,48]

Considering these mechanisms, fibrates may have beneficial renoprotective effects over statins in patients with DM. This is due to fibrates' favorable effect on HDL, TG levels, sdLDL, VLDL levels, and VLDL TG content, which are crucial risk factors for DKD.

Other risk factors associated with diabetic kidney disease

Statins can impair insulin response and secretion, raise blood glucose levels, increase insulin resistance, and elevate T2DM risk.[49-52] Long-term statin use may worsen DM progression, leading to earlier exogenous insulin dependence, hyperglycemia, and its complications.[16] While generally safe, statins are linked to higher new-onset T2DM risk with prolonged use.[53]

In contrast, fibrates have shown promising effects in improving insulin sensitivity and protecting DM by reducing tissue fat, pancreatic stress, and inflammation.[44,45] As previously discussed, since insulin resistance and hyperglycemia are linked to lipid abnormalities, particularly high TG and low HDL, fibrates may be especially beneficial in DKD. Furthermore, elevated TG is a key lipid change in diabetes, and the TG/HDL ratio strongly predicts insulin resistance, albuminuria, and declining GFR.[54-56] Fibrates effectively lower this ratio,[57] offering potential advantages over statins in DKD patients with insulin resistance and dyslipidemia.

Statins and fibrates in diabetes mellitus: renal outcomes and diabetic kidney disease – Clinical evidence and controversies

Statins

Short-term benefits of statin therapy (up to 5 years)

Statins represent the first-line pharmacological treatment for lipid management in patients with DM, primarily due to

their established cardiovascular risk reduction.[12] Statins are also theorized to protect patients with DM and dyslipidemia from dyslipidemia-induced kidney damage.[58] However, the impact of statin use, particularly long-term use, on the development and progression of DKD remains a subject of ongoing debate.

Several meta-analyses have evaluated the renal effects of statins in DKD. Shen *et al*.(2016) analyzed 14 randomized controlled trials (RCTs) and found statins significantly reduced albuminuria and urinary albumin excretion (UAE) compared to placebo in patients with DKD. However, no significant effects were observed on eGFR, serum creatinine, or blood urea nitrogen levels. Most studies had follow-ups of less than 12 months.[15] Qin *et al*.(2017) obtained similar results by investigating trials with a follow-up period of 3–12 months.[14] Lv *et al*.(2021) investigated 9 RCTs and demonstrated that statins significantly increased eGFR and reduced serum creatinine in DKD patients compared to controls. Seven studies had follow-ups ≤ 6 months, with only one extending to 3.9 years.[13]

These findings primarily reflect short-term outcomes and cannot definitively establish statins' long-term effects on DKD incidence or progression. The variation in results suggests that statin effects may depend significantly on intervention duration.

Limitations of current clinical evidence

Large trials with follow-up periods of around 5 years have shown positive, albeit modest, effects of statins compared to placebo on eGFR in diabetic populations, with some studies reporting reduced incidence of CKD and kidney failure.[59-64] However, these studies have important limitations:

1. Assessment criteria: Many studies rely solely on creatinine-based eGFR.[59-64] Current guidelines recommend considering multiple markers, including albuminuria and cystatin C-estimated GFR, for comprehensive kidney function assessment, particularly in patients with DM.[65] Analyzing the comparative incidence of CKD and ESKD, alongside systematic evaluation of kidney disease stage progression, creates a crucial link between laboratory findings and clinical outcomes, enhancing translational understanding of the disease process[64]
2. Albuminuria findings: Albuminuria, the most sensitive marker for kidney dysfunction and the hallmark of early DKD, may not improve with statin therapy.[60,66] GFR decline and albuminuria can develop independently in DKD, each reflecting distinct pathophysiological mechanisms and risk factor profiles. Notably, albuminuria without reduced GFR may be the earliest clinical manifestation of glomerular damage.[67] In the CARDS trial (3.9-year follow-up), despite modest eGFR benefits, atorvastatin did not significantly prevent albuminuria or promote regression to normoalbuminuria. Albuminuria can also predict adverse cardiovascular outcomes independently from eGFR in patients with DM[60]
3. Comparison standards: Studies typically compare statins against placebo or no treatment rather than against other effective lipid-lowering interventions.[59-64] The observed modest renoprotective effects may reflect the benefit of treating dyslipidemia versus leaving it untreated
4. Confounding factors: Cardiovascular complications associated with poor lipid management in placebo groups may contribute to GFR decline, potentially exaggerating statins' apparent renoprotective effects[68]
5. Patient selection: Studies often randomize and clinically manage patients based on LDL levels alone without considering other lipid parameters like HDL and TG.[59-64] Furthermore, study populations and interventions may not be representative of real-world practice[69]
6. Follow-up duration: The progressive nature of DKD and long-term and life-long use of anti-dyslipidemic medications may require observation periods beyond typical 5-year clinical trials. Trials examining the long-term effects of statin therapy on DKD were predominantly conducted several years ago.[59-64] Advanced care has resulted in longer durations of statin treatment exposure.[70] These shorter timeframes likely miss important long-term renal outcomes, potential benefits and adverse effects, that may develop over decades of treatment
7. Variations based on patient characteristics, statin type, and dose: Treatment efficacy may vary among patients with different degrees of renal impairment, necessitating individualized therapeutic approaches based on kidney function, an area that remains understudied.[60,61,64,71] Moreover, whether specific statin types offer superior benefits in slowing kidney function decline and reducing proteinuria has not been conclusively established. Additionally, different statins and their respective dosages may exhibit varying renal effects.[72-74]

Concerns about long-term statin use

Evidence raising concerns about long-term statin use comes from several sources:

1. Animal studies: Huang *et al*. demonstrated potential renal damage from long-term statin use in a diabetic mouse model (40-week follow-up). This study found that long-term statin use worsens insulin resistance, promotes renal ectopic fat deposition in kidneys, and impairs kidney function in db/db mice. Statins increased inflammation, disrupted lipid metabolism, and sped up DN by enhancing fat synthesis and storage through the PI3K/Akt/mTOR pathway[16]
2. Genetic evidence: Using Mendelian randomization, Zhao *et al*. found that genetic inhibition of HMGCR,

the primary target of statins, is linked to a higher risk of DKD and diabetic retinopathy, likely through mechanisms unrelated to LDL-C lowering effects associated with HMGCR inhibition. The MR approach employs genetic variants near the HMGCR gene as instrumental variables to simulate the effects of HMGCR inhibition. These variants are fixed at conception and thus proxy lifelong exposure to reduced HMGCR activity, providing insights into potential long-term consequences that may not be evident in short-term clinical trials or observational studies of statin use[17]

3. Clinical findings: Several observational studies with long-term follow-up (approximately more than 5 years) have associated statin administration with adverse effects on GFR, albuminuria, DN progression, and ESRD occurrence in patients with DM[18-21,75]
4. Time-dependent effects: Some studies indicate that statin benefits may diminish after 4–5 years, with kidney function parameters in statin groups beginning to resemble those of control groups.[76,77]

Fibrates

Safety

Until recently, evidence has addressed concerns about fibrate nephrotoxicity. While fibrates initially increase serum creatinine and reduce GFR, major trials (Fenofibrate Intervention and Event Lowering in Diabetes (FIELD), Action to Control Cardiovascular Risk in Diabetes (ACCORD), and Diabetes Atherosclerosis Intervention Study (DAIS)) demonstrate that these changes may not indicate impaired kidney function.[78-81] A 2022 systematic review and meta-analysis of 29 RCTs, including over 12,000 patients, found that fibrates improve albuminuria in diabetic and nondiabetic patients with hyperlipidemia. Different fibrates caused a short-term decline in eGFR within 3 months, particularly with fenofibrate alone or versus placebo. The combination of fenofibrate and statins showed no significant effect. These results showed significant heterogeneity. These findings indicate that both short- and long-term changes in creatinine and eGFR are similar, suggesting an initial rise stabilizing with continued fibrate use. Therefore, a moderate increase in creatinine may not justify withholding fibrates in patients with preserved renal function or mild CKD. However, the included RCTs had relatively short follow-up durations.[81]

The 2022 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for DM management in CKD recommends statin therapy for all patients with type 1 or 2 DM and CKD, which is in line with the 2024 Association of British Clinical Diabetologists and UK Kidney Association (ABCD-UKKA) guideline for lipid management in adults with DKD.[59,82] The ABCD-UKKA guideline, based on current evidence, does not prohibit fibrates in these patients. Instead, it restricts their use to specialist advice, preferably in younger patients with fewer advanced complications and preserved kidney function. These medications are recommended for patients with pre-G3b-G5 DKD who maintain an eGFR above 30 mL/min/1.73 m^2.[59]

Combining fibrates with statins slightly increases rhabdomyolysis risk, though the absolute risk remains very low. While fenofibrate increases creatinine and homocysteine levels, the ACCORD Lipid trial showed no significant increase in DN or thrombotic events with fenofibrate/simvastatin versus simvastatin alone.[83]

Creatinine elevation: Possible involved mechanisms and clinical significance

Fenofibrate increases serum creatinine levels, but this effect appears reversible mainly upon discontinuation, even after long-term treatment.[84-86] The mechanism remains unclear, with several hypotheses:[22]

1. Reduced renal blood flow: Some studies suggest reduced flow due to decreased vasodilator prostaglandins via PPARα activation
2. Tubular dysfunction: Biopsy-proven tubular damage has been reported in some cases
3. Impaired creatinine secretion: Some evidence suggests impaired tubular secretion of creatinine rather than GFR decline
4. Increased creatinine production: Other studies suggest increased creatinine production rather than renal function decline
5. Conflicting data exists, some reports show parallel increases in cystatin C (supporting true GFR decline), while others do not.

Despite these uncertainties, large trials suggest fenofibrate reduces cardiovascular risk in CKD patients without worsening long-term renal outcomes and may have renoprotective effects, such as reducing proteinuria.[22]

Fibrates and diabetic kidney disease: Clinical evidence

Diabetes Atherosclerosis Intervention Study

In a 3-year follow-up study by Ansquer *et al*. of DAIS participants, fenofibrate treatment was associated with reduced progression from normal UAE to microalbuminuria compared to placebo in patients with type 2 diabetes. These effects were not influenced by age or changes in lipid levels, creatinine, body weight, or blood pressure.[80]

FIELD study

The FIELD study, with a 5-year follow-up, demonstrated that fenofibrate (200 mg/day) maintained eGFR, reduced urinary albumin levels, slowed disease progression, and reduced cardiovascular events compared to placebo. These benefits were particularly pronounced in patients with high TG or low baseline HDL cholesterol. While

fenofibrate initially increased serum creatinine levels, this increase was reversible without evidence of renal injury. After the washout period, eGFR declined less in the fenofibrate group (1.9 ml/min/1.73 m^2) compared to placebo (6.9 ml/min/1.73 m^2), preserving an average of 5.0 ml/min/1.73 m^2 more function with fenofibrate. ESRD occurrence was similar between the two groups.[87-89]

ACCORD trial

The ACCORD trial investigated adding fenofibrate to simvastatin therapy in type 2 diabetes patients. *Post hoc* analysis by Frazier *et al*. showed that this combination reduced albuminuria progression and eGFR decline over a median follow-up of 4 years compared to simvastatin alone. However, the rate of treatment discontinuation (1.1% vs. 2.4%) or intensity reduction (7.0% vs. 15.9%) due to significant GFR decrease was approximately twice as high in the fenofibrate group versus placebo.[90] The extended ACCORDION trial, which followed a subset of ACCORD patients for 6.5 years, revealed that long-term treatment with fenofibrate and simvastatin combination was associated with adverse renal outcomes compared to simvastatin alone, with effects varying significantly across gender and race, indicating the necessity of individualized treatment.[91]

Other findings

Jun *et al*.'s systematic review, including three clinical trials, indicated that fibrate administration in patients with DM is associated with reduced progression and improved regression of albuminuria.[92] Similarly, a 2016 systematic review of 13 clinical trials demonstrated the positive effects of micronized fenofibrate on UAE.[93]

In a study by Nagai *et al*., benzofibrate and pravastatin showed similar effects in maintaining serum creatinine levels and UAE during a 4-year follow-up in noninsulin-dependent DM patients, supporting the temporary nature of fibrate-induced creatinine increases.[94]

In a study by Hyun *et al*. involving matched statin and fibrate users, fenofibrate users had a lower incidence of ESRD compared to nonusers (0.885 vs. 0.960 per 1000 person-years, $P < 0.0001$) and a reduced hazard ratio (0.763, 95% CI: 0.8–10) during a median follow-up of 3.9 years. This benefit was most significant in patients with hypertension, proteinuria, or eGFR < 60 mL/min/1.73 m^2, indicating the clinical significance of patient characteristics in treatment response and the necessity of individualized lipid management.[95]

According to ABCD-UKKA 2024 Guidelines, there is no clear evidence of increased progression to ESRD with fibrate use in DKD.[59]

Limitations of current clinical evidence

Fibrates in DKD have been less extensively studied than statins. While statin research in DKD is abundant, fibrate trials are more limited and primarily evaluate fibrate-statin combinations versus statin monotherapy, or the results were obtained with adjusting statin treatment effects.[87-91,94,95] This approach has reduced the confounding effect of poor lipid control seen in placebo groups of statin trials, as dyslipidemia and CVD risk are better managed in both study arms. More recent fibrate studies typically include more comprehensive outcome measures than earlier statin trials, particularly albuminuria assessment. However, significant limitations persist, including insufficient long-term follow-up beyond 5 years and heterogeneity in patient populations, fibrate formulations, and dosing regimens. In addition, as previously mentioned, several observational studies have reported neutral or adverse renal effects of statins in patients with DM, whereas fibrates have not demonstrated such outcomes.

Statins versus fibrates

Based on the available evidence, lipid management in patients with DM focuses primarily on reducing cardiovascular risk. However, in the context of DKD, dyslipidemia management strategies may still require further optimization to achieve the most favorable renal outcomes. Statins and fibrates take different approaches to managing dyslipidemia in DM, resulting in distinct effects on DKD. Meta-analyses show that statins provide modest short-term renal benefits, such as reduced albuminuria and improved eGFR, usually within 12 months.[13-15] However, the long-term benefits remain uncertain, as evidence from animal studies, Mendelian randomization analyses, and observational research raises concerns about potential adverse effects associated with statin use, particularly beyond 5 years.[16-21,75,96] The main limitations of the evidence include insufficient follow-up periods and incomplete kidney function assessment.

Like statins, fibrates have demonstrated short-term renoprotective effects in patients with DKD. Fibrates may cause an initial increase in serum creatinine, but this increase may be reversible mainly upon discontinuation and may not indicate kidney function impairment. The FIELD study showed that fenofibrate maintained eGFR, reduced albuminuria, and preserved kidney function compared to placebo over 5 years.[87-89] The ACCORD trial found that combining fenofibrate with simvastatin reduced albuminuria progression compared to simvastatin alone, though the extended ACCORDION follow-up suggested monitoring for potential long-term effects.[90,91] There is no clear evidence of increased progression to ESRD with fibrate use in DKD.[59]

Both medication classes lack sufficient long-term studies beyond 5 years, a significant limitation given DKD's progressive nature. Fibrate studies, while fewer in number, typically include more comprehensive kidney outcome measures, particularly albuminuria. Notably, observational studies identifying potential adverse effects of statins on DKD progression have not shown similar concerns with fibrates. The optimal approach likely involves personalized treatment strategies based on individual patient characteristics, kidney function, and specific lipid abnormalities.

Future research directions

Given diabetes' chronic nature and the long-term use of lipid-lowering therapies, follow-up periods of 5 years may be insufficient to assess statins' renal effects fully. For establishing therapies to optimize renoprotection in patients with DM, future research should address the following:

1. Personalized treatment approaches based on baseline kidney function
2. Comparative effectiveness of different statin types and dosages
3. Focusing on novel and multiple kidney function, inflammation, and fibrosis parameters. Novel integrated diagnostic protocols can be explored for better accuracy.[97]
4. Long-term outcomes beyond 5 years
5. Comparisons with other effective lipid-lowering strategies
6. Given the critical cardiovascular benefits of statins in patients with diabetes, which have established them as a cornerstone of DM dyslipidemia management, it is reasonable to explore the effects of combining statins with fibrates or other lipid-lowering therapies on DKD
7. Increased emphasis on subgroup analysis to advance personalized lipid management protocols related to DKD (e.g., considering disease phenotype, genetics, demographics, and other DM comorbidities)
8. Given findings from studies such as FIELD,[87-89] recent research,[90,91,94,95] and the role of HDL and TG in DKD,[34] further investigation into the renal effects of combining fibrates and statins is needed.

This comprehensive approach would better determine the optimal anti-dyslipidemic regimen for renoprotection in diabetic patients.

Limitations

This review has several limitations that should be acknowledged. As a narrative review, it is susceptible to selection bias in the literature search and inclusion. The conclusions rely on indirect comparisons between statins and fibrates due to the lack of large-scale, head-to-head trials comparing these medications for renal outcomes in patients with DM. Additionally, significant study heterogeneity in design, populations, dosages, follow-up periods, and endpoints limits the direct comparison and generalizability of findings. The absence of temporal restrictions in our search strategy broadened study inclusion but may have raised heterogeneity in the quality and relevance of older investigations. We attempted to acknowledge temporal influences and evolving disease management in our evidence synthesis.

CONCLUSION

Dyslipidemia represents a significant modifiable risk factor for DKD, with HDL and triglyceride abnormalities showing stronger associations with disease progression than LDL alone. While statins demonstrate modest short-term renoprotective effects, concerns exist regarding their long-term kidney impact and limited efficacy in addressing the dyslipidemic profile most relevant to DKD. Evidence limitations include insufficient follow-up periods and incomplete kidney function assessment. Fibrates more effectively target HDL and triglyceride abnormalities, with clinical trials suggesting preservation of kidney function despite initial creatinine elevation. Fibrates have also indicated promising results regarding improvement in albuminuria patients with DM. Both medication classes lack sufficient long-term studies beyond 5 years. Current evidence suggests potential advantages of fibrates in specific patient populations, particularly those with low HDL and elevated TG. However, robust evidence establishing the superiority of fibrates is lacking. Furthermore, possible limitations in fibrate use in advanced CKD could suggest that their therapeutic role might be better suited for primary prevention of DKD or early intervention to prevent progression. The optimal approach may require personalized treatment strategies based on individual patient characteristics, kidney function, and specific lipid abnormalities, as well as consideration of combination lipid therapies. Future research should prioritize extended follow-up periods, comprehensive kidney function assessment, and investigation of combination therapies to determine the most effective strategies for preserving kidney function in patients with diabetes.

Declaration of AI assistance in the writing process

In the preparation of this work, generative AI and AI-assisted technologies, including ChatGPT, Claude, Gemini, Grok, and Grammarly, were used to assist with translation, enhance clarity, and proofread the manuscript. Following their use, the authors meticulously reviewed and revised the content to ensure accuracy and coherence. The authors assume full responsibility for the final content of this published article.

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Supplementary Table 1: A summary of the utilized search strategy for identifying the relevant studies

Topic	MeSH term	Title/Abstract Terms*
Statins	Hydroxymethylglutaryl-CoA Reductase Inhibitors	"hydroxymethylglutaryl-CoA reductase inhibitors", "HMG-CoA reductase inhibitor*", "statin*", "atorvastatin", "rosuvastatin", "simvastatin", "pravastatin", "lovastatin", "pitavastatin", and "fluvastatin"
Fibrates	Fibric Acids	"fibric acid*", "fibrate*", "fenofibrate", "bezafibrate", "ciprofibrate", and "gemfibrozil"
DKD and renal outcomes	Diabetic Nephropathies Kidney Failure, Chronic Albuminuria Proteinuria Creatinine Cystatin C Renal Dialysis	"diabetic kidney disease*", "nephropath*", "Diabet* Kidney", "DKD", "albuminuria", "microalbuminuria", "macroalbuminuria", "GFR", "eGFR", "glomerular filtration rate", "creatinine", "cystatin C", "proteinuria", "kidney*", "renal", "ESRD", "ESKD", "CKD", "dialysis", "hemodialysis"
Diabetes mellitus	Diabetes Mellitus Prediabetic State	"diabet*", "prediabet*"

HMG-CoA=Hydroxymethylglutaryl-CoA; DKD=Diabetic kidney disease; ESKD=End-stage kidney disease; ESRD=End-stage renal disease; GFR=Glomerular filtration rate; eGFR=Estimated glomerular filtration rate