REVIEW ARTICLE

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# Evaluating the Effect of Fenofibrate Towards the Progression of Diabetic Retinopathy: A Systematic Review

**Livinia Gabriela Pontoh[1], Karel Pandelaki[2], Yuanita Asri Langi[2*], Bisuk Parningotan Sedli[2], Gloria Notaria Pandelaki[2]**

[1]Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University/Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia
[2]Endocrine and Metabolic Subdivision, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University/Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia

***Corresponding author:**
Yuanita Asri Langi. Endocrine and Metabolic Subdivision, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University/Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia.
Email: meralday@yahoo.co.id

## ABSTRACT

The rising prevalence of diabetic retinopathy (DR) among diabetic patients necessitates innovative therapeutic strategies. Fenofibrate, primarily known for its lipid-lowering effects, has gained attention for its potential role in mitigating DR progression. This study aims to evaluate the efficacy of fenofibrate in reducing the progression of diabetic retinopathy. A comprehensive search was done on three electronic databases, including PubMed, Scopus, and ProQuest up to 3 January 2025. We included all studies that are clinical trials or observational by design published within the last 15 years. The outcome of interest in this study is the progression or worsening of DR. All eligible studies were assessed using the Cochrane risk of bias tool 2.0 for randomized clinical trials, and the risk of bias in non-randomized studies - of interventions. A total of 5 studies encompassing 2 RCT and 3 retrospective cohort studies with a total of 250.835 patients, consisting of 101.026 (40.3%) males, with an overall mean age of 64.3 ± 9.5 years old. Based on the risk of bias assessment, all five studies fall in the low to moderate risk of bias. Four studies show that fenofibrate significantly reduces the risk of DR progression, while one study shows no significant reduction. Two studies also indicate the efficacy of fenofibrate in reducing the development of macular edema. This study solidifies the efficacy of fenofibrate in reducing the risk of DR progression and the development of macular edema.

**Keywords**: Fenofibrate, diabetic retinopathy, macular edema

## INTRODUCTION

Diabetic retinopathy (DR) stands as a leading cause of vision impairment among adults worldwide, particularly affecting those with diabetes mellitus. This microvascular complication arises from prolonged hyperglycemia, leading to progressive retinal damage and, if untreated, potential blindness. The global burden of DR is substantial; in 2020, approximately 103 million individuals were affected, with projections estimating an increase to 160.5 million by 2045.[1] The pathophysiology of DR involves complex mechanisms, including inflammation, oxidative stress, and the breakdown of the blood-retinal barrier. Traditional management strategies have focused on stringent glycemic control, blood pressure regulation, and lipid management to mitigate the risk of DR development and progression. Despite these measures, the incidence of DR remains high, underscoring the need for additional therapeutic interventions.[2,3]

Fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR$\alpha$) agonist, is conventionally utilized for its lipid-modifying properties, particularly in reducing triglyceride levels and increasing high-density lipoprotein cholesterol. Beyond its lipid-lowering effects, fenofibrate has demonstrated potential benefits in ocular health. Notably large-scale randomized controlled trials, such as the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.[4] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study.[5], have reported a significant reduction in the progression of DR among patients with type 2 diabetes treated with fenofibrate.[6]

The FIELD study, encompassing 9,795 participants, revealed that fenofibrate therapy led to a notable decrease in the requirement for laser treatment for DR, independent of baseline lipid levels. Similarly, the ACCORD Eye study corroborated these findings, indicating that fenofibrate reduced the progression of DR, suggesting mechanisms beyond mere lipid modulation.[4,5]

The exact pathways through which fenofibrate exerts its protective effects on the retina are not entirely elucidated. Proposed mechanisms include anti-inflammatory actions, inhibiting vascular endothelial growth factor (VEGF) expression, and preserving the blood-retinal barrier integrity. These pleiotropic effects position fenofibrate as a promising adjunctive therapy in DR management.[7] In light of these findings, this systematic review aims to comprehensively evaluate the efficacy of fenofibrate in attenuating the progression of diabetic retinopathy.

## METHODOLOGY

This systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[8,9] A thorough systematic literature search was conducted on three electronic databases such as PubMed, ProQuest, and Scopus. Keywords associated with literature searching are summarized in Table 1. This systematic review includes randomized controlled trials, non-randomized controlled trials, observational studies, and pilot studies published in the last 15 years.

**Table 1.** Keywords associated with literature searching for databases.

| Databases | Search terms |
|---|---|
| PubMed | ("fenofibrate"[MeSH Terms] OR "fenofibrate"[All Fields] OR "fenofibrates"[All Fields] OR "fenofibric"[All Fields]) AND ("diabetic retinopathy"[MeSH Terms] OR ("diabetic"[All Fields] AND "retinopathy"[All Fields]) OR "diabetic retinopathy"[All Fields]) |
| ProQuest | fenofibrate AND (diabetic retinopathy OR retinopathy diabetic OR Retinopathy of diabetes) |
| Scopus | fenofibrate AND (diabetic retinopathy OR retinopathy diabeticum OR Retinopathy of diabetes) |

In this study, studies associated with the use of fenofibrate in patients with diabetic retinopathy that were published in English in the last 15 years are included. We excluded studies with irrelevant outcome measurements, animal or cadaveric studies, review articles, meta-analyses, case reports, case series, and publications not in English. Two researchers working in pairs independently did study selection and data extraction from published papers. Any disagreements were settled by conversation or involving the third researcher through discussions until a consensus was reached. In this study, we performed quality assessments using the Cochrane risk of bias tool (ROB) 2.0 for randomized clinical trials (RCT) and the risk of bias in non-randomized studies - of interventions (ROBINS-I).[10,11] The risk of bias or quality assessment for each study was conducted by three researchers, with any differences resolved through discussion until a consensus is reached. Outcomes measured for this systematic review are progression of diabetic retinopathy, defined as diabetic retinopathy that has progressed into proliferative diabetic retinopathy or any progression that significantly affects the patients.

## RESULT

A total of 893 studies were obtained from three databases. After removing duplicates, totaling 543 entries, and assessing publications based on their titles and abstracts, 288 articles were deemed unfit and are therefore not included in further research. After careful consideration, 62 articles were chosen for additional analysis. Of those, 51 reports could not be received, leaving 11 publications; a thorough evaluation was performed on their whole texts, excluding 6 articles. The reasons for exclusion included 2 articles having different outcomes of interest (e.g., the incidence of DR), 1 article with unclear intervention protocol, and another 1 with other tools to measure the outcome and 1 is not published within 15 years. Five papers met the specific criteria for inclusion. Therefore, these papers were chosen for additional examination and data extraction, as shown in figure 1.

The composition of the study design is as follows: 3 randomized controlled trials, and 3 were cohort studies. The origin of each survey is varied, with six conducted in the United Kingdom, Canada, Korea, USA, and Taiwan. The characteristics of the included studies and patient demographics are described in Table 2. A total of 250,835 patients were included, with a mean age of 64.3 ± 9.5 years old across 5 studies and gender predominance towards the males (40.3%). Two studies used a regimen of fenofibrate 200 mg once daily, two used 160 mg once daily, and one study used 145 mg once daily. Based on the risk of bias assessment, all studies fall into the low to moderate risk of bias. (Figure 2 and 3)

Four studies show that fenofibrate significantly reduces the risk of DR progression, while one study shows no significant reduction when compared to placebo. One study also showed that fenofibrate as an addition to statin therapy significantly reduced DR progression compared to statin + placebo. A study by Preiss, et al.[12] stated that patients in the fenofibrate group are 0.73 times more likely to experience progression of diabetic retinopathy or maculopathy and 0.50 times more likely to develop macular edema compared to placebo. No significant effect was observed in terms of visual function, quality of life, or visual acuity. The ACCORD study group expresses similar findings, with patients receiving fenofibrate 0.67 times progressing their diabetic retinopathy compared to placebo.[5] Stepping into the cohort studies, Kim, et al found that patient receiving statin – plus fenofibrate are 0.88 more likely to experience the development of their diabetic retinopathy compared patient receiving statin only, in addition, they are also

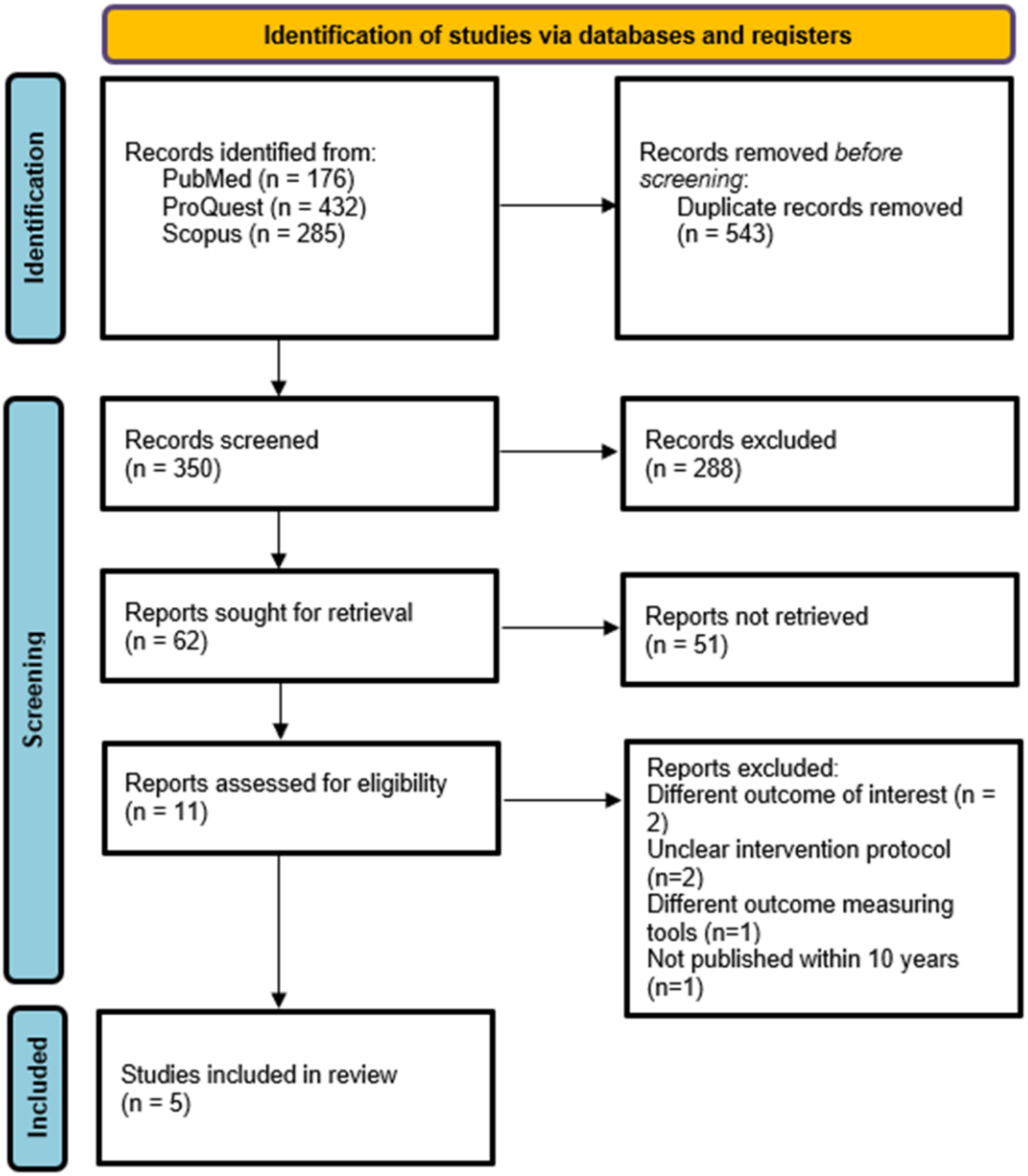


**Figure 1.** PRISMA diagram Depicting The Detailed Process of Study Selection for The Systematic Review and Meta-analysis.

**Table 2.** Study and patient characteristics

| No. | Author | Year | Study Design | Country | Fenofibrate regimen | Patients (N) | Male (%) | Age [Mean (SD)] |
|---|---|---|---|---|---|---|---|---|
| 1 | Preiss, et al (LENS trial) | 2024 | RCT | UK | 145 once daily | 1.151 | 43.6% | N/A |
| 2 | ACCORD study group | 2010 | RCT | Canada | 160 once daily | 1.593 | 68.5% | 61.9 (6.2) |
| 3 | Kim, et al | 2023 | Retrospective Cohort | Korea | 200 once daily | 65.586 | 67.5 | 54.9 (11) |
| 4 | Meer, et al | 2022 | Retrospective Cohort | USA | 160 once daily | 150.252 | 51.3% | 65.3 (10.4) |
| 5 | Lin, et al | 2020 | Retrospective Cohort | Taiwan | 200 once daily | 32.253 | 50.3% | 60.7 (12.8) |

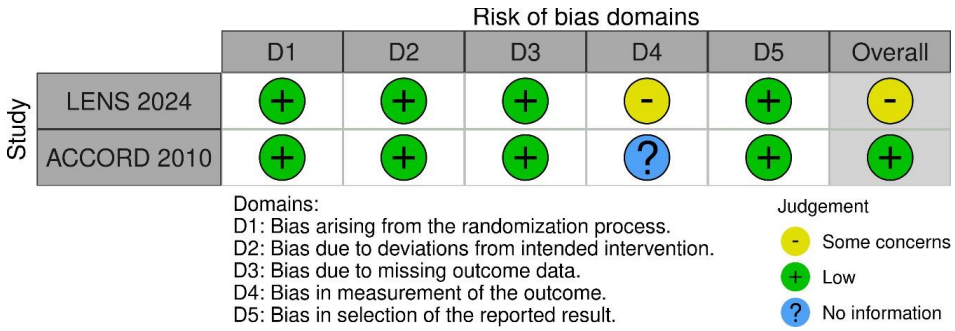


**Figure 2.** Study assessment of RCT using ROB 2.0

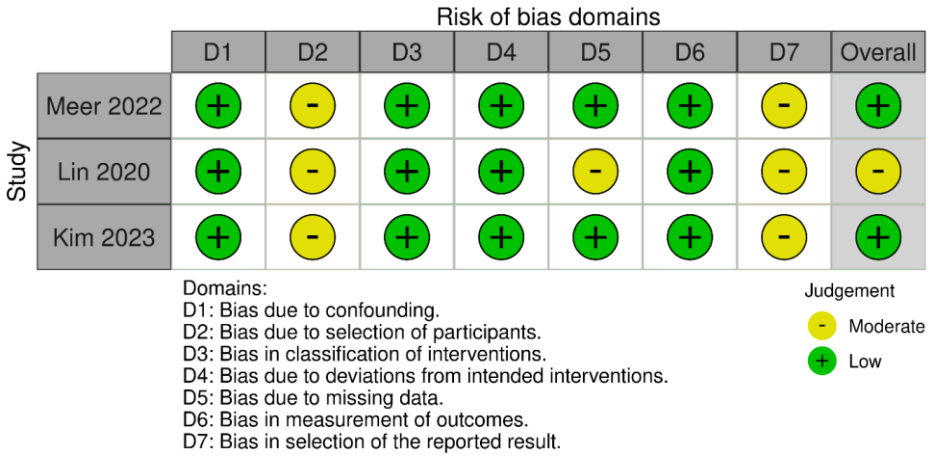


**Figure 3.** Study assessment of cohort studies using ROBINS-I

**Table 3: Summary of the findings in each study**

| No. | Author | Key results | Additional results |
|---|---|---|---|
| 1 | Preiss, et al (LENS trial) | Fenofibrate reduced progression of diabetic retinopathy compared with placebo among participants with early retinal changes | Reduces incidence of macular edema |
| 2 | ACCORD study group | Demonstrated that fenofibrate, when added to statin therapy, slows the progression of diabetic retinopathy in patients with type 2 diabetes | N/A |
| 3 | Kim, et al | Fenofibrate reduces DR progression | less likely to experience vitreous hemorrhage, needing laser photocoagulation and intravitreous injection |
| 4 | Meer, et al | No significant difference between the group that receives fenofibrate vs the placebo | No significance in reducing macular edema |
| 5 | Lin, et al | Significant reduction in DR progression in the group that received fenofibrate vs placebo | Decreases risk of developing macular edema |

significantly less likely to experience vitreous hemorrhage, needing laser photocoagulation, and intravitreous injection therapy.[13] Meer, et al., standing out from the other study, found that those in the fenofibrate group are not significantly different compared to the control group in terms of progression (HR:0.99; 95% CI 0.93-1.05; p=0.67), they also found no significant difference in terms of macular edema development.[14] Lastly, a study by Lin, et al shows a hazard ratio of 0.59, favouring the fenofibrate group in terms of DR progression, compared to other medications.

They also find that fenofibrate significantly decreases development of macular edema.[15] Table 3 summarises the findings of each study.

## DISCUSSION

The present systematic review evaluated the impact of fenofibrate on the progression of DR by analyzing six studies, including two RCTs and three retrospective cohort studies, encompassing 250.835 patients. Most of these studies indicate that fenofibrate significantly reduces the risk of DR progression, with five out of six studies demonstrating a beneficial effect. Additionally, two studies reported that fenofibrate contributes to a reduction in the development of macular edema. These findings reinforce the potential of fenofibrate as an adjunctive therapy in DR management.

The protective effects of fenofibrate on DR appear to extend beyond its traditional lipid-lowering properties. As a PPAR$\alpha$ agonist, fenofibrate modulates several metabolic pathways that may contribute to its retinal benefits.[16] One proposed mechanism involves reducing oxidative stress and inflammation, which play significant roles in DR progression.[17,18] Fenofibrate has been shown to inhibit the activation of nuclear factor-kappa B (NF-$\kappa$B), a key regulator of inflammatory cytokines contributing to retinal damage.[19] Additionally, fenofibrate is believed to exert anti-angiogenic effects by downregulating VEGF, a key mediator of pathological neovascularization in DR. The suppression of VEGF expression could explain the observed reduction in macular edema among fenofibrate-treated patients.[20,21] Furthermore, fenofibrate may help preserve the integrity of the blood-retinal barrier, reducing vascular leakage and preventing the accumulation of extracellular fluid in the retina.[22] These pleiotropic effects position fenofibrate as a promising pharmacological intervention for DR beyond conventional glucose and lipid control.

When comparing fenofibrate with other pharmacological treatments for DR, anti-VEGF agents such as aflibercept, bevacizumab, and ranibizumab have been extensively studied.[23–25] They are considered the standard of care, particularly for diabetic macular edema (DME). The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study compared these three agents in patients with center-involved DME. At the one-year mark, all three drugs improved visual acuity, with aflibercept showing superior outcomes in patients with worse baseline vision (20/50 to 20/320). By the two-year follow-up, aflibercept remained superior to bevacizumab but not to ranibizumab in this subgroup. These findings highlight the efficacy of anti-VEGF therapies in managing DME, though they require repeated intravitreal injections, which can be burdensome and carry potential risks such as endophthalmitis and retinal detachment.[26]

Corticosteroids, including triamcinolone acetonide and dexamethasone intravitreal implants, have also been evaluated for DR treatment due to their potent anti-inflammatory effects. The MEAD trial demonstrated that dexamethasone implants significantly improved visual acuity and reduced central retinal thickness in patients with DME.[27] However, these benefits were accompanied by increased risks of cataract formation and elevated intraocular pressure.[28,29] Compared to fenofibrate, corticosteroids provide localized treatment but are associated with ocular side effects, limiting their long-term use. Traditional glucose-lowering therapies, such as metformin and sodium-glucose co-transporter-2 (SGLT2) inhibitors, have been investigated for their potential retinal benefit.[30] A retrospective cohort study reported that metformin use was associated with a lower risk of DR progression in patients with type 2 diabetes, independent of glycemic control.[31] In observational studies, SGLT2 inhibitors have

been linked to improved vascular function and a reduced incidence of DR progression.[32,33] However, the direct effects of these therapies on retinal health remain inconclusive, and unlike fenofibrate, they have not been the primary focus of DR-specific interventional trials.

Despite the promising findings, several limitations and potential biases should be considered. Including both RCTs and retrospective cohort studies introduces variability in study design, which may affect the consistency of the findings. While all six studies were assessed to have a low to moderate risk of bias, inherent biases in retrospective studies, such as selection and information bias, cannot be entirely ruled out. Additionally, differences in the definitions and assessments of DR progression and macular edema across studies may lead to inconsistencies in reported outcomes. Furthermore, variations in the duration of follow-up among studies could influence the observed effects of fenofibrate on DR progression.

## CONCLUSION

In conclusion, fenofibrate presents a unique advantage in DR management due to its systemic benefits, anti-inflammatory properties, and ability to preserve the blood-retinal barrier. Compared to anti-VEGF agents and corticosteroids, fenofibrate offers a non-invasive, oral treatment option with fewer ocular complications, making it a viable alternative or adjunctive therapy. However, further well-designed, large-scale RCTs with standardized outcome measures and longer follow-up periods are needed to confirm these findings and to elucidate the underlying mechanisms of fenofibrate's protective effects on the retina.

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