

Role of lipid-lowering agents in the management of diabetic retinopathy

Estelle Ioannidou, Vasilis-Spyridon Tseriotis, Konstantinos Tziomalos

Estelle Ioannidou, Vasilis-Spyridon Tseriotis, Konstantinos Tziomalos, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 54636 Thessaloniki, Greece

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Correspondence to: Konstantinos Tziomalos, MD, PhD, Assistant Professor of Internal Medicine, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 1 Stilponos Kyriakidi street, 54636 Thessaloniki, Greece. ktziomalos@yahoo.com
 Telephone: +30-2310-994621
 Fax: +30-2310-994773

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Abstract

Diabetic retinopathy affects a substantial proportion of patients with diabetes mellitus (DM) and is the leading cause of blindness in working-aged adults. Even though

the incidence of diabetic retinopathy has declined in the last decades, its prevalence increased and is expected to rise further as a result of the increasing incidence of type 2 DM (T2DM) and the longer life expectancy of patients with DM. The pathogenesis of diabetic retinopathy is multifactorial. Some observational studies suggested an association between dyslipidemia and the development and progression of retinopathy in patients with DM but others did not confirm this association. Regarding lipid-lowering agents, studies that evaluated the role of statins in the management of these patients are mostly small and yielded discrepant results. Large randomized studies with statins in patients with T2DM showed no benefit of these agents on diabetic retinopathy but were not designed to address this effect. In contrast, both preclinical data and two large randomized controlled studies, the FIELD and the ACCORD trial, showed that fenofibrate delays the progression of diabetic retinopathy. Even though the mechanisms underpinning this favorable effect are not entirely clear, these findings suggest that fenofibrate might represent a useful tool for the management of diabetic retinopathy.

Key words: Diabetes mellitus; Lipid-lowering agents; Statins; Fibrates; Ezetimibe; Colesevelam; Retinopathy

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Core tip: Even though it is unclear whether dyslipidemia is implicated in the pathogenesis of diabetic retinopathy, both preclinical data and two large randomized controlled studies showed that treatment with fenofibrate delays the progression of diabetic retinopathy. In contrast, statins do not appear to play a role in the management of this complication despite the promising findings of animal studies.

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INTRODUCTION

Diabetic retinopathy affects 27%-40% of patients with diabetes mellitus (DM)^[1-4] and is the leading cause of blindness in working-aged adults^[5]. Even though the incidence of diabetic retinopathy has declined in the last decades^[6,7], its prevalence increased and is expected to rise further as a result of the increasing incidence of type 2 DM (T2DM) and the longer life expectancy of patients with DM^[1,8].

The pathogenesis of diabetic retinopathy is complex and involves many different pathways (Figure 1). Hyperglycemia is a major culprit and induces: (1) accumulation of advanced glycation end-products (AGE), which promote retinal pericyte loss; (2) inflammation, which increases vascular permeability and apoptosis of endothelial and neural cells; (3) protein kinase C (PKC) activation, which increases expression of matrix proteins and induces pericyte apoptosis; (4) accumulation of sorbitol through the polyol pathway, which damages endothelial cells and pericytes; (5) activation of the renin-angiotensin system, which induces vascular endothelial growth factor (VEGF) expression; and (6) oxidative stress, which further increases AGE accumulation and activation of PKC and the polyol pathway^[9,10]. The above pathogenetic mechanisms result in endothelial dysfunction, which in turn induces retinal ischemia and increases retinal vascular permeability^[9,10]. The former up-regulates the expression of VEGF, erythropoietin, carbonic anhydrase and growth hormone, which in turn promote neovascularization^[9,10]. On the other hand, increased retinal vascular permeability might result in macular edema^[9,10]. In addition to microvascular disease, neuroretinal damage is also implicated in the development and worsening of diabetic retinopathy, since increased neuronal apoptosis is observed in the retina in these patients^[9,10]. Accordingly, tight glycemic control and aggressive blood pressure-lowering, particularly with blockers of the renin-angiotensin system, considerably reduce the risk for diabetic retinopathy^[11-14]. However, only a minority of patients with DM achieves glycemic and blood pressure targets^[15,16]. Moreover, hyperglycemia and hypertension only partly account for the risk of development and progression of diabetic retinopathy, suggesting that other pathogenetic mechanisms also play a role^[9,10,17].

LIPIDS AND DIABETIC RETINOPATHY

In this context, some observational studies suggested that elevated serum low-density lipoprotein cholesterol (LDL-C) levels are associated with increased incidence for diabetic retinopathy^[18-20]. However, others did not confirm this association^[21-23]. Elevated serum triglyceride

levels also increased the risk for diabetic retinopathy in some reports^[22,24] but not in others^[23] whereas elevated high-density lipoprotein cholesterol levels were protective in some studies^[22] but not in others^[20,23]. In addition, perivascular deposition of lipid-laden macrophages has been reported in the retina of patients with diabetic retinopathy^[25]. Moreover, small uncontrolled studies suggest that low-fat diet reduces hard exudates^[26,27].

STATINS IN THE MANAGEMENT OF DIABETIC RETINOPATHY

Statins act by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase. This results in reduced serum LDL-C levels but also inhibits the mevalonate pathway, which results in reduced production of isoprenoids, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate^[28]. The latter leads to reduced prenylation (*i.e.*, addition of farnesyl and geranylgeranyl to cysteine residues of proteins), which modulates a host of pathogenetic mechanisms involved in diabetic retinopathy, including inflammation, oxidative stress, angiogenesis and endothelial dysfunction^[28]. In retinal endothelial cells, statins exhibit antiangiogenic actions by suppressing VEGF phosphorylation^[29]. In retinal pigment epithelial cells, statins decrease the expression of matrix metalloproteinases (MMP), preventing the breakdown of the blood-retinal barrier^[30]. Moreover, in animal models of diabetic retinopathy, treatment with statins prevented the upregulation of VEGF and preserved the blood-retinal barrier by exerting antioxidant^[31-33] and anti-inflammatory effects^[34,35]. In other preclinical studies, statins induced endothelium-dependent, nitric oxide-mediated vasodilation in retinal arteries^[36].

In subjects without DM, statins improve endothelial function in the choroidal vasculature^[37] and increase the blood flow in retinal arteries and veins^[38]. In patients with diabetic retinopathy, statins reduce vascular resistance in the ophthalmic and central retinal arteries^[39]. In addition, vitreous concentrations of VEGF, angiopoietin-2, MMP-9 and transforming growth factor β 1 are lower in patients with diabetic retinopathy treated with statins^[40].

A recent observational study showed that treatment with statins prior to vitrectomy is associated with greater improvement in visual acuity, particularly in patients who also underwent laser photocoagulation or received treatment with antibodies against VEGF and in those who had macular edema, vitreous hemorrhage, retinal detachment or proliferative retinopathy^[41]. Treatment with statins also reduced the risk for repeat vitrectomy^[41]. In a recent nationwide matched cohort study from Denmark ($n = 62716$), patients who were using statins prior to the diagnosis of DM had 40% lower risk for developing diabetic retinopathy^[42]. However, other observational studies did not show a protective role of statins against retinopathy in patients with established DM^[21,43].

Early case reports in patients with either type 1 DM (T1DM) or T2DM reported reduction of hard exudates and microaneurysms after treatment with statins^[25,44]. Studies

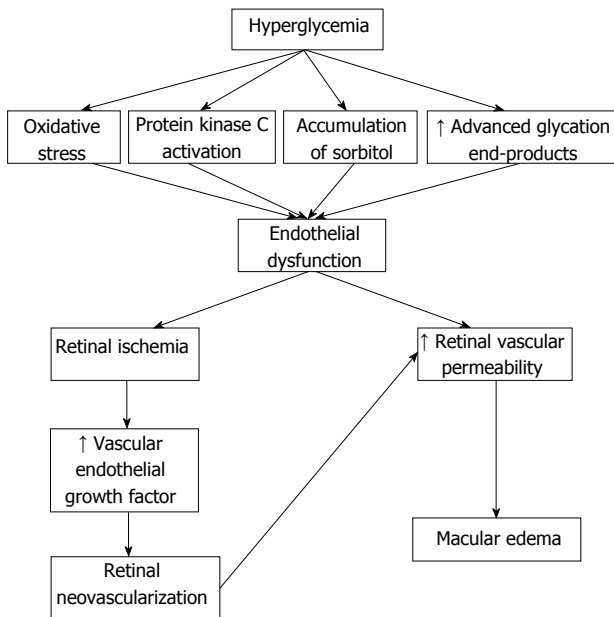


Figure 1 The most important pathogenetic mechanisms involved in the development of diabetic retinopathy.

evaluating the effects of statins on diabetic retinopathy are shown in the Table 1. In a randomized study in 50 patients with T1DM or T2DM, treatment with simvastatin for 6 mo retarded the progression of retinopathy compared with placebo^[45]. In an uncontrolled study in 18 patients with diabetic maculopathy, treatment with atorvastatin for 12 mo reduced hard exudates and fluorescein leakage^[46]. In a randomized study in 30 patients with T2DM and macular edema, treatment with atorvastatin for 18 wk reduced the number of hard exudates compared with no lipid-lowering treatment but did not affect macular edema or visual acuity^[47]. In addition, in a more recent randomized study in 30 patients with macular edema, treatment with atorvastatin for 6 mo had no effect on hard exudates, macular edema or visual acuity compared with no lipid-lowering treatment^[48].

In addition to the conflicting results of these observational and small interventional studies, randomized, placebo-controlled trials did not show a beneficial effect of statins on diabetic retinopathy. In the Collaborative Atorvastatin Diabetes Study, treatment with atorvastatin 10 mg/d for 3.9 years had no effect on the risk of laser therapy or progression of retinopathy in 2838 patients with T2DM^[49]. In the Heart Protection Study ($n = 5963$ patients with T2DM followed-up for 4.8 years), the incidence of laser treatment also did not differ between patients treated with simvastatin 40 mg/d and those who received placebo^[50]. However, neither of these studies was designed to evaluate the effect of statins on diabetic retinopathy.

FIBRATES IN THE MANAGEMENT OF DIABETIC RETINOPATHY

Fibrates act by inhibiting the nuclear receptor peroxisome

proliferator-activated receptor- α (PPAR α). PPAR α activation not only mediates the lipid-lowering effects of fibrates but also results in inhibition of inflammation by suppression of nuclear factor κ B and by direct binding to genes encoding proinflammatory cytokines^[51]. Fenofibrate prevents the apoptosis of retinal endothelial cells^[52] and of retinal pigment epithelial cells^[53]. It also reduces retinal vascular permeability by exerting antiinflammatory effects and by suppressing the upregulation of fibronectin and collagen IV in the basal membrane of retinal capillaries^[54,55]. Moreover, fenofibrate prevents the disruption of the retinal pigment epithelium^[56]. Similar with statins, fenofibrate induces endothelium-dependent, nitric oxide-mediated vasodilation in retinal arteries^[57].

Early studies reported a decrease in hard exudates after treatment with clofibrate^[58]. More importantly, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial ($n = 9795$ patients with T2DM), treatment with fenofibrate for 5 years reduced the need for laser photocoagulation by 31% ($P = 0.002$) and the risk of progression of retinopathy by 79% ($P = 0.004$) compared with placebo^[59]. It was estimated that 17 patients with retinopathy had to be treated with fenofibrate for 5 years to prevent one laser treatment^[59]. Interestingly, these benefits were apparent within 8 mo of initiation of fenofibrate treatment, suggesting that other mechanisms than lipid-lowering might be implicated^[59]. However, fenofibrate had no effect on the development of retinopathy in patients without retinopathy at baseline and did not prevent the deterioration of visual acuity^[59]. More recently, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study ($n = 2856$ patients with T2DM), treatment with fenofibrate for 4 years reduced the rate of progression of retinopathy by 40% ($P = 0.006$) compared with placebo but again did not affect the occurrence of moderate vision loss^[60].

OTHER LIPID-LOWERING AGENTS IN THE MANAGEMENT OF DIABETIC RETINOPATHY

In an early study, administration of omega-3 fatty acids to streptozotocin-induced diabetic rats did not affect pericyte loss and increased the formation of acellular, occluded capillaries in the retina^[61]. However, in more recent animal studies, treatment with omega-3 fatty acids preserved retinal function^[62,63]. However, there are no studies that evaluated the effects of omega-3 fatty acids on diabetic retinopathy in humans. There are also no studies evaluating the safety and efficacy of colessevelam or ezetimibe in animal models or patients with diabetic retinopathy.

CONCLUSION

It is unclear whether dyslipidemia is implicated in the pathogenesis of diabetic retinopathy. Observational

Table 1 Studies evaluating the effects of statins and fibrates on diabetic retinopathy

Ref.	Type of diabetes mellitus	n	Treatment	Dose (mg/d)	Follow-up (mo)	Outcome
[45]	1 and 2	50	Simvastatin	20	6	Delayed progression of retinopathy
[46]	2	18	Atorvastatin	20	12	Reduction of hard exudates and fluorescein leakage
[47]	2	30	Atorvastatin	10	4.5	Reduction of hard exudates but no effect on macular edema or visual acuity
[48]	2	30	Atorvastatin	20	6	No effect on hard exudates, macular edema or visual acuity
[49]	2	2838	Atorvastatin	10	47	No effect on the incidence of laser treatment or progression of retinopathy
[50]	2	5963	Simvastatin	40	58	No effect on the incidence of laser treatment
[59]	2	9795	Fenofibrate	200	60	Reduction of the need for laser photocoagulation and the risk of progression of retinopathy but no effect on the development of retinopathy in patients without retinopathy at baseline or on the risk of deterioration of visual acuity
[60]	2	2856	Fenofibrate	160	48	Reduction of the rate of progression of retinopathy but no effect on the occurrence of moderate vision loss

studies reported conflicting findings regarding the association between lipids and development or progression of diabetic retinopathy. Moreover, studies that evaluated the role of statins in the management of these patients are mostly small and yielded discrepant results. Large randomized studies with statins in patients with T2DM showed no benefit of statins on diabetic retinopathy but were not designed to address this effect. In contrast, both preclinical data and two large randomized controlled studies, the FIELD and the ACCORD trial, showed that fenofibrate delay the progression of diabetic retinopathy. Even though the mechanisms underpinning this benefit are still not entirely clear, these findings suggest that fenofibrate might represent a useful tool for the management of this diabetic retinopathy.

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