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THE ROLE OF FENOFIBRATE (TRICOR) IN THE COMPLEX TREATMENT OF MICROANGIOPATHIC COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES

Najmutdinova D.Q.,
Parpibaeva D.A.,
Salaeva M.S.,
Salimova N.D.,
Ergashov N.Sh.,
Sultonova D.A.

Abstract:

The results of numerous studies convincingly prove that fenofibrate, by affecting the activity of PPAR receptors, has hypolipidemic, anti-inflammatory and antioxidant effects. Activation of PPAR receptors in the liver leads to a decrease in the level of lipids that cause atherosclerosis (VLDL, small dense LDL), and an increase in the level of antiatherogenic HDL. Activation of PPAR-α in vascular cells allows to reduce the activity of inflammatory markers, such as C-reactive protein, tumor necrosis factor-β, interleukin-6, fibrinogen, etc. These advantages ultimately reduce the risk of development and progression of macro- and microvascular complications in diabetes mellitus.This abstract will review Evidence-based summary of the efficacy of fenofibrate (Tricor) in the complex treatment of microangiopathic complications in patients with type 2 diabetes.

Keywords:

Diabetes mellitus, FIELD, ACCORD-eye, Diabetic microangiopathy, dyslipidemia, fenofibrate (tricor).

INTRODUCTION

Nowadays, diabetes mellitus is considered a "Pandemic" and this disease is currently the most common endocrine disease. In 2017, according to the IDF, 425 million people worldwide were diagnosed with diabetes, and by 2045, this figure is expected to reach 629 million. Almost 50% of people suffering from this disease remain undiagnosed due to the asymptomatic course of the disease. In parallel with the continuous spread of the disease, the complications of diabetes and the percentage of disability and death caused by them are also increasing. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Especially in these patients, the addition of atherosclerosis of blood vessels aggravated the negative consequences of the process and even accelerated the process. The role of dyslipidemia is especially important in the pathogenesis of atherosclerosis, and it usually occurs in the form of the "cholesterol triad" (hypertriglyceridemia, increased LDL, and decreased HDL).

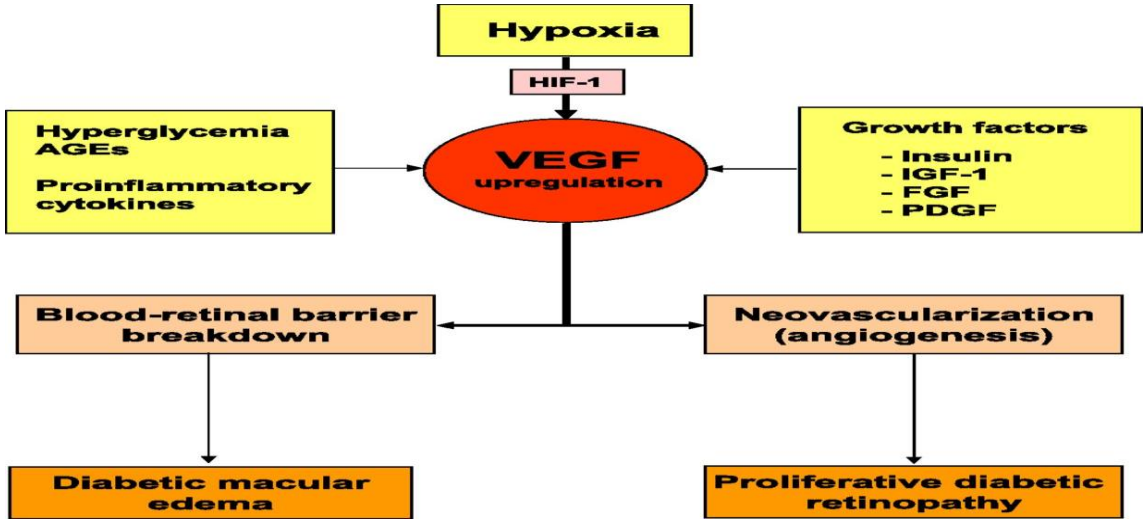
Diabetic retinopathy is one of the serious causes of deterioration of visual acuity, especially this complication often begins to appear during the working age of a patient with diabetes. Although laser therapy is considered the main treatment for diabetic retinopathy, this method is performed in almost the last stages of retinopathy and does not

always give the expected result, and as a result, the patient may lose the ability to see for life. In fact, the ideal situation for doctors is to prevent this complication from progressing to the next stages and reduce the need for laser therapy. This has caused increased attention to the drug fenofibrate in the world in recent years. To date, 2 large studies have been conducted that have studied the effect of the drug fenofibrate in the long term. The first of them: FIELD (The Fenofibrate Intervention and Event Lowering in Diabetes, 2005) studies show that fenofibrate (Tracor) effectively reduced the need for laser treatment of maculopathy and proliferative retinopathy in patients receiving the drug. According to another large study called ACCORD-Eye (2010), patients who received fenofibrate and a statin in combination significantly reduced the progression of retinopathy compared to patients who received statin drugs alone. In October 2013, Australia became the first country in the world to add this drug to its standard of care.

FENOFIBRATE

Fenofibrate has a hypolipidemic, anti-inflammatory and antioxidant effect by activating PPARα receptors. The effect of fenofibrate on the lipid spectrum is primarily related to reducing the amount of free fatty acids. In turn, this process is associated with increased synthesis of proteins responding to the transport of FFAs through this receptor and increased ß-oxidation of FFAs. Depletion of FFA inhibits the formation of triglycerides and very low density lipoproteins (VLDL). Another feature of PPARα receptors is that their activation increases the synthesis of apolipoprotein A-I and A-II, as well as high-density lipoproteins (HDL). It seems that they reduce the amount of atherogenic lipoproteins and increase the amount of antiatherogenic lipoproteins.

Activation of PPARα receptors reduces the activity of inflammatory markers in blood vessel cells, such as C-reactive protein, α-tumor necrosis factor, interleukin-6, fibrinogen, etc. These properties are important in preventing macro- and micro-angiopathic complications in privord. Fenofibrate prevents the synthesis of VEGF (Vascular endothelial growth factor), i.e., the factor that grows the blood-vessel endothelial layer, and blocks the proliferation and neovascularization of retinal vessels and prevents diabetic edema.



FIELD study. This study was a prospective, randomized controlled trial conducted over 5 years at 63 medical centers in Australia, New Zealand, and Finland. In this study, 9795 patients aged between 50-75 years and suffering from type 2 diabetes were observed. Patients did not take statin drugs during the study. All patients had initial plasma cholesterol levels of 3.0-6.5 mmol/l, total cholesterol/cholesterol-HDL ratio of 4:0 or higher, and triglyceride levels of 1.0-5.0 mmol/l. Patients were randomized 1 time to receive fenofibrate 200mg or placebo daily. The FIELD study showed that treatment with fenofibrate did not significantly reduce coronary events. However, it reduced overall cardiovascular events (mainly nonfatal myocardial infarction), but no significant changes in overall mortality. Studies conducted in Australia did not change the previous recommendations, and statin remained the first-line drug even in patients with diabetes. Fenofibrate is mainly indicated for hypertriglyceridemia or mixed dyslipidemia, especially abnormal increase in triglycerides.

However, the FIELD study provided important findings regarding diabetic retinopathy. All patients were initially given any information related to retinopathy and treatment with laser photocoagulation from their anamnesis, and subsequently, the cases and documents related to laser photocoagulation were recorded at each patient's appointment. In addition, in a certain group of 1012 patients, patients were evaluated according to standard ETDRS (Early Treatment of Diabetic Retinopathy Study) scale. Ophthalmologists evaluating this condition were not given information about the drugs the patients were taking. In the FIELD study, it was also found that 535 patients receiving placebo underwent laser therapy, compared to 337 patients receiving fenofibrate (37% less when receiving fenofibrate, P = 0, 0003). Treatment with fenofibrate in patients with maculopathy and proliferative retinopathy reduced the need for laser therapy by 36% (P = 0.003) and 38% (P = 0.009), respectively. These data are presented in Table 1.

1-table

Table 1. The results of FIELD showed that the need for laser therapy was reduced in those taking fenofibrate.

	Placebo (n=4900)	Fenofibrate (n=4895)	(95% CI)	P value
First laser therapy in any maculopathy	167	115	0.69(0.54-0.87)	0.002
The first laser therapy in proliferative retinopathy	108	75	0.7(0.52-0.93)	0.015
All laser therapy in any maculopathy	342	218	0.64(0.48-0.86)	0.003
All laser therapy in proliferative retinopathy	193	119	0.62(0.43-0.89)	0.009
General laser therapy for all patients	535	337	0.63(0.49-0.81)	0.0003

The ACCORD-EYE study. The ACCORD study was a large, multicenter, prospective, randomized controlled trial supported by multiple US institutions, including: the US National Heart, Lung, and Blood Institute, the National Institute of Diabetes, Kidney and Gastrointestinal Diseases, National Institute of Eye Diseases and National Institute of

Disease Control and Prevention. ACCORD-Eye was a subgroup of 2,856 patients (total of 10,251 patients in the larger group) that evaluated the efficacy of fenofibrate treatment in reducing the progression of diabetic retinopathy and the need for laser therapy and vitrectomy. studied. Including 1593 patients included in the lipid control component of ACCORD-Eye. At the beginning and during the 4th year, patients underwent complex standardized examinations of the fundus of the eye in 7 standard stereoscopic fields by ophthalmologists and optometrists. All the specialists who evaluate the fundus images are specially trained and have no knowledge about treatment methods. At the same time, information was obtained from a large group, through questionnaires and supporting documents about whether or not the patients received laser therapy or vitrectomy. After 4 years, the number of patients with progression of diabetic retinopathy grade 3 or more on the ETDRS scale or requiring laser photocoagulation or vitrectomy was 6.5% in patients receiving fenofibrate and a statin, compared to 10.2% in patients receiving a statin alone.

2-table. ACCORD-Eye

	Simvastatin and placebo	Simvastatin and fenofibrate	(95% CI)	P value
Progression of diabetic retinopathy	10.2%	6.5%	0.60 (0.42-0.87)	0.006
Moderate vision loss	24.5%	23.7%	0.95 (0.79-1.14)	0.57

3-table. Recommendation in the treatment of dyslipidemia.(17)

Recommendatiton	Recommendation class	Confidence level
Fibrates are effective in reducing TG levels	**I**	**B**
Use of nicotinic acid when there is an indication against fibrates	**IIa**	**B**
When using fibrates and nicotinic acid is not possible, use omega-3 fatty acid	**IIa**	**B**
Statin + nicotinic acid when GTG comes with low amount of ZYLPs	**IIa**	**A**
Statin + fibrates combination is effective in preventing macro- and micro-angiopathic complications in patients with diabetes and metabolic syndrome when the amount of GTG and ZYLP is low	**IIa**	**C**

4-table Efficacy of fenofibrate in the treatment and prevention of complications of diabetic nephropathy in the FIELD and ACCORD-Lipid studies.

Trial	Diabetic nephropathy	Placebo n (%)	Fenofibrate n (%)	%, p-value
FIELD	Progression of albuminuria	539(11)	466(9.5)	−13.6
FIELD	Regression of albuminuria	400(8.2)	462 (9.4)	+14.6(0.0022)
ACCORD	Microalbuminuria (after randomization)	1137(41.6)	1050(38.2)	−8.1 (0.01)
ACCORD	Macroalbuminuria (after randomization)	337(12.3)	289(10.5)	−14.6(0.03)

* In both the FIELD and ACCORD-Lipid studies, fenofibrate reduced the development of diabetic nephropathy (19)

5-table. In various studies, diabetes microangiopathic complications against the background of treatment with fenofibrate:

Trials n	Micro/macroangiopathy	Changes in relative risk, %	p-value
DAIS (Diabetes Atherosclerosis Intervention Study) (18)	Diabetik nefropatiya	-40 (slowing down the development of albuminuria)	<0.05
FIELD (11)	Diabetic nephropathy	-14	0.002
	Diabetic retinopathy	-31	<0.001
	Limb amputation	-36	0.02
	Diabetic neuropathy	-40	0.009
ACCORD-Lipid (13)	Diabetic nephropathy	-20 (decrease in the frequency of development of microalbuminuria)	0.01
		-24(decrease in the frequency of development of proteinuria)	0.01
ACCORD-EYE (14)	Diabetic retinopathy	-40	0.006

In addition to this, our research conducted by our professors and associate professors at the 3rd clinic of the Tashkent Medical Academy can be an addition to the above work. According to him, the results of the research conducted for 6 months showed that the glycated hemoglobin and arterial blood pressure in the patients, against the background of the target index, the lipid spectrum in the patients had the following indicators: group 1 LDL 2.4 ±0.2 mmol/l, triglyceride <1.8±0.1 mmol/l, HDL >0.7±0.12 mmol/l. Group 2 LDL 2.5±0.1 mmol/l, triglyceride <1.7±0.15 mmol/l, HDL >1.2±0.12 mmol/l. After special examinations of changes in the fundus of the eye, group 2 patients had a 27% lower rate of complications in the later stages compared to group 1 patients. In this study, it was found that adding fenofibrate (Tricor) drug to the standard treatment tactics of patients with type 2 diabetes can prevent complications of diabetic microangiopathy in the later stages.

Conclusion

There is sufficient evidence that fenofibrate slows the progression of diabetic retinopathy and reduces the need for laser photocoagulation and surgical vitrectomy. These findings suggest that fenofibrate has significant public health implications and benefits by slowing the progression of retinopathy and reducing the need for expensive and invasive treatments. In various other based studies conducted around the world, fenofibrate has also been shown to be effective in preventing microangiopathic complications of type 2 diabetes.

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