

Potential of oral fenofibrate in boosting corneal nerve regeneration in type 2 diabetes

Aims: To explore the effects of peroxisome proliferator-activated receptor- α (PPAR- α) agonist, oral fenofibrate, in individuals with type 2 diabetes.

Methods: Thirty participants with type 2 diabetes and twenty age-matched controls participated in this single-arm, open-label, interventional study, receiving oral fenofibrate for 30 days with dosages adjusted based on creatinine clearance time. The comprehensive assessment included clinical laboratory tests, neuropathic ocular surface assessment, corneal confocal microscopy (CCM), analysis of tear and plasma neuromediators and tear proteomics.

Results: At baseline, patients with diabetes exhibited significantly lower corneal nerve density (CNFD) ($P=0.04$) and length (CNFL) ($P=0.03$), along with higher corneal nerve fibre width (CNFW) ($P=0.03$). Following fenofibrate treatment, CNFD increased significantly ($P=0.01$) to healthy controls level and CNFW decreased significantly ($P=0.01$), indicating reduced nerve swelling. While not significant, there was a trend of improvement in other corneal parameters. After the treatment, epithelial cell morphology, tear film stability, and ocular surface punctuate keratopathy also showed significant improvement. Tear substance P (SP) concentrations significantly increased post-treatment. Tear proteomic analysis revealed that fenofibrate significantly upregulated and modulated neurotrophin signalling pathway, linoleic acid metabolism, and cholesterol and fat metabolism.

Conclusions: Oral fenofibrate demonstrated significant efficacy in improving ocular surface integrity and presents a potential novel treatment for diabetic corneal neuropathy.

Comments. Previous evidence supports the correlation between intensive glycemic control and the repair of corneal nerves. Also, improvements in corneal nerve morphology have been observed with enhanced control of blood pressure, HbA1c and total cholesterol. Furthermore, interventions like bariatric surgery, simultaneous pancreas and kidney transplantation have demonstrated efficacy in corneal nerve repair. Experimental and clinical studies have shown that neurotrophic factors, supplements of fatty acids possess the ability to promote corneal nerve regeneration.

This open-label clinical trial marks the first-time revelation of the neurotrophic effects of oral fenofibrate. This study not only demonstrates tangible improvements in corneal nerve metrics but also highlights significant improvements in epithelial cell morphology and tear substance P levels. The observed enhancements in epithelial morphology underscore the fenofibrate's pivotal role in promoting neurotrophin signalling and advancing corneal health. Clinical outcomes affirm fenofibrate's effectiveness in promoting ocular surface homeostasis, as evidenced by improved tear stability, and reduced punctuate keratopathy.

While acknowledging certain limitations, such as the need for longer endpoint durations and potential underestimation of nerve parameters in automated analysis, the study remains a signal of hope for advancing treatment options for diabetic corneal neuropathy. The comprehensive approach, integrating clinical assessments and molecular insights offers a robust foundation for further exploration and evaluation of fenofibrate's therapeutic potential in diabetes.

Alise Kalteniece

Reference. Teo CHY, Lin MT, Lee IXY, Koh SK, Zhou L, Goh DS, Choi H, Koh HWL, Lam AYR, Lim PS, Mehta JS, Kovalik JP, Coffman TM, Tan HC, Liu YC. Oral Peroxisome Proliferator-Activated Receptor- α Agonist Enhances Corneal Nerve Regeneration in Patients With Type 2 Diabetes. *Diabetes*. 2023 Jul 1;72(7):932-946

<https://diabetesjournals.org/diabetes/article/72/7/932/147959/Oral-Peroxisome-Proliferator-Activated-Receptor>