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Article

A systematic review of preclinical animal studies on fenofibrate's potential role in type 1 diabetic micro-vascular complications

Resia Varghese[1], Sadagoban Gopal Krishnamoorthy[1], Hassan Elrufaie Hassan Abdalla[1], Aiswarya Baiju[1], Swathi Swaroopa Borra*[1]

[1]Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, Nilgiris, Tamil Nadu, India

Fenofibrate is a peroxisome-proliferator-activator α agonist and it is a widely used drug for hyperlipidemia since its approval in 2004. So, in this review we are focusing on the effect of fenofibric acid's mechanism to alleviate type 1 diabetic micro vascular complications like diabetic retinopathy, diabetic cardiomyopathy in animal models, since the drug is safe, efficacious and more economical when compared with the currently available treatment strategies for juvenile diabetic complications and also a profound observation is needed due to the rarity of research in these therapeutic areas. Important preclinical animal studies published from January 2001 to June 2020 were recognised from databases like PubMed and Cochrane central register of controlled trials. Reviewers screened the articles based on the selection criteria and risk of bias was determined using Systematic Review Centre for Laboratory animal Experimentation risk of bias tool for animal studies. Our literature search yielded a total of 5 studies and after pooling up the data from the 5 preclinical studies, we found that Fenofibrate have the efficacy to prevent type 1 diabetic complications, chiefly diabetic retinopathy and those mechanisms are dependent on peroxisome-proliferator-activator and fibroblast growth factor-21 pathways. Fenofibrate is a well safe and moreover, cost effective medication in preventing type 1 diabetic micro vascular complications especially diabetic retinopathy and also in maintaining the glucose homeostasis in apart from its anti-dyslipidemic effect.

Keywords: Diabetic cardiomyopathy. Diabetic retinopathy. Fenofibrate. Sphingolipid. Type 1 diabetic microvascular complications. Type 1 Diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) is the most common metabolic disease, and Type 1 diabetes mellitus (T1DM), also known as insulin-dependent diabetes or juvenile diabetes, accounts for only 5-10% of diabetic cases worldwide. (Wild *et al*., 2004) (CDC, 2019) (UN, 2019). About 422 million people worldwide have diabetes, and as per a recent study, the global incidence of T1DM in Asia, Africa, Europe, and America is 15 per 100 000, 8 per 100 000, 15 per 100 000, and 20 per 100 (WHO, 2020; Mobasseri *et al*., 2020). Microvascular and macrovascular complications caused by poorly managed T1DM have a major influence on the patient's quality of life, and around 50% of type 1 diabetic patients have diabetic retinopathy (DR) (Dimeglio, Evans-Molina, Oram, 2018; Nentwich, Ulbig, 2015). One in every three diabetics develops DR, and one in every ten has vision-threatening conditions such as diabetic macular edema (DME) and proliferative diabetic retinopathy(PDR) (IDF, 2020). Hyperglycemia causes retinal ischemia and increased production of vascular endothelial growth factor (VEGF). As a result, neovascularization happens which would progress into proliferative stages (Nentwich Ulbig, 2015). Similarly, a 1% increase in glycated hemoglobin (HbA1c) in T1DM was related to a 30% increase in the risk of heart failure

***Correspondence:** S. S. Borra. Department of Pharmacy Practice. JSS College of Pharmacy. JSS Academy of Higher Education & Research. Ooty, Tamil Nadu, India, 643001. Phone: 0091-9629547089**.** E-mail**:** swathimasthani@hotmail.com. ORCID: 0000-0003-1139-4124

(Jia, Hill, Sowers, 2018) and the most commonly seen cardiac abnormality is reduced diastolic compliance, accompanied by systolic dysfunction (Wang *et al.*, 2006). Based on the preclinical studies, altered metabolism of pancreatic sphingolipids, which is an essential part of the cell membrane, may also facilitate diabetic complications. However, the exact mechanism behind this adverse event remains unexplored (Fox *et al.*, 2011).

Fenofibrate is an orally febric acid derivative which has been labeled to treat hypertriglyceridemia or dyslipidemia, low level of high-density lipoprotein (HDL), or as an adjunct to statins in dyslipidemia with an off-label indication in primary biliary cholangitis (Lexicomp, 2020). After absorption, Fenofibrate is rapidly metabolized to its active metabolite, fenofibric acid, which is a peroxisome proliferator–activated receptor-α (PPARα) agonist (Cheung, Mitchell, Wong, 2010). Fibrates are effective by lowering total plasma triglycerides and LDL cholesterol, which aids lipoprotein lipolysis and promotes hepatic fatty acid (FA) absorption. Induction of the β-oxidation pathway with a concomitant lower in FA synthesis decreases the availability of FAs for triglyceride synthesis. This mechanism is facilitated through the fibrate induced inhibition of hormone-touchy lipase in adipose tissue. (Staels *et al.*, 1998; Klein, 1992).

Repositioning therapeutics has to be implemented in many insufficiently researched areas. Initially considered to be a lipid-modifying drug, it now seems that fenofibrate's effect on diabetic microvascular complications may be explained by a variety of mechanisms such as prevention of angiogenesis, inflammation, apoptosis and oxidative stress. (Noonan *et al.*, 2013) Fibrates are PPARα agonists, that might elucidate their pleiotropic effects, and there is substantial evidence indicating their benefits in microvascular and macrovascular complications particularly in diabetes (Malur *et al.*, 2017). According to Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies, it is relevant that there is an established mechanism for Fenofibrate in the reduction of microvascular complications in type 2 diabetes mellitus(T2DM) (Keech *et al.*, 2007; Buse *et al.*, 2007). Cases also have been reported that this drug is also effective in T1DM (Buschard, Holm, Fedt-Rasmussen, 2020). Action of fibric acid derivative in type 2 DR has already been proved using human randomized controlled trials and its protective mechanisms in juvenile diabetic complications are yet to be established in human trials. To establish its effectiveness in alleviating diabetic cardiomyopathy, diabetic retinopathy, we gathered preclinical records of Type 1 diabetic mice and rats from both genders, which were treated with Fenofibrate. As a result, the objective of this review is to focus on the beneficial effects of fenofibrate on the complications of insulin-dependent diabetes mellitus, as the only therapeutic choices for T1DM and its complications are insulin therapy and surgery. Management of DR specifically, is provided based on its severity stage such as intravitreal administration of anti-angiogenic agents for mild to high-risk, laser photocoagulation for severe to high-risk, steroids for DME (Flaxel *et al.*, 2020; Corcóstegui *et al.*, 2017). Mostly, all these medications are delivered parenterally, which is really uneasy especially in case of juvenile diabetes and also remains to be exorbitant this would rather end up in non-compliance and thereby deteriorating the patient's medical condition (Balfour, McTavish, Heel, 1990; Flaxel *et al.*, 2020; Corcóstegui *et al.*, 2017). The high prevalence of T1DM in developing countries, proven benefits of fibrates in T2DM, and the reliance solely on parenteral treatment in T1DM altogether provide reasonable grounds for performing this study on the beneficial effects of fibrates in T1DM. Extensive future research on currently accessible and economically viable management techniques is necessary.

METHODS

Eligibility criteria

Inclusion criteria

We included animal experimental studies with an aim to find Fenofibrate's additional effect in complications of T1DM. We combined preclinical records with Type 1 diabetic mice and rats of both genders, which were treated with Fenofibrate.

Exclusion criteria

We excluded preclinical records with T2DM, reviews, abstract only records, foreign language papers, studies with wrong population and intervention.

Outcome Measures

Primary endpoint

- Retinoprotective effect of Fenofibrate

Secondary endpoint

- Cardioprotective effect of Fenofibrate
- Neuroprotective effect of Fenofibrate

Search Methods

Preclinical studies were identified without any restriction based on inclusion and exclusion criteria.

Electronic searches

Following databases were used to conduct the search for articles published from January 2001 to June 2020: PubMed and Google scholar was also used to retrieve relevant literatures. Important articles were identified manually and also from the references of previously published content-related reviews, systematic reviews and Meta analyses. Whole studies were imported to Zotero where they converted into 'ris' format. The 'ris' file was then exported to Rayyan for the selection of records based on selection criteria.

Keywords

Studies were retrieved using search terms like 'Fenofibrate', 'Fibric acid derivative', 'Type 1 Diabetes mellitus', 'Insulin dependent diabetes', 'Microvascular complications', 'Diabetic retinopathy', 'Diabetic neuropathy', 'Diabetic nephropathy', 'Diabetic cardiomyopathy', 'Cardiomyopathy'.

Data Collection

Study selection

RV, HEHA and AB involved in the process of selecting the studies based on the eligibility criteria. Using Rayyan online portal, studies were included and reasons were stated for study exclusion. Duplicates were removed and all the disagreements were resolved by SSB and SGK.

Data extraction

RV and HEHA extracted the essential information like first author, year of publication, animal model, animal gender, intervention administered, duration of treatment, analytic methods, primary and secondary endpoints from the included studies. All the conflicts were discussed and sorted out by SSB and SGK.

Quality assessment

To draw a decent conclusion, risk if bias was assessed by RV for all the included studies and following domains were critically appraised using Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) risk of bias tool for animal studies: Selection bias, Performance bias, Detection bias, Attrition bias, Reporting bias and other bias to check whether the experimental study has got the ethical approval or not. Accuracy and validity of the included studies were assessed and they were labeled as Low, High and Unclear with proper judgments. All the discrepancies were sorted out by SSB.

RESULTS

Search results

A total of 31 records were retrieved from the databases like PubMed and Google Scholar. Among them, 30 studies underwent abstract screening after removing duplicates. From this set, 25 studies were excluded as 8 were unrelated studies, 6 had wrong study design, 6 reviews, and 4 had wrong population and 1 foreign language article (French). Finally, we included 5 studies for the qualitative analysis. The complete flow chart has been illustrated as a Figure 1.

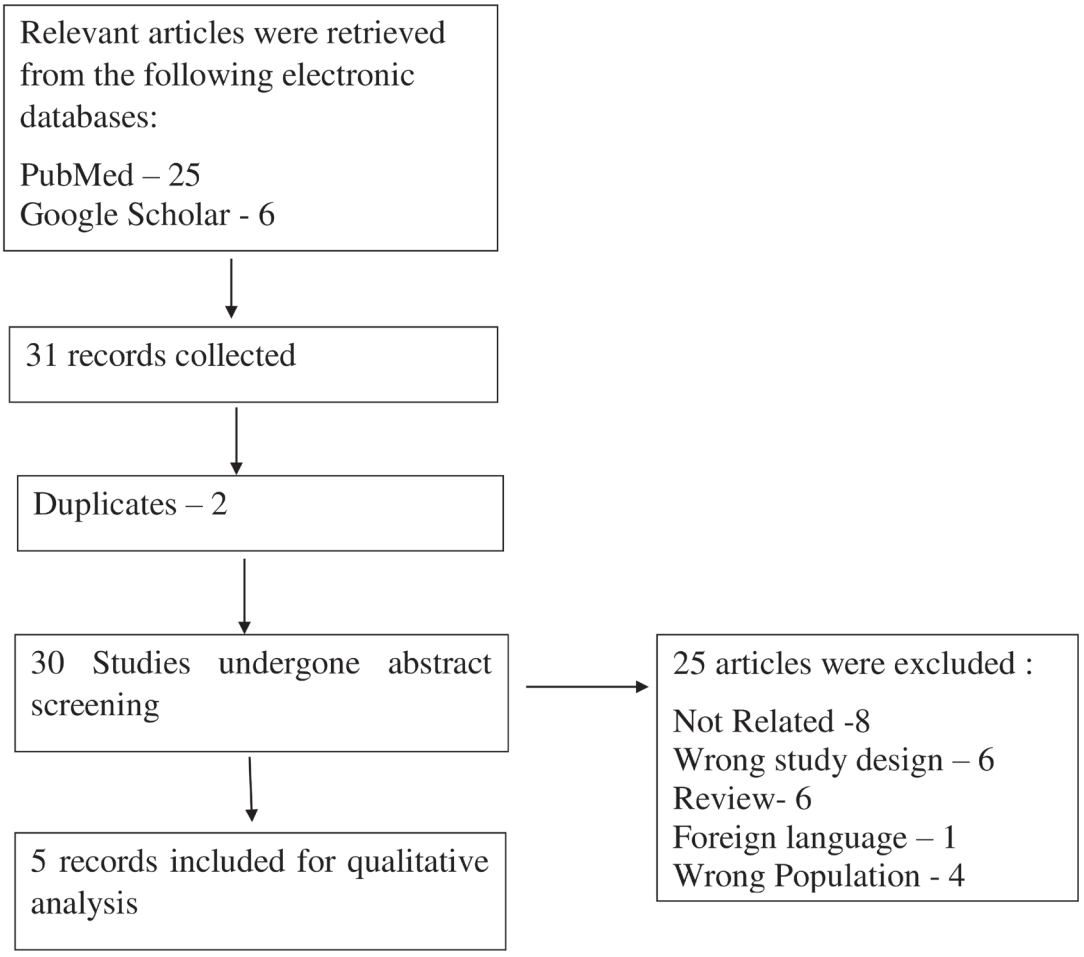

FIGURE 1- Flow chart of systematic literature search for preclinical animal studies on fenofibrate's potential role in type 1 diabetic micro-vascular complications.

Study Characteristics

Characteristics of the 5 included studies have been illustrated in Table I. Out of the whole set, 3 studies contributed to the Fenofibrate's efficacy in DR, 1 study to the diabetic cardiomyopathy and the remaining 1 study to its ability to retain pancreatic lipid and neuronal volume.

TABLE I - Study Characteristics

Author, Year	Animal Sex	Animal Age	Animal model/species		Treatment Given	Analysis Performed	Outcome measures
			Experimental Animal	Control			
Chen *et al*., 2012	Male	Not Specified	Diabetic Brown Norway rats, Akita mice, Wild-type littermates (C57BL/6 mice), PPARα 2/2 mice	Non- diabetic Brown Norway rats, Akita mice, Wild-type littermates (C57BL/6 mice), PPARα 2/2 mice	FF- 0.25 or 0.15% admixture with rodent chow for 3 and 7 weeks	Western blot analysis & Immunohistochemistry - Expression of inflammatory markers in retinal cells, Fluorescein retinal angiography- Retinal neovascularization, Endothelial cell scratch wound assay- Detection of REC tube formation, Transwell inserts cell migration assay- Migration of REC	Therapeutic efficacy of Fenofibrate in diabetic retinopathy
Holm *et al*., 2019	Female	Three-week-old	Female NOD mice	Female NOD mice	0.1% FF	Immunofluorescence- Pancreatic cell nature; Lipid measurement	Therapeutic efficacy of fenofibrate in pancreatic lipidome
Pearsall *et al*., 2019	Female Brown Norway rats; Male Sprague Dawley rats; Wild type mice, *Pparα-/-* mice	Brown Norway and Sprague Dawley rats -10 weeks old; Wild type mice and PPARα -/- mice- 24 weeks old	Diabetic Brown Norway and Sprague Dawley rats; Diabetic Wild type mice and PPARα -/- mice	Non- diabetic Brown Norway and Sprague Dawley rats; Non-diabetic Wild type mice and PPARα -/- mice	Brown Norway - 0.03% and 0.015% FF; Sprague Dawley - Feno-FA 10 mg/kg/day intraperitoneally for 1 week	Optokinetic tracking- Visual acuity, Electroretinograms- Retinal function, DNA fragmentation ELISA- Retinal apoptosis, MTT assay- Retinal cell viability, NADH oxidation assay- Retinal mitochondrial function, Seahorse extracellular flux analysis- PPARα's effect on retinal mitochondria, Fluorescent detection of intracellular ROS, Mass spectrometry- Retinal proteomic analysis	Neuroprotective efficacy of fenofibrate in diabetic retinopathy
Liu *et al*., 2018	Not Specified	12 weeks	C57BL/6J-Ins2^{Akita}	Littermate mice	0.1% FF for 4 weeks	Immunohistochemistry- Retinal cell oxidation, Nuclear extraction kit- Retinal nuclear protein extraction, Fluorometric assay- Retinal oxidative stress detection, Retinal vascular leakage assay, Western blot analysis- Expression of retinal nuclear of β-catenin, Nox4, p-LRP6, Nox2, SOD1; RT-PCR- RNA extraction from ARPE-19 cells	Therapeutic efficacy of fenofibrate in diabetic retinopathy

TABLE I - Study Characteristics

Author, Year	Animal Sex	Animal Age	Animal model/species		Treatment Given	Analysis Performed	Outcome measures
			Experimental Animal	Control			
Zhang *et al.*, 2016	Male C57BL/6J mice, Male FGF21-KO mice	8-10 weeks	Non- diabetic C57BL/6J mice with FF treatment; Diabetic C57BL/6J mice; Diabetic C57BL/6J mice with FF treatment	Non- diabetic C57BL/6J mice;	FF- 100 mg/kg of body weight every other day for 3 or 6 months	Echocardiography- Cardiac Functioning; Histological staining (H & E; Sirius Red, Oil Red O)- Fibre disruption, collagen and lipid accumulation in myocardium; Western blot assay- Autophagic markers examination; RT-qPCR- Protein and mRNA expression of Sirt1; Plasma biochemical index assay- FGF21, Triacylglycerol and cholesterol level in plasma	Therapeutic efficacy of fenofibrate in diabetic cardiomyopthy
			WT with FF treatment, Diabetic WT, Diabetic WT with FF treatment; FGF21-KO with FF treatment, Diabetic FGF21-KO; Diabetic FGF21-KO with FF treatment.	WT mice; FGF21-KO mice			

FF- Fenofibrate; REC- Retinal endothelial cell; NOD- non-obese diabetic; Feno FA- Fenofibric acid; DNA fragmentation ELISA- Deoxyribonucleic Acid fragmentation and enzyme-linked immunosorbent assay; PPAR- peroxisome-proliferator-activator; ROS- Reactive oxygen species; Nox 2 & 4- nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 & 4; LRP6- Low Density Lipoprotein Receptor Related Protein 6; SOD1- Superoxide dismutase 1; RT-PCR- Reverse transcription polymerase chain reaction; ARPE-19- Adult Retinal Pigment Epithelial cell line-19; FGF21-KO- Fibroblast growth factor 21- knockout; RT-qPCR- Quantitative reverse transcription PCR; Sirt 1- Sirtuin1; FGF21- Fibroblast growth factor 21

Risk of bias Assessment

Risk assessment for the included studies has been depicted in the Table II. The methods used to generate sequences and conceal the allocation remains as a high risk for all the included studies. 4 studies have taken the baseline characteristics of the animals at the initial study phase and labeled as low risk. Whole studies have reported all the primarily mentioned outcomes at the end of the study along with ethical committee approval from the beginning with a low risk.

Table II - Quality assessment of the included studies

Author, Year	Sequence generation (Selection bias)	Baseline characteristics (Selection bias)	Allocation concealment (Selection bias)	Random housing (Performance bias)	Blinding (Performance bias)	Random outcome assessment (Detection bias)	Blinding (Detection bias)	Incomplete outcome data (Attrition bias)	Selective outcome reporting (Reporting bias)	Ethical Committee approval (Other bias)
Chen *et al.*, 2012	High Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	Low risk	Unclear	Low risk	Low risk
Holm *et al.*, 2019	Unclear	Low Risk	High Risk	Low Risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Pearsall *et al.*, 2019	High Risk	Low risk	High Risk	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk

Table II - Quality assessment of the included studies

Author, Year	Sequence generation (Selection bias)	Baseline characteristics (Selection bias)	Allocation concealment (Selection bias)	Random housing (Performance bias)	Blinding (Performance bias)	Random outcome assessment (Detection bias)	Blinding (Detection bias)	Incomplete outcome data (Attrition bias)	Selective outcome reporting (Reporting bias)	Ethical Committee approval (Other bias)
Liu *et al.*, 2018	High Risk	Low Risk	High Risk	High Risk	High Risk	High Risk	High Risk	Unclear	Low Risk	Low Risk
Zhang *et al.*, 2016	High Risk	Low Risk	High Risk	High Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk

Fenofibrate and Diabetic retinopathy

3 of the included studies have examined the effect of Fenofibrate in type 1 DR and they have found a positive result as it reduces the retinal inflammation through many pathways. Chen *et al.* (2013) found that PPARα agonist like Fenofibrate could reduce retinal vascular permeability and leukostasis which was assessed through Sigma-Aldrich assay and later via perfusion of anesthetized rats with phosphate-buffered saline (PBS) and counterstaining with fluorescein isothiocyanate (FITC) -conjugated concanavalin- A. They also found that Fenofibrate could diminish the level of various inflammatory markers which was confirmed with western blot analysis, enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry hence proving that it could ameliorate the vascular leakage and leukocyte adhesion to the retinal wall. Intraocular administration of Fenofibrate could lessen the formation, invasion of microvascular networks in to the cornea thereby inhibiting retinal endothelial cell (REC) tube formation and also retinal inflammation. Another study by Liu *et al.* (2019) found that fenofibrate could arrest the hyperglycemia induced Wnt/β-catenin pathway and also reactive oxygen species (ROS) generation on adult retinal pigment epithelial cell line-19 (ARPE-19) cells. Other pathogenic mechanism of hyperglycemia is the alteration of superoxide-generating enzyme system, which was also corrected with the treatment of Fenofibrate. They also suggested that Fenofibrate could prevent the retinal vascular leakage in diabetic C57BL/6J-Ins2 Akita mice, which is one of the hallmark complications of DR. Pearsall *et al.* (2019) found that long term treatment with Fenofibrate could boost the visual acuity which was lost once and verified using optokinetic tracking in streptozocin (STZ)-induced brown norway (BN) rats. A reduction in the retinal apoptosis was also demonstrated in STZ induced BN rats through deoxyribonucleic acid (DNA) fragmentation and ELISA. They also found that fenofibric acid could impose a neuroprotective action in DR after assessing the retinal function through electroretinogram (ERG), in wild-type (WT) STZ induced BN mice and diabetic PPARα-/- mice at 24th weeks of being diabetic. Direct neuroprotective action was verified after treating R28 rod precursor cells with 4-hydroxynonenal (4-HNE), a diabetic stressor and later with PPARα agonist, which showed that Fenofibrate could restore viability among the precursor cells, partially. Intraperitoneal administration of febric acid derivative restored the mitochondrial respiration and functioning in retinal neuronal cells of 4 week diabetic STZ and non-diabetic rats. They also found that ablation of PPARα expression in retina would contribute to the generation of ROS and finally leads to cellular oxidative stress in vitro R28 cells. Similar results shown with in vivo studies of STZ induced diabetic WT and PPARα -/- mice.

Fenofibrate and Diabetic cardiomyopathy

Zhang *et al.* (2016) found that Fenofibrate could abolish dimensional changes in the left ventricular chamber like increased left ventricular internal dimension (LVID), left ventricular volume and decreased ejection fraction (EF), fractional shortening (FS), left ventricular

mass and also wall motion abnormalities hence preventing systolic dysfunction, which was more prevalent in WT Diabetes mellitus/Fenofibrate (DM/FF) mice than fibroblast growth factor 21- knockout mice (FGF21- KO) DM/FF mice. Prevention of myocardial fiber impairment and abnormalities in cardiac matrix was also notified with Fenofibrate through H & E and Sirius red staining techniques. Cardiac fibrotic changes were more severe in FGF21- KO DM/FF mice and Fenofibrate could not bring any improvements in the accumulation of collagen in this animal model. Another staining with oil red O showed Fenofibrate could forestall inflammatory responses in the cardiac cells and also oxidative stress markers only in WT mice, not in FGF21-KO mice. Fenofibric acid's underlying mechanism behind balancing autophagy was elucidated using autophagy markers like LC3BII and sequestosome-1/p62 (SQSTM1/p62) expression. Fenofibrate's ability to direct autophagy signaling is exclusively depends on Sirtuin 1 (Sirt1) expression which was confirmed with sirtinol, a Sirt1 inhibitor. Diabetes Mellitus induced reduction in Sirt1 and FGF21 mRNA expression was also inhibited by PPARα agonist like Fenofibrate. Western bloating showed that there is an elevated expression of transforming growth factor beta (TGF-β) and connective tissue growth factor (CTGF) in FGF21-KO DM mice and those pathogenic alterations were not changed with Fenofibrate treatment. An in vitro study with H9C2 cardiac cell line showed that Fenofibrate prevented hyperglycemia - induced decrease in LC3BII and increase in SQSTM1/p62 levels, significantly. Similarly in response to Fenofibrate treatment, there was an increase in Sirt1 expression. Diabetes mediated inflammation, oxidative stress and fibrotic changes in the H9C2 cardiac cell line was found to be autophagy dependent but Sirt1 independent.

Fenofibrate and Sphingolipid production

Holm *et al.* (2019) suggesting that Fenofibrate boost up the production of long chain sphingomyelin like C22:1 and C24:0 in pancreatic islets. As a total, they found an overall increase in the sulfatide amount in pancreas especially in long chain sphingolipids with a reduction in C16. They verified these processes using liquid chromatography–mass spectrometry (LC-MS) analysis and shot gun approach. However it showed that Fenofibrate promotes the degradation of glycerophospholipid (GPL) and enhances the formation of lysophosphatidylcholine (LPC). But the anti-inflammatory feature of LPC found to be dominant than the inflammatory feature. Another interesting effect of Fenofibrate is the increase of Phosphatidylcholine: phosphatidylethanolamine (PC:PE) ratio. Fenofibrate could also increase the sympathetic neuronal volume in the pancreatic islets which was verified using a sympathetic neuronal marker, tyrosine hydroxylase (TH).

DISCUSSION

This is the first systematic review to investigate the effect of a PPARα agonist like Fenofibrate in T1DM. The beneficial molecular mechanism of Fenofibrate in T2DM induced animal models has already been established. Many reports clearly stated that fenofibric acid has proved its efficacy in preventing microvascular complication like retinopathy of diabetes.

Study by Chen *et al.*(2013) shows that Fenofibrate could reduce the retinal complications entangled with T1DM in animal models thereby preventing the incidence of DR and DME. They found that Fenofibrate has the ability to safeguard the blood-retinal barrier (BRB) by reducing the retinal vascular permeability and accumulation of leukocytes (leukostasis) in the small retinal blood vessels, diminishing the levels of MCP-1, Intercellular adhesion molecule 1 (ICAM-1), nuclear factor like NF-κB thereby promoting anti-inflammatory effects and abating the pathological development of new vessels (retinal neovascularization) and REC tube formation through the suppression of hypoxia-induced activation of the hypoxia-inducible factor-1 (HIF-1) pathway and over expression of VEGF. Another study by Liu *et al.* (2019) proposed a possible mechanism behind the attenuation of retinal damage and they suggested that it was mediated through the activation of Wnt/β-catenin signaling. Hyperglycemia activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (Nox2) and NADPH oxidase 4 (Nox4), oxidant enzymes primarily and stimulates Wnt/β-catenin signaling pathways through

phosphorylation of low-density lipoprotein receptor related protein-6 (LRP6). Fenofibrate's partial retinoprotective effect in T1DM was through the reduction of Nox2 over expression since Nox4 is controlled in transcriptional phase but depletion of Nox4 in genetic level inhibited cerebral hypoxia-induced neuronal damage. They also are suggesting that Fenofibrate inhibit the Wnt/β-catenin cascade in a PPARα - dependent manner. Similarly, Pearsall *et al.* (2019) found that this medication could also improve the mitochondrial functioning, thereby adding a neuroprotective effect in type 1 DR. The imbalance between increased superoxide generation and decreased antioxidant properties would result in ROS production and it is found to be detrimental to the retinal neuronal cells. This study found that fenofibrate could restore nicotinamide adenine dinucleotide (NADH) -linked respiration in the mitochondria of retinal cells and inhibits the excessive oxygen consumption and ROS generation, partially. After comparing aforesaid 3 studies, we found one of the possible pathway through which Fenofibrate reducing type 1 DR and this innovational efficacy is really need to be analyzed further.

Zhang *et al.* (2016) suggested that Fenofibrate is a cardiac protective medication in animal models with T1DM and it is independent of its systemic effects which has been proved using FGF21-deficient animal models. This study proposes that the synthetic ligand like Fenofibrate's binding to PPARα can prevent many aberrant cellular functions by dint of FGF21-reliant mechanisms. Resveratrol-induced Sirt 1 activation shown to be effective in improving autophagy and cardiac functioning.

A study by Holm *et al.* (2019) proposed that Fenofibrate has an additional neuroprotective effect and also increases the expression of sulfatide in the pancreatic beta cells. It also regulates metabolism of sphingolipid, thereby preventing the incidence of abnormal onset of T1DM in non-obese diabetic (NOD) mice. Other than pancreatic lipidome maintenance, they also found Fenofibrate's ability to increase TH-positive neuronal volume in pancreatic islets. It could control hyperglycemia as well as hypoglycemia via pancreatic neural fibre preservation and proved to be capable of maintaining glucose homeostasis in NOD mice.

Its efficacious role in T2DM is already been proved and only animal model studies are available currently, to show its importance in T1DM. However a human trial has been initiated in 2011 based on results with the preclinical studies with an estimated study completion in 2025 (ClinicalTrials). The strength associated with this study is that it could find a possible mechanism behind Fenofibrate's ability to ameliorate the occurrence of microvascular complications, especially DR and diabetic cardiomyopathy in T1DM. All the included studies were properly analyzed and the results were closely monitored which led to a positive impact on the outcomes. The results are dependable since they were conducted using proper diagnostic methods. Limitations associated with this study including country restrictions on using certain databases and foreign language publications. Now, the demand for future researches is heightened to portray its pharmacological part in juvenile diabetic micro vascular complications, since the incidence of these complications is really high.

INTERPRETATION AND CONCLUSION

When an individual become diabetic, the risk of getting into other diseases should also be considered during the commencement of the therapeutic plan. Lack of studies and financial crisis makes it difficult to discover novel agents with an essentiality to conduct further researches. After analyzing the results from the included preclinical studies, we found that Fenofibrate is an effective PPARα agonist in slowing down type 1 diabetic complications especially DR in animal models. However, human trials are awaiting and this review supports for more studies on humans for its beneficial effects.

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CONFLICTS OF INTEREST

No conflicts of interest have been declared.

CONTRIBUTION STATEMENT:

Swathi Swaroopa Borra and Sadagoban GK were involved in the selection of topic and assisted Resia Varghese, Hassan Elrufae Hassan Abdalla and Aiswarya Baiju in identifying appropriate articles in literature search as per the inclusion criteria. Data extraction and Risk of bias assessment were done by RV and HEHA. Any disagreements were discussed and resolved with SSB and SGK. Tables, Figures, first draft and the following corrected drafts of the manuscript, based on the comments provided by SSB and SGK were prepared by RV with help of AB for multiple times, in to the final version for publication.

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