COMMENTARY

Fenofibrate for Treating Diabetic Eye Disease

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Diabetes affects different structures of the eye as part of its deleterious systemic effects, with the retina being the main target. In fact, diabetic retinopathy (DR) is the most frequent and feared complication of diabetes and remains the leading cause of preventable blindness among working-age individuals in developed countries. Less attention, however, has been paid to other ocular structures located in the anterior chamber, such as the lens and the cornea. In this regard, it should be noted that cataracts are twice as common in people with diabetes as in those without diabetes (1). In addition, diabetes can also affect the cornea, which is the most richly innervated structure in the human body.

Corneal nerves represent part of the peripheral nervous system and arise from the ophthalmic branch of the trigeminal nerve. These nerves are responsible for touch, pain, and temperature sensation of the cornea and are vital in the blink reflex, wound healing, and tear production (2). Diabetic corneal neuropathy (DCN) can be considered the herald of diabetic keratopathy, which is also named diabetic corneal epitheliopathy. This is a degenerative disease characterized by delayed corneal re-epithelialization, reduced corneal sensitivity, neurotrophic corneal ulcers, and corneal edema. The prevalence of DCN has been reported in up to 64% of clinically examined patients with diabetes (3); however, diagnosis based on patient complaints is much less frequent. This divergence could be because patients with DCN are often asymptomatic due to corneal hypoesthesia. In recent years, in vivo confocal microscopy has become the standard method to assess the cornea at the cellular level. This method has shown that patients with diabetes present a reduction of corneal nerve metrics (3), with corneal fiber density being the most consistently decreased (4). Notably, the corneal fiber density is a powerful and reliable marker of peripheral diabetic neuropathy (5). However, in vivo confocal microscopy is still rarely available in the clinical setting.

Treatments for diabetic keratopathy include the use of topical lubricants, topical antibiotic ointments, patching, soft bandage contact lenses, tarsorrhaphy, and corneal transplants. None of these methods are greatly effective (3). Topically administered nerve growth factor (eye drops) improved corneal sensitivity and promoted corneal epithelial healing in both moderate and severe neurotrophic keratitis (6,7), and it has been approved by the U.S. Food and Drug Administration for treatment of patients with neurotrophic keratitis. Recent experimental research provided evidence that fenofibrate, a peroxisome proliferator–activated receptor-α (PPAR-α) agonist, also protects corneal nerves from diabetes-induced neurodegeneration, which was associated with restoration of corneal levels of brain-derived neurotrophic factor and glial cell–derived neurotrophic factor (8). Topical administration of PPAR-α agonists (e.g., fenofibrate) also improved corneal damage induced by causes unrelated to diabetes through the reduction of NF-κB (nuclear factor-κB) expression and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1β, and interleukin-6) (9,10). Taken together, these findings suggest fenofibrate is a good candidate to treat DCN.

In this issue of *Diabetes*, Teo et al. (11) evaluated the efficacy of fenofibrate as a treatment for patients with DCN. For this purpose, 30 patients with type 2 diabetes (without previous diagnosis of DCN) were treated with oral fenofibrate for 30 days. To assess the presence of corneal pathology at baseline and after fenofibrate treatment, a comprehensive examination was performed, including corneal nerve quantifications using in vivo confocal microscopy, corneal sensitivity, Shirmer I test, tear break-up time, and ocular surface integrity. The same examinations were performed in 20 individuals without diabetes (control group), but only at baseline. The authors found that treatment with fenofibrate significantly improved several corneal nerve parameters, including the regeneration of nerve fiber, as well as epithelial cell morphology, but no significant changes in Shirmer I test or corneal sensitivity were observed. Regarding the underlying mechanisms, the authors provided evidence that fenofibrate increases the tear levels of substance P, a neuropeptide that, through interactions

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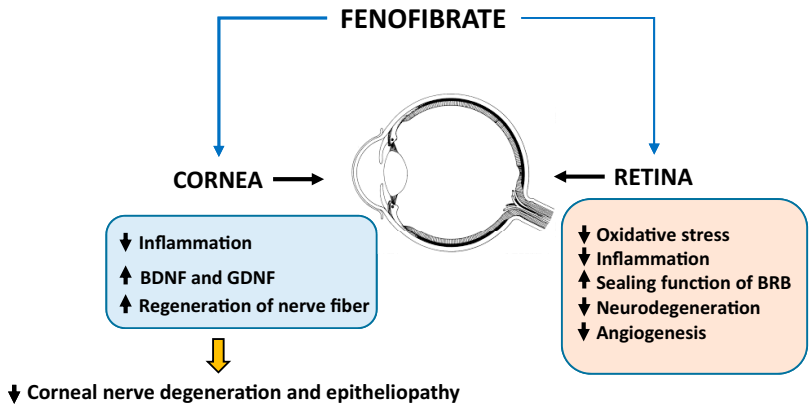

Figure 1—Schematic representation of the main underlying mechanisms by which fenofibrate exerts its beneficial actions in diabetes-induced corneal and retinal disease. BDNF, brain-derived neurotrophic factor; BRB, blood-retinal barrier; GDNF, glial cell–derived neurotrophic factor.

with neurokinin receptors, is involved in wound healing and inflammatory modulation (12). In addition, the tear proteomic analysis suggests that lipid modulation and neurotrophic, anti-inflammatory, and anticoagulation responses contribute to the observed beneficial effects of fenofibrate. Unfortunately, this study has serious limiting factors. First, it did not have a placebo control. Second, the potential corneal changes in the control group were not evaluated. Third, the small sample size could contribute to the lack of effect of fenofibrate in relevant outcomes such as corneal sensitivity and Shirmer I test. Finally, it is strongly recommended that the corneal complaints (symptoms) from patient-reported outcomes be collected before and after fenofibrate treatment using a validated visual discomfort scale as well as vision-related quality of life.

With regard to its effect on diabetes eye disease, fenofibrate is well-known for its reduction of the progression of DR in type 2 diabetes in two major prospective randomized controlled trials, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (13) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study (14). However, it is not currently used for treating DR because it is not approved for this use in most countries. This is because randomized trials primarily designed to test its effect on DR outcomes are needed. A large randomized double-masked placebo-controlled clinical trial to evaluate the effect of fenofibrate on the prevention of DR worsening is ongoing in the U.S. (NCT04661358). This study, comprising 910 participants with 4 years of follow-up, is expected to finish in April 2027 and should further enlighten the scientific community regarding the usefulness and safety of fenofibrate for treating early stages of DR. Overall, the nonlipidic actions of fenofibrate seem more important in accounting for its ability to reduce the progression of DR than the lipid-mediated mechanisms (15). Chen et al. (16) demonstrated the direct effects of fenofibrate in inhibiting proinflammatory mediators and vascular endothelial growth factor in experimental models of diabetes. It should be noted that in addition to its vasculotropic effects, fenofibrate has a neuroprotective effect in the diabetic retina that reduces glutamate excitotoxicity, reactive gliosis, and apoptosis (17). In addition, fenofibrate attenuates oxidative stress and neuroinflammation in diabetic retinas by modulating Nrf2 expression and NLRP3 inflammasome activation (18).

In summary, oral administration of fenofibrate could be an effective and safe method for treating DR and DCN, but the results of specific and robust clinical trials are still needed. The main underlying mechanisms by which fenofibrate exerts its multifaceted actions are displayed in Fig. 1.

Because transparency is of prime importance, the cornea does not have blood vessels. It receives nutrients via diffusion from the tear fluid on the outside and the aqueous humor on the inside as well as from neurotrophins supplied by nerve fibers that innervate it. In addition, PPAR-α is downregulated in the corneas of humans with diabetes. Therefore, due to the direct accessibility of the cornea by the topical route, the ocular administration of fenofibrate (eye drops) could be more efficient than the oral route. On the other hand, emerging experimental evidence suggests that fenofibrate (19), like some other drugs (20), can be delivered efficiently to the retina through topical administration (eye drops), abrogating the diabetes-induced vascular leakage. In summary, topical administration of fenofibrate could be useful for treating DCN and DR simultaneously. Future clinical trials should consider strategies that permit assessment of this dual effect by incorporating specific end points.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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