Efficacy of fenofibrate for diabetic retinopathy
A systematic review protocol

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Abstract

Background: Numerous studies have reported the efficacy of fenofibrate for patients with diabetic retinopathy (DRP). No systematic review has, however, addressed its efficacy for DRP. Thus, this systematic review will firstly evaluate the efficacy and safety of fenofibrate for patients with DRP.

Methods: This study will search the following databases: PUMBED, EMBASE, CINAHL, ACMDO, CENTRAL, CBM, CNKI, VIP, and WANGFANG, along with grey literature from inception to the present. We will accept randomized controlled trials on evaluating the efficacy and safety of fenofibrate for DRP. The primary outcome is the progression of DRP. The secondary outcomes are vision loss, development of diabetic macular edema, aggravation of hard exudates, quality of life, and any adverse events. Methodological quality of each included study will be assessed by using Cochrane Collaboration risk of bias tool. In addition, Grading of Recommendations Assessment, Development and Evaluation tool will also be used to evaluate the overall strength of the evidence. Two independent reviewers will conduct all procedures of study selection, data extraction, and methodological assessment. Any disagreements will be consulted with a third reviewer. RevMan 5.3 software will be used to pool data and to carry out the meta-analysis if it is possible.

Results: In present study, we anticipate to find a considerable number of published studies presenting evidence on efficacy and safety of fenofibrate for DRP.

Conclusion: The findings of this systematic review will provide latest evidence of fenofibrate for patients with DRP.

Dissemination and ethics: The findings of this scoping review will be disseminated in print, conferences, or by peer-reviewed journals. No ethical approval is needed for this systematic review, because it is a literature-based study.

Systematic review registration: PROSPERO CRD42019121869.

Abbreviations: CI = confidence interval, DRP = diabetic retinopathy, GRADE = Grading of Recommendations Assessment, Development and Evaluation, RCT = randomized controlled trial.

Keywords: diabetic retinopathy, efficacy, fenofibrate, safety, systematic review

1. Introduction

Diabetic retinopathy (DRP) is one of the most common microvascular complications among patients with diabetes.[1–3] It has been reported that DRP is responsible for 4.8% of 37 million cases of blindness worldwide.[4] Unfortunately, no symptoms can be detected in early stage of DRP.[5–7] When the visual issues are identified, it has already developed as advanced stage with a point of no return.[8,9]

Currently, intravitreal injections of antivascular endothelial growth factor are accepted as standard management for DRP.[10–13] It still, however, has limited efficacy for some patients. Thus, alternative therapies are still needed to be explored. Fenofibrate is reported to be an alternative intervention for DRP.[14–16] Numerous clinical trials have reported that it has promising efficacy for patients with DRP.[17–24] No systematic review has, however, addressed this issue. Therefore, this systematic review will assess the efficacy and safety of fenofibrate for patients with DRP.

2. Methods and analysis

2.1. Study registration

This systematic review has been registered on PROSPERO (CRD42019121869). It is reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocol.[25]

2.2. Study selection criteria

2.2.1. Type of studies: We will include randomized controlled trials (RCTs) of fenofibrate for DRP. Nonclinical trials, noncase control studies, non-RCTs, and quasi-RCTs will, however, be excluded.
2.2.2. Type of participants. We will include any clinically diagnosed criteria of DRP regardless of race, sex, and age.

2.2.3. Type of interventions. We will accept studies that have implemented fenofibrate alone as an experimental treatment in any forms. Control treatment can be any kinds of interventions, except fenofibrate.

2.2.4. Types of outcomes. The study reporting at least one of the following outcomes will be included. The primary outcome includes the progression of DRP. The secondary outcomes consist of vision loss, development of diabetic macular edema, aggravation of hard exudates, quality of life, and any adverse events.

2.3. Identifying relevant studies

This systematic review will summarize evidence published by primary trials and grey literature. The following databases will be searched from the inception to the present: PUMBED, EMBASE, CINAHI, ACMD, CENTRAL, CBM, CNKI, VIP, and WANG-FANG. In addition, grey literature, such as relevant articles from the reference lists, Web sites of clinical trial registry, and doctoral dissertation will also be searched. The detailed search strategy for CENTRAL is presented in Table 1. The identical search strategies will also be applied to other electronic databases.

2.4. Study selection

Two reviewers will independently select the studies by scanning titles and summaries, and reading full-texts if it is necessary according to the predefined eligibility criteria. Any disagreements regarding the study selection will be solved by consulting a third reviewer through discussion. The whole process of study selection is summarized as flowchart in Figure 1.

2.5. Data extraction and management

Endnote 7 will be used to manage data by 2 independent reviewers. All data will be extracted according to the predefined standard data extraction sheet. It includes information of study characteristics (title, first author, year of publication, journal, country, and funding sources); patient characteristics (diagnosis criteria, comorbidities, race, sex, age); study method (sample size, randomization, concealment, blindness, and other potential risk biases); intervention details (type, dosage, frequency, and duration); and outcomes (primary, secondary, and other outcomes). Any discrepancies regarding the data extraction will be settled down by consulting a third author.

2.6. Dealing with missing data

If any data are missing, we will contract authors of primary studies. If we cannot achieve those data, then we will just analyze the available data and also discuss its potential impacts.

2.7. Risk of bias assessment

Two reviewers will independently assess the methodological quality for each included trial by using Cochrane Handbook for Systematic Reviews of Interventions Tool. Each item will be judged according to the standard criteria of Cochrane risk of bias tool. Any disagreements will be solved by consensus with a third author.

2.8. Quality of evidence rating

Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool will be used to evaluate the overall strength of the evidence. Its results will be summarized in tables of Summary of Findings.

2.9. Statistical analysis

RevMan 5.3 software will be used to pool the data and to conduct the meta-analysis. All continuous data are expressed as mean difference or standardized mean difference with 95% confidence intervals (CIs). All dichotomous data will be expressed as risk ratio with 95% CIs.

Heterogeneity will be checked by $I^2$ test. Acceptable heterogeneity will be considered if $I^2 \leq 50$, and a fixed-effect model will be used to synthesize the data. Otherwise, substantial heterogeneity will be considered, and a random-effect model will be used to synthesize the data. Under such situation, subgroup analysis will be carried out according to the different interventions, research scenario, and outcome tools. If significant heterogeneity is still identified after subgroup analysis, then data will not be recommended to synthesize, and meta-analysis will not be carried out. Instead, a narrative summary will be presented.
Whenever possible, sensitivity analysis will be performed to check the robustness of pooled results data by removing low quality of studies. In addition, Funnel plot and Egg’s regression will be conducted if >10 eligible trials are included in this study.

3. Discussion
In this systematic review, we will evaluate the methodological quality by using Cochrane risk of bias tool and assess the quality of evidence with GRADE tool. Two independent reviewers will conduct the study selection, data extraction, and methodological quality assessment, whereas any disagreements will be settled down with a third reviewer through discussion. This study will generate present evidence of fenofibrate for patients with DRP, and will help to reduce the uncertainty about the efficacy and safety of fenofibrate management. The findings of this study will encourage further suggestions for clinicians or guideline, and will draw wide attention for both patients and researchers.

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