Original Article

Efficiency of fenofibrate in facilitating the reduction of central macular thickness in diabetic macular edema

Srilakshmi Srinivasan, Prathibha Hande, Jyoti Shetty, Sindhu Murali

Purpose: The purpose of this study is to study the benefit of addition of oral fenofibrate to the current regimen of diabetic macular edema (DME) management and quantify its effect on macular thickness and visual function in DME. **Methods:** Fifty-three eyes of 50 patients were randomized into treatment (Group A) (oral fenofibrate 160 mg/day) and control groups (Group B). Both groups underwent treatment of DME as per the standard treatment protocol of our hospital including intravitreal injections (anti-vascular endothelial growth factor/steroid) and grid laser. Patients were followed up every 2 months to note the visual acuity and central macular thickness (CMT) for 6 months. **Results:** Our groups were matched with respect to age (P = 0.802), mean diabetic age (P = 0.878), serum HbA1C levels (P = 0.523), and serum triglyceride levels (P = 0.793). The mean reduction in CMT was 136 μ in Group A and 83 μ in Group B at the end of 6 months. This difference was statistically significant (P = 0.031). Visual acuity improvement was 0.15 in Group A and 0.11 in Group B at the end of 6 months (P = 0.186). On subgroup analysis in Group A, we found that there was no difference in reduction of CMT between hypertensives and normotensives (P = 0.916), in patients with normal triglyceride levels and increased triglyceride levels (P = 0.975). **Conclusion:** Addition of fenofibrate to the standard protocol of DME management seems to facilitate reduction of CMT and probably have an added benefit on the visual functions.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_566_17

Quick Response Code:

Key words: Diabetic macular edema, facilitating reduction of edema, fenofibrate

The management of diabetic macular edema (DME) has seen a phenomenal change in the past decades: From the use of macular photocoagulation[1] alone for several decades to multiple intravitreal injection and implants.[2-5] Established patients with DME undergo multiple intravitreal injections, few sessions of laser apart from a strict emphasis on control of systemic parameters. Despite this, the treatment is prolonged, recurrences are common, and failures are frequent.[6]

Systemic therapy for DME largely meant control of diabetes, hypertension, and lipid levels.[7-9] It had nothing in specific predominantly due to inadequate evidence, associated complications along with dramatic benefits and safety profile of the injectable drugs.[10-14] A revival in the use of systemic medication for a local condition caused by a systemic disease does seem to have occurred in the recent times with hypolipidemic drugs, namely, Atorvastatin[15] and Fenofibrate. Two multicentric trials FIELD[16] and ACCORD[17] studies have established that fibrates can be used in the control of diabetic eye disease. Fenofibrate reduced the frequency of first laser treatment for macular edema by 31% and for proliferative retinopathy by 30%. Furthermore, it reduced the progression of diabetic retinopathy by 5.0% over 5 years (P = 0.022, FIELD) and 3.7% over 4 years (P = 0.006, ACCORD-eye). These two trials, however, have not evaluated the effect of fenofibrate on the preexisting macular edema requiring treatment.

Whether the addition of this drug in patients with DME will enhance the response of DME to the current available treatment and give better visual outcome is the question, we have set out to answer.

Methods

This is a prospective randomized controlled trial conducted in the retina department of a tertiary eye care center in the south Indian population. The study involved 50 patients with type 2 diabetes having treatment naïve, center-involving DME. The inclusion criteria were central macular thickness (CMT) measured on stratus optical coherence tomography (OCT) of equal to or more than 250 μ, HbA1c of <9, normal creatinine levels and systemic blood pressure <140/90 mmHg.

Patients with abnormal renal parameters, known liver disease, media opacities preventing good macular evaluation, macular ischemia, foveal hard exudates, coexisting macular diseases other than DME were excluded from the study. Patients with high-risk proliferative diabetic retinopathy (PDR) and those treated previously with laser photocoagulation or intravitreal injections were excluded from the study. Patients with known allergy to fenofibrate were also excluded. The study was conducted after approval from the institutional review board.

Department of Vitreo Retina, Bangalore West Lions Super Speciality Eye Hospital, Bengaluru, Karnataka, India

Correspondence to: Dr. Srilakshmi Srinivasan, "Swashti", No 202, Spring Woods, Near Nisarga Layout, Kallabalu Post, Bengaluru - 560 083, Karnataka, India. E-mail: veena_sri79@yahoo.com

Manuscript received: 29.07.17; Revision accepted: 21.09.17

Cite this article as: Srinivasan S, Hande P, Shetty J, Murali S. Efficiency of fenofibrate in facilitating the reduction of central macular thickness in diabetic macular edema. Indian J Ophthalmol 2018;66:98-105.

Methodology

Patients were included in the study after obtaining an informed written consent. All patients underwent complete ophthalmic examination including detailed history, best corrected visual acuity (Snellen), slit lamp examination, detailed fundus examination, Fundus fluorescein angiography (Topcon TRC.50EX retinal camera), and OCT on the stratus OCT (Carl Zeiss Meditec, USA). A complete physical evaluation by an internist and blood parameters including serum glucose, glycated hemoglobin, serum creatinine, blood urea, liver function tests, and lipid profile were done. Patients were randomized by coin tossing. Our study included 28 eyes of 25 patients in Group A, and 25 eyes of 25 patients in Group B. Twenty-two of our patients had DME only in one eye. In three patients having DME in both eyes, both eyes were included in the study in Group A. In Group B, all our patients had unilateral DME.

All patients underwent treatment for DME according to the current treatment protocols of our hospital [Fig. 1]. This protocol was modified from DRCR, net protocol to suit the needs of developing country population.

Patients in Group A were in addition given oral fenofibrate 160 mg/day for 6 months as a single evening dose.

Anti-vascular endothelial growth factor (VEGF)/triamcinolone (IVTA) was given 3.5 mm/4 mm from limbus in the inferotemporal quadrant. One session of grid/focal laser photocoagulation using 532 nm frequency doubled Nd:Yag (Oculight, Iridex Inc., USA) was given in the leaking areas as seen on the FFA as per the DRCR guidelines[18] after edema subsided (achievement of normal foveal contour). Patients were given a trial of topical steroids for steroid responsiveness before IVTA and carefully followed up for the same.

Patients with nonhigh risk PDR were treated with pan-retinal photocoagulation in three sittings, power adjusted to obtain a light grey burn.

Patients were followed up every 2 months with complete ophthalmic evaluation and OCT. Results were analyzed after 6 months.

Statistical analysis

The sample size was calculated to give a power of 0.8 to the study. Qualitative data were analyzed by Chi-square test, Mann–Whitney test and Student's *t*-test. In all the above tests, a $P \leq 0.05$ was accepted as indicative of statistical significance with 95% confidence interval.

Results

Demographic data

We studied 28 eyes of 25 patients in Group A and 25 eyes of 25 patients in Group B. Most of our patients were in age

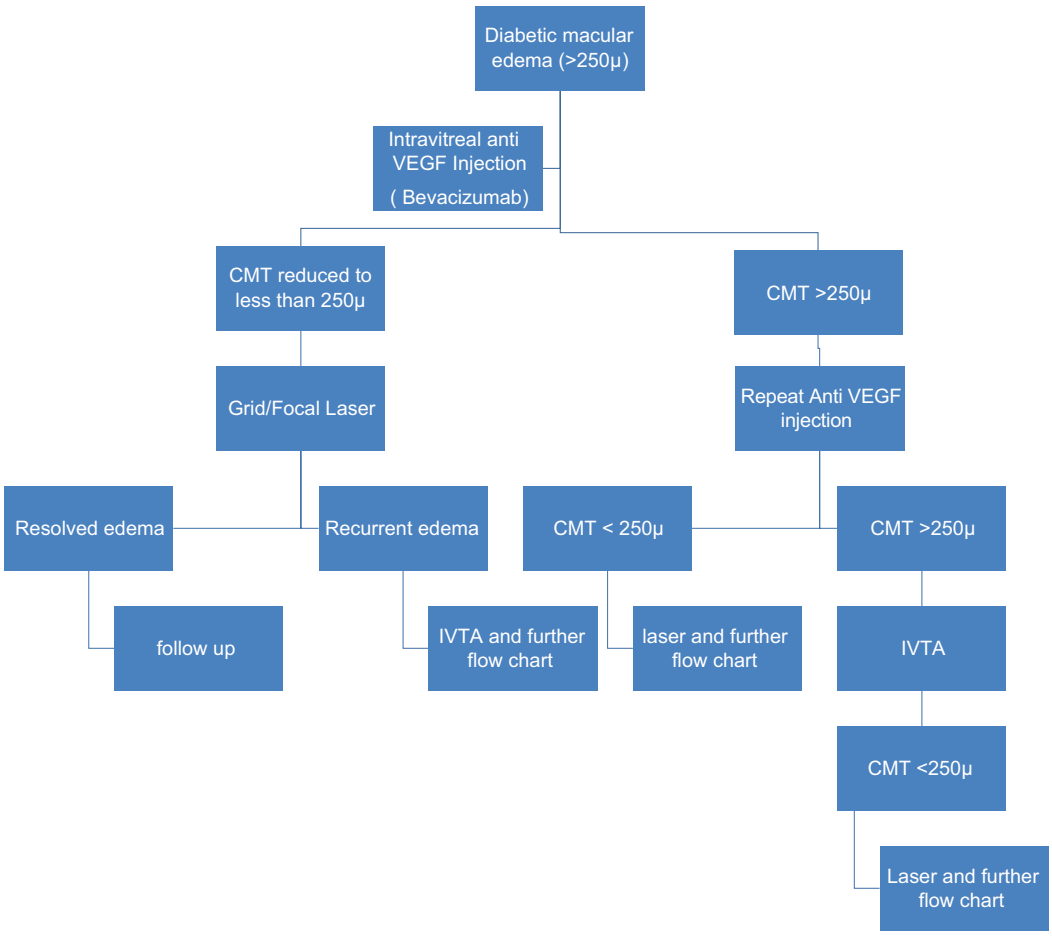

Figure 1: Treatment algorithm for patients with diabetic macular edema followed in our study. CMT=Central macular thickness; IVTA=Intravitreal triamcinolone acetate

Table 1: Comparison of various laboratory parameters between the two groups

Parameter	Group	Number of patients	Mean	SD	SEM	Mean difference	*t/z*	*P*
HbA1c	Group A	25	7.85	1.29	0.26	−0.250	−0.643	0.523
	Group B	25	8.10	1.45	0.29			
FBS	Group A	25	139.96	45.13	9.03	−17.120	−1.182	0.243
	Group B	25	157.08	56.65	11.33			
PPBS†	Group A	25	218.40	51.92	10.38	−17.880	−0.534	0.594
	Group B	25	236.28	75.72	15.14			
Blood urea	Group A	25	29.28	7.24	1.45	−2.560	−1.020	0.313
	Group B	25	31.84	10.25	2.05			
Serum creatinine	Group A	25	0.91	0.30	0.06	−0.073	−0.815	0.419
	Group B	25	0.98	0.34	0.07			
TC†	Group A	25	198.00	76.52	15.30	−18.960	−2.553	0.011*
	Group B	25	216.96	43.66	8.73			
TG†	Group A	25	197.84	72.22	14.44	−16.880	−0.262	0.793
	Group B	25	214.72	110.01	22.00			
LDL†	Group A	25	102.46	18.69	3.74	−18.380	−0.010	0.992
	Group B	25	120.84	75.09	15.02			
VLDL†	Group A	25	37.25	11.56	2.31	−12.072	−2.116	0.034*
	Group B	25	49.32	22.84	4.57			
HDL†	Group A	25	45.12	9.37	1.87	4.564	−0.944	0.345
	Group B	25	40.56	11.22	2.24			

*TC and VLDL were statistically significant. HbA1c: Glycated hemoglobin, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, TC: Total cholesterol, TG: Triglyceride, LDL: Low density lipoprotein, HDL: High density lipoprotein, VLDL: Very low density lipoprotein, SD: Standard deviation, SEM: Standard error of mean, †*P* value of <0.05 was considered significant

Table 2: Baseline clinical data

	Phakics	Pseudophakics	NPDR	PDR	Diffuse edema	Focal edema
Group A	21	7	20	8	20	8
Group B	18	7	16	9	15	10
P	0.805		0.563		0.384	

PDR: Proliferative diabetic retinopathy, NPDR: Non-PDR

group of 51–70 years. Mean age in Group A was 60.16 years and Group B was 59.40 years. Males predominated in both groups (74% in Group A and 76% in Group B). Mean duration of diabetes was 11.38 years in Group A and 11.09 years in Group B. Most of our patients had diabetes for 5–15 years. More than 50% of the patients in each group were hypertensives on treatment, and there was no statistically significant difference in the distribution of hypertensives in the two groups. Our groups were comparable based on the demographic data.

Baseline laboratory parameters

Baseline laboratory data are shown in Table 1. The two groups were matched with respect to mean HbA1C, mean PPBS levels ($P = 0.593$), mean FBS levels (0.234), mean blood urea ($P = 0.313$), mean serum creatinine ($P = 0.419$), mean triglyceride levels ($P = 0.793$), mean low-density lipoprotein (LDL) levels, and mean high-density lipoprotein levels. Incidentally, we found a significant difference in the mean serum cholesterol and mean very LDL (VLDL) levels in the two groups in favor of Group B.

Despite the statistically significant difference the actual value of these parameters was within the normal limits and did not warrant any treatment.

Baseline clinical data

Seventy-five percent of the eye in Group A and 72% in Group B were phakic. 20 of the 28 eyes in Group A had non-PDR versus 16 of 25 eyes in Group B [Tables 2 and 3]. This difference was not statistically significant ($P = 0.563$). Rest of patients had early PDR. 71% and 60% of patients respectively in Group A and Group B had diffused macular edema and rest had focal edema.

Clinical results

Results in control group (Group B)

Group B received an average of 2.23 injections in 6 months. We found a statistically significant reduction in the macular edema from 404 μ (±91.59) to 319 μ (±57.29 μ) in the control group (Group B). Visual acuity improved from 0.41 log mar to 0.33 log mar. This was statistically significant with $P < 0.001$ at the end of 6 months. Three eyes (12%) had ≥2 line improvement 13 eyes (52%) had ≥1 line improvement in vision, and 9 eyes (36%) had stabilized vision [Table 3].

Results in fenofibrate group (Group A)

Clinical photograph and OCT of one of our patient in fenofibrate group is shown in Figs. 2-5. Patients in Group A received an average of 2.1 injections in 6 months. In the fenofibrate group (Group A), we found that CMT decreased from 429 μ (±130 μ) to 293.96 μ (±83.05 μ). This was statistically significant with a $P < 0.001$ at the end of 6 months. Visual acuity improved from 0.41 log mar to 0.26 log mar at the end of 6 months. More than two line improvement in vision was seen in 7 eyes (25%), more than one line improvement was seen in 14 eyes (50%) and stabilized in 7 (25%) eyes [Table 4].

Comparative analysis of treatment outcomes in case and control group (Group B)

Effect on central macular thickness

Initial CMT was higher in the fenofibrate group (Group A) compared to control group (Group B) without statistical significance indicating that we could compare the two groups. The mean CMT was reduced by 136 μ in Group A and about 83 μ in Group B from the baseline at the end of 6 months. The results were statistically significant at the end of 6 months with a *P* value of 0.031 [Table 5]. The difference between the CMT of two groups steadily decreased from baseline to 6th month. Mean CMT in Group A became lower than Group B at month 4 and the difference was statistically significant at 6 months [Fig. 6].

Effect on visual acuity

The improvement in mean visual acuity in Group A was 0.15 log mar units as compared to 0.11 log mar units in Group B at the end of 6 months [Table 6 and Fig. 7]. Although the visual acuity was higher in Group A at 6th month this difference was not statistically significant with *P* value of 0.186. A higher number of patients achieved a two-line improvement in the vision in Group A compared to Group B (7 vs. 3).

Reduction of hard exudates

The reduction in hard exudate was noted in 6 eyes (19%) in Group A and 4 eyes (16%) in Group B at the end of the follow-up period, but the difference between the two groups was not statistically significant.

Results within the fenofibrate group (Group A)

Subgroup analysis in the Group A showed that there was no statistically significant difference in reduction of CMT between eyes with PDR and NPDR (NPDR – 150 μ, PDR – 120 μ) (*P* = 0.746). There was no statistically significant difference in CMT reduction between hypertensives and normotensives (hypertensives – 130 μ, normotensives – 141 μ) (*P* = 0.916). We also did not find a statistically significant difference between normal and abnormal triglyceride levels and normal and abnormal cholesterol levels (Normal TG - 136 μ, high TG - 134 μ, *P* = 0.975) (normal cholesterol - 122 μ, high cholesterol - 183 μ, *P* = 0.247) [Table 7].

Table 3: Results in control group (Group B)

	Baseline	At the end of 6 months
CMT (μ)	404	319
Visual acuity (logMAR)	0.41	0.33
Improvement in visual acuity		
>3 lines	0	
>2 lines	3	12%
>1 line	13	52%
Stabilized	9	36%

LogMAR: Logarithm of the minimum angle of resolution

Table 4: Results in fenofibrate group (Group A)

	Baseline	At the end of 6 months
CMT (μ)	429	293
Visual acuity (logMAR)	0.41	0.26
Improvement in visual acuity		
>3 lines	-	-
>2 lines	7 eyes	25%
>1 line	13 eyes	46%
Stabilized	7 eyes	25%

CMT: Central macular thickness, LogMAR: Logarithm of the minimum angle of resolution

Discussion

Our study found that addition of fenofibrate to an established protocol for management of DME improves the reduction of

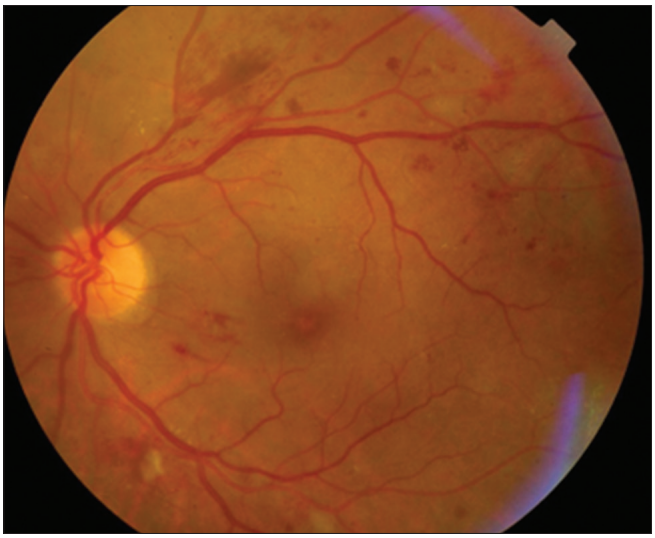

Figure 2: Baseline photograph of patient with diabetic macular edema and PDR

Table 5: Comparison of mean central macular thickness between the two groups (Mann-Whitney test)

CMT	Group	Number of eyes	Mean*	SD*	SEM*	Mean difference	*Z*	*P*
Baseline	Group A	28	429.29	130.16	24.60	25.006	−0.392	0.695
	Group B	25	404.28	91.59	18.32			
2 months	Group A	28	363.46	95.80	18.10	8.744	−0.009	0.993
	Group B	25	354.72	76.06	15.21			
4 months	Group A	28	328.79	81.01	15.31	−1.334	−0.374	0.708
	Group B	25	330.12	65.55	13.11			
6 months	Group A	28	293.96	83.05	15.69	−25.196	−2.156	0.031*
	Group B	25	319.16	57.29	11.46			

*Microns. CMT: Central macular thickness, SD: Standard deviation, SEM: Standard error of mean

Table 6: Comparison of mean best corrected visual acuity (logarithm of the minimum angle of resolution) between the two groups (Mann-Whitney test)

Visual acuity	Group	Number of eyes	Mean	SD	SEM	Mean difference	*Z*	*P*
Baseline	Group A	28	0.41	0.17	0.03	−0.033	−0.299	0.765
	Group B	25	0.44	0.23	0.05			
2 months	Group A	28	0.38	0.18	0.03	−0.053	−1.022	0.307
	Group B	25	0.43	0.24	0.05			
4 months	Group A	28	0.32	0.14	0.03	−0.039	−0.769	0.442
	Group B	25	0.36	0.19	0.04			
6 months	Group A	28	0.26	0.14	0.03	−0.068	−1.323	0.186
	Group B	25	0.33	0.20	0.04			

SD: Standard deviation, SEM: standard error of mean

Table 7: Subanalysis of fenofibrate group (Group A) with respect to central macular thickness

	NPDR	PDR	Normotensives	Hypertensives	Higher TG	Normal TG	Higher TC	Normal TC
Group A (μ)	150	120	130	141	134	136	183	122
P	0.746		0.916		0.975		0.247	

PDR: Proliferative diabetic retinopathy, NPDR: Non-PDR, TC: Total cholesterol, TG: Triglyceride

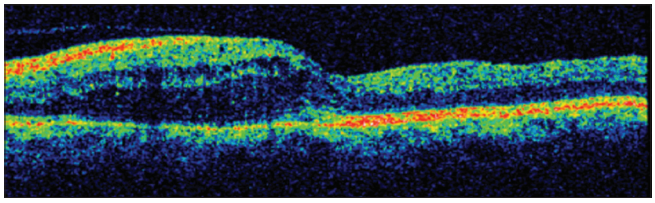

Figure 3: Baseline optical coherence tomography

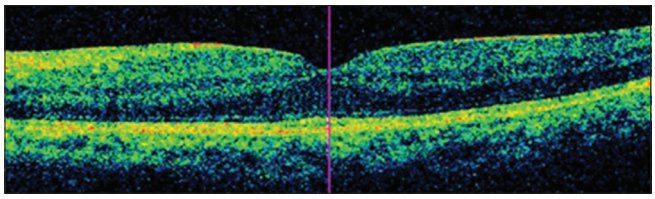

Figure 5: Optical coherence tomography at six months

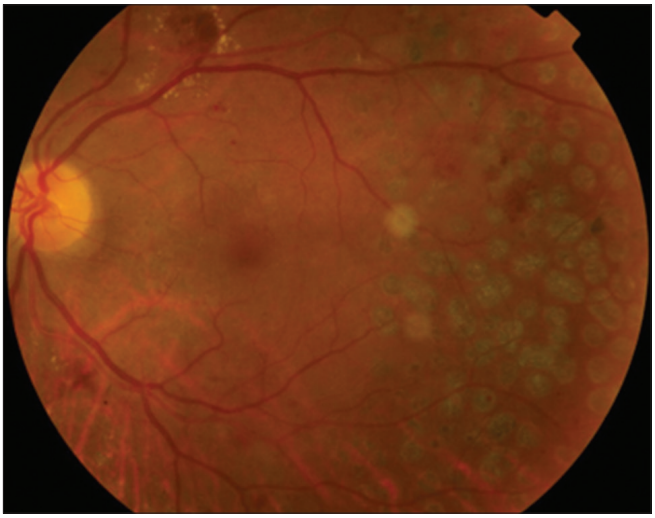

Figure 4: Clinical picture at six months

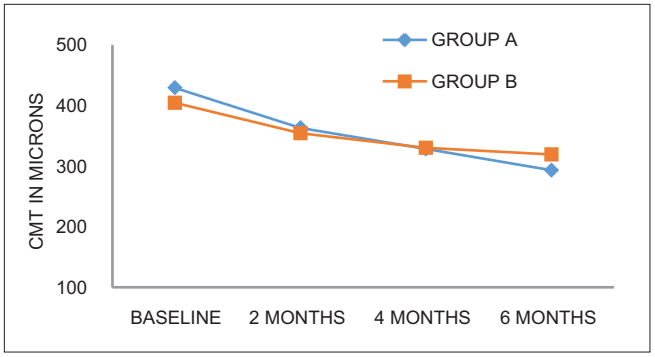

Figure 6: Comparative change in the central macular thickness between Group A and Group B over 6 months

CMT significantly irrespective of triglyceride, hypertensive, and the diabetic retinopathy status. In addition, it improves the visual acuity though the improvement is not statistically significant at 6 months.

In this study, two groups were matched with respect to chronological age, diabetic age, diabetic control, staging of diabetic retinopathy, and systemic parameters except serum cholesterol and serum VLDL levels (these two parameters were tilted in favor of Group B and these patients were not started on anti-cholesterol therapy as they were with in normal limits of serum cholesterol levels).

Both groups received the same treatment protocol for DME at the same institute under two ophthalmologists. The only difference thereby is the introduction of oral Fenofibrate in Group A.

Our study was done with a time domain OCT machine. This could have underestimated the CMT compared to spectral domain OCT. Since both initial and final scans were done in the same TD-OCT the decrease in the CMT could be evaluated.[19]

Statistically significant decrease in CMT and the improvement in the visual acuity was achieved in both groups. Independently, both the treatment protocols have shown improvement in the

functional and anatomical outcome. Hence, any difference in the outcome either functional or anatomical in Group A compared to Group B can be attributed to the only difference between the groups, namely, 160 mg of oral Fenofibrate in Group A.

Fenofibrate and proposed mechanism of action in diabetes: Fenofibrate is a peroxisome proliferator-activated receptor α agonist. It is used in hypertriglyceridemia and mixed dyslipidemia.[20] Fenofibrate is converted to fibric acid in plasma and stimulates PPRFα which works through various mechanisms at the cellular level [Fig. 8].

Pathogenesis of diabetic retinopathy involves an increase in nitric oxide levels, increased inflammatory mediators through the cyclooxygenase pathway, increased production of oxygen free radicals due to advanced glycosylation end products and high intracellular glucose-induced capillary cell apoptosis.[21] Multiple biochemical actions after stimulation of PPRFα seems to counter these pathological mechanisms giving a sound biochemical basis for the use of fenofibrate in diabetes.[22-37]

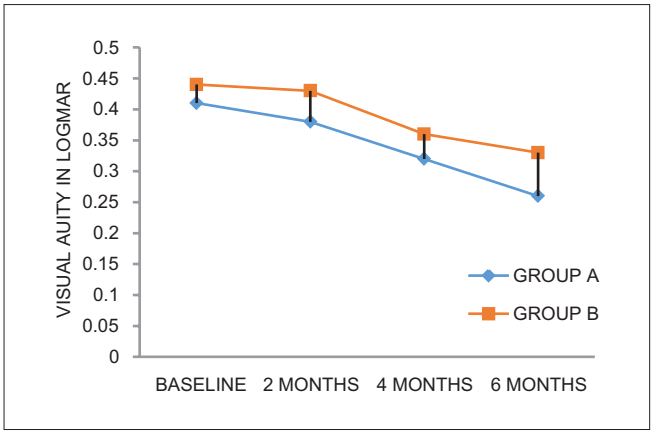

Figure 7: Comparative change in visual acuity between Group A and Group B over 6 months

Clinical evidence provided by FIELD and ACCORD studies also support the utility of this PPRFα agonist in diabetes.

FIELD study a multicentric study by Keech *et al*. concluded that requirement for the first laser was significantly lower in the fenofibrate group ($P = 0.0002$, HR – 0.69) and 2 step progression in retinopathy was significantly lower in patients with preexisting retinopathy ($P = 0.004$). In this study, laser treatment of macular edema specifically reduced by 31% ($P = 0.002$). Each pathology showed an accumulation of benefit over time with crossing over of curves at 8 months. Our study also showed statistically significant improvement in CMT at 6th month with a gradual widening of the gap between the two groups.

ACCORD study observed that the beneficial effects were maximum in mild-to-moderate NPDR (steps 2–4 at enrollment) (P = 0.00009) and addition of fenofibrate had synergistic effect with intensive glycemic control. In steps 5–7, fenofibrate group showed a significant benefit whereas the intensive glycemic control group did not. However, there was no significant benefit in the progression of DME in 3 steps ($P = 0.78$). This study involved only initial and the 4th year retinal photograph to comment on the progression of macular edema. The absence of frequent follow-up could result in loss of critical information underestimating the effect of the drug. The treatment used in ACCORD study was grid/focal laser photocoagulation alone. In our study, we found that addition of fenofibrate to an established regimen of anti-VEGF injection and laser reduced the CMT significantly at 6 months. The

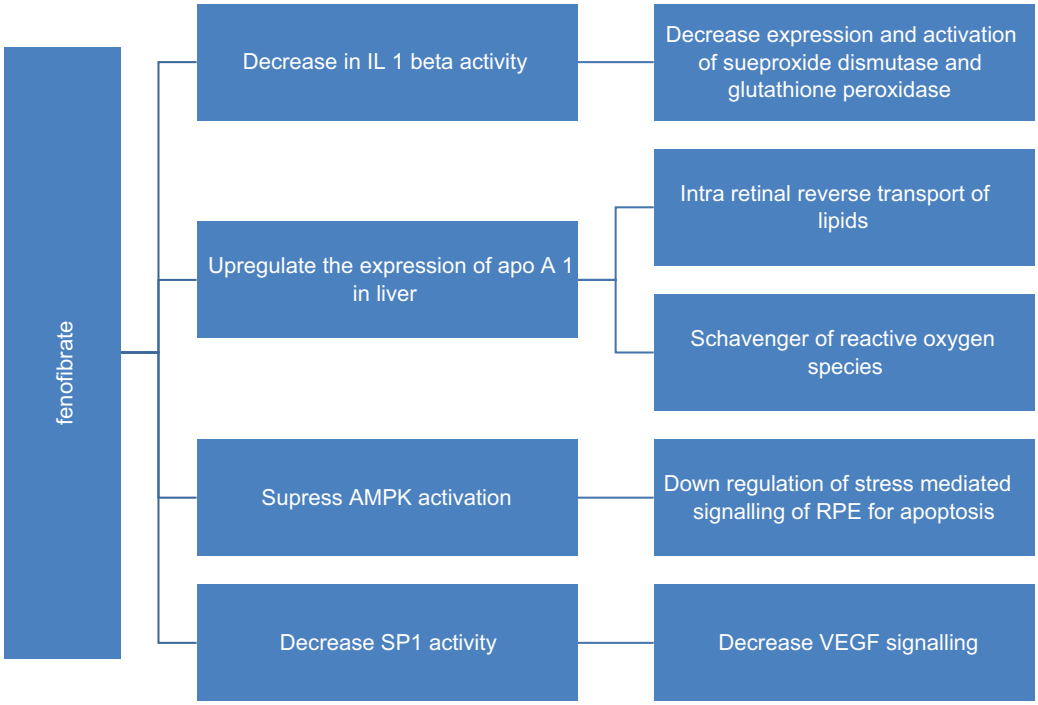

Figure 8: Biochemical actions of fenofibrate after conversion to fibric acid in plasma. Fibric acid activates PPAR to bring about the above mentioned changes

synergistic effect of fenofibrate may be enhanced when added to a regimen of anti-VEGF injection and laser.

The MacuFen study (n = 100) by Massin *et al*. found that use of 135 mg of fenofibrate moderately reduced the total macular volume in patients with non-center involving macular edema but the reduction was not statistically significant.[38] This could be due to lower drug dosage. Dosage of drug used in FIELD and ACCORD were 200 mg and 160 mg, respectively. There was a 5% and 3.7% risk reduction in FIELD and ACCORD, respectively. Our study found that 160 mg of drug was beneficial to the patients of DME. Whether the differences seen in various studies are due to different dosages of drug used needs to be studied, and there is need to zero in on the optimal dosage of the drug. Another possibility as highlighted by the FIELD and ACCORD studies is that higher stage of diabetic retinopathy shows higher benefit with addition of fenofibrate. This could be the case in our study where all patients had a center-involving DME requiring treatment.

FIELD and ACCORD studies observed that the effect of fenofibrate on slowing progression of diabetic retinopathy was seen irrespective of triglyceride levels which our study also corroborated.

Earlier trials with fibrates were limited due to the incidence of rhabdomyolysis.[39] FIELD and ACCORD did not report any musculoskeletal side effects. Our study also did not have any incidence of musculoskeletal side effects.

Limitations

Small sample size, single-center study, single dosage arm, and follow-up duration of 6 months are our limitations. Despite our limitations, our study provides important information regarding the utility of Fenofibrate in DME.

Conclusion

Fenofibrate seems to facilitate reduction of CMT in DME. Larger, multicentric, and longer duration studies with different dosage of fenofibrate would throw more light on this initial finding.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Photocoagulation for diabetic macular edema. Early treatment diabetic retinopathy study report number 1. Early treatment diabetic retinopathy study research group. Arch Ophthalmol 1985;103:1796-806.
2. Wenick AS, Bressler NM. Diabetic macular edema: Current and emerging therapies. Middle East Afr J Ophthalmol 2012;19:4-12.
3. Comer GM, Ciulla TA. Pharmacotherapy for diabetic retinopathy. Curr Opin Ophthalmol 2004;15:508-18.
4. Simó R, Hernández C. Intravitreous anti-VEGF for diabetic retinopathy: Hopes and fears for a new therapeutic strategy. Diabetologia 2008;51:1574-80.
5. Girach A, Lund-Andersen H. Diabetic macular oedema: A clinical overview. Int J Clin Pract 2007;61:88-97.
6. Virgili G, Parravano M, Menchini F. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database Syst Rev 2014;24;10:CD007419.
7. Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. The diabetes control and complications trial research group. Diabetes 1997;46:1829-39.
8. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK prospective diabetes study group. BMJ 1998;317:703-13.
9. Kohner EM, Aldington SJ, Stratton IM, Manley SE, Holman RR, Matthews DR, *et al.* United Kingdom Prospective Diabetes Study, 30: Diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. Arch Ophthalmol 1998;116:297-303.
10. Shen LQ, Child A, Weber GM, Folkman J, Aiello LP. Rosiglitazone and delayed onset of proliferative diabetic retinopathy. Arch Ophthalmol 2008;126:793-9.
11. Ryan EH Jr., Han DP, Ramsay RC, Cantrill HL, Bennett SR, Dev S, *et al.* Diabetic macular edema associated with glitazone use. Retina 2006;26:562-70.
12. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004;364:685-96.
13. PKC-DMES Study Group. Effect of ruboxistaurin in patients with diabetic macular edema: Thirty-month results of the randomized PKC-DMES clinical trial. Arch Ophthalmol 2007;125:318-24.
14. Davis MD, Sheetz MJ, Aiello LP, Milton RC, Danis RP, Zhi X, *et al.* Effect of ruboxistaurin on the visual acuity decline associated with long-standing diabetic macular edema. Invest Ophthalmol Vis Sci 2009;50:1-4.
15. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. Am J Ophthalmol 2004;137:675-82.
16. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, *et al*. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): A randomised controlled trial. Lancet 2007;370:1687-97.
17. ACCORD Study Group, Buse JB, Bigger JT, Byington RP, Cooper LS, Cushman WC, *et al*. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: Design and methods. Am J Cardiol 2007;99:21i-33i.
18. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early treatment diabetic retinopathy study report number 2. Early treatment diabetic retinopathy study research group. Ophthalmology 1987;94:761-74.
19. Forte R, Cennamo GL, Finelli ML, de Crecchio G. Comparison of time domain Stratus OCT and spectral domain SLO/OCT for assessment of macular thickness and volume. Eye (Lond) 2009;23:2071-8.
20. Yang LP, Keating GM. Fenofibric acid: In combination therapy in the treatment of mixed dyslipidemia. Am J Cardiovasc Drugs 2009;9:401-9.
21. Ehrlich R, Harris A, Ciulla TA, Kheradiya N, Winston DM, Wirostko B, *et al*. Diabetic macular oedema: Physical, physiological and molecular factors contribute to this pathological process. Acta Ophthalmol 2010;88:279-91.
22. Lyons TJ, Jenkins AJ, Zheng D, Lackland DT, McGee D, Garvey WT, *et al.* Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. Invest Ophthalmol Vis Sci 2004;45:910-8.
23. Miranda S, González-Rodríguez Á, García-Ramírez M, Revuelta-Cervantes J, Hernández C, Simó R, *et al.* Beneficial effects

of fenofibrate in retinal pigment epithelium by the modulation of stress and survival signaling under diabetic conditions. J Cell Physiol 2012;227:2352-62.

24. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC, *et al.* Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998;98:2088-93.
25. Trudeau K, Roy S, Guo W, Hernández C, Villarroel M, Simó R, *et al*. Fenofibric acid reduces fibronectin and collagen type IV overexpression in human retinal pigment epithelial cells grown in conditions mimicking the diabetic milieu: Functional implications in retinal permeability. Invest Ophthalmol Vis Sci 2011;52:6348-54.
26. Bordet R, Ouk T, Petrault O, Gelé P, Gautier S, Laprais M, *et al.* PPAR: A new pharmacological target for neuroprotection in stroke and neurodegenerative diseases. Biochem Soc Trans 2006;34:1341-6.
27. Simó R, García-Ramírez M, Higuera M, Hernández C. Apolipoprotein A1 is overexpressed in the retina of diabetic patients. Am J Ophthalmol 2009;147:319-250.
28. Wong TY, Simó R, Mitchell P. Fenofibrate – A potential systemic treatment for diabetic retinopathy? Am J Ophthalmol 2012;154:6-12.
29. Rosenson RS. Fenofibrate: Treatment of hyperlipidemia and beyond. Expert Rev Cardiovasc Ther 2008;6:1319-30.
30. Simó R, Hernández C. Fenofibrate for diabetic retinopathy. Lancet 2007;370:1667-8.
31. García-Ramírez M, Canals F, Hernández C, Colomé N, Ferrer C, Carrasco E, *et al.* Proteomic analysis of human vitreous fluid by fluorescence-based difference gel electrophoresis (DIGE): A new strategy for identifying potential candidates in the pathogenesis of proliferative diabetic retinopathy. Diabetologia 2007;50:1294-303.
32. Arakawa R, Tamehiro N, Nishimaki-Mogami T, Ueda K, Yokoyama S. Fenofibric acid, an active form of fenofibrate, increases apolipoprotein A-I–mediated high-density lipoprotein biogenesis by enhancing transcription of ATP-binding cassette transporter A1gene in a liver X receptor– protein kinase (AMPK) activation. Arterioscler Thromb Vasc Biol 2005;25:1193-7.
33. Kim J, Ahn JH, Kim JH, Yu YS, Kim HS, Ha J, *et al.* Fenofibrate regulates retinal endothelial cell survival through the AMPK signal transduction pathway. Exp Eye Res 2007;84:886-93.
34. Cheung N, Wong TY. Fenofibrate and diabetic retinopathy. Lancet 2008;371:721-2.
35. Villarroel M, Garcia-Ramírez M, Corraliza L, Hernández C, Simó R. Fenofibric acid prevents retinal pigment epithelium disruption induced by interleukin-1β by suppressing AMP-activated protein kinase (AMPK) activation. Diabetologia 2011;54:1543-53.
36. Meissner M, Stein M, Urbich C, Reisinger K, Suske G, Staels B, *et al.* PPARalpha activators inhibit vascular endothelial growth factor receptor-2 expression by repressing sp1-dependent DNA binding and transactivation. Circ Res 2004;94:324-32.
37. Varet J, Vincent L, Mirshahi P, Pille JV, Legrand E, Opolon P, *et al.* Fenofibrate inhibits angiogenesis *in vitro* and *in vivo*. Cell Mol Life Sci 2003;60:810-9.
38. Massin P, Peto T, Ansquer JC, Aubonnet P, MacuFEN Study Investigators FT. Effects of fenofibric acid on diabetic macular edema: The MacuFen study. Ophthalmic Epidemiol 2014;21:307-17.
39. Wu J, Song Y, Li H, Chen J. Rhabdomyolysis associated with fibrate therapy: Review of 76 published cases and a new case report. Eur J Clin Pharmacol 2009;65:1169-74.