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Statins for prevention of diabetic-related blindness: a new treatment option?

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Diabetic retinopathy (DR), the most feared complication of diabetes, compromises vision and quality of life of approximately 50 million people worldwide, with its prevalence projected to double by 2025 [101]. DR, the leading cause of blindness in working-age adults in the USA, is characterized by early neurodegeneration, glial activation and vascular injury, which includes breakdown of the blood–retina barrier (BRB) and acellular capillary formation that eventually leads to retinal neo-vascularization and blindness (reviewed in [1]). Interestingly, early clinical trials including the Hoorn study, the Early Treatment Diabetic Retinopathy Study (ETDRS), and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [2–4] indicated that elevated serum lipids, including total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol, were associated with the presence of hard exudates and increased risk of DR. These results suggested that lipid-lowering therapies might be beneficial in the reduction of hard exudates and the associated vision loss in patients with DR.

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that lower total and LDL-cholesterol in diabetic patients with or without cardiovascular disease. They inhibit the generation of mevalonate, a precursor of cholesterol, and inhibit isoprenoid synthesis. The beneficial effects of statins may extend beyond their cholesterol-lowering effects, to so-called pleiotropic effects, which include improving endothelial function, attenuating vascular and myocardial remodeling, inhibiting vascular inflammation and

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oxidation, and stabilizing atherosclerotic plaques. Statins' pleiotropic effects are mainly attributed to blocking the isoprenylation of small GTPase proteins such as Rac-1, Rho and Cdc42 (reviewed in [5]). Although statins have reported benefits in diabetic microvascular diseases, their efficacy for DR has not been thoroughly investigated [6–8].

Evidence from clinical studies

Currently, the exact benefits of statins on DR remain controversial. Clinical studies using small sample sizes have demonstrated promising reductions in the progression of DR. The beneficial effect of statins on retinopathy in diabetic patients was reported for the first time in 1991 by Gordon *et al.* in six patients, where pravastatin improved the appearance of hard exudates and microaneurysms [9]. In later studies, simvastatin improved visual acuity in diabetic patients with hypercholesterolemia [10]. Atorvastatin prevented the appearance of hard exudates and microaneurysms in patients with diabetic macular edema [11,12], and improved retinal blood flow velocities in patients with background or proliferative DR [13].

Recently, the Collaborative Atorvastatin Diabetes Study (CARDS), a large randomized controlled trial, studied 2838 patients with Type 2 diabetes randomized to atorvastatin (10 mg) or placebo. Analyses of the microvascular end points in CARDS demonstrated that patients on atorvastatin needed less laser therapy ($p = 0.14$); however, the progression of DR was not reduced [14]. Results from other prospective studies such as Atorvastatin Study for Prevention of Coronary Heart Disease End points in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) are pending [15]. The possible protective effects of higher statin doses on the progression of DR are not yet available. However, recent results from The Action to Control Cardiovascular Risk in Diabetes (ACCORD)-eye studies demonstrated that intensive control of dyslipidemia using combined simvastatin–fenofibrate treatment can significantly (40%) delay the progression of DR in patients with Type 2 diabetes [16].

Evidence from experimental studies

In contrast to clinical studies, the molecular mechanisms underlying the pleiotropic, nonlipid-lowering effects of statins have been widely demonstrated in experimental models. The role of oxidative stress and peroxynitrite formation has been well characterized as a critical and upstream event of several pathologies in DR. Diabetes-induced retinal vascular dysfunction is a direct result of excessive reactive oxygen species (ROS) and diminished availability of nitric oxide due to formation of peroxynitrite [17]. Although several metabolic sources of ROS have been identified in diabetes, the molecular targets for statins have been relatively limited to either NADPH or mitochondrial oxidase. Treatment of diabetic retinas and retinal endothelial cells in culture with simvastatin reduced levels of ROS via NADPH oxidase subunit Nox2 expression [18], as well as the production of mitochondrial ROS [18,19]. Lovastatin reduced ROS formation via blocking NADPH oxidase Nox4 subunit expression [20]. In addition, our previous studies demonstrated that simvastatin or atorvastatin blocked diabetes-induced lipid peroxidation and peroxynitrite formation [18,21].

Diabetic retinopathy is now perceived as a chronic inflammatory disease. Upregulation of inflammatory mediators such as VEGF, TNF- α and intercellular adhesion molecules (ICAMs) have been documented in the diabetic retina. Several studies attributed the vascular protective action of statins to reducing retinal inflammation. Studies have demonstrated that simvastatin attenuated leukocyte–endothelial cell interactions and subsequent BRB breakdown via the suppression of VEGF-induced ICAM-1 expression in the retinas of streptozotocin (STZ)-diabetic rats [18,22]. In addition, lovastatin prevented diabetes-induced elevation of ICAM and TNF- α in a Type 2 diabetic mouse model, as well as in retinal endothelial cells via inhibition of the proinflammatory transcription factor NF- κ B [23].

Beneficial effects of pravastatin in preventing retinal inflammatory mediators TNF- α , IL-1 β and ICAM-1 have been shown in STZ-diabetic rats with or without ischemia-reperfusion insult [24].

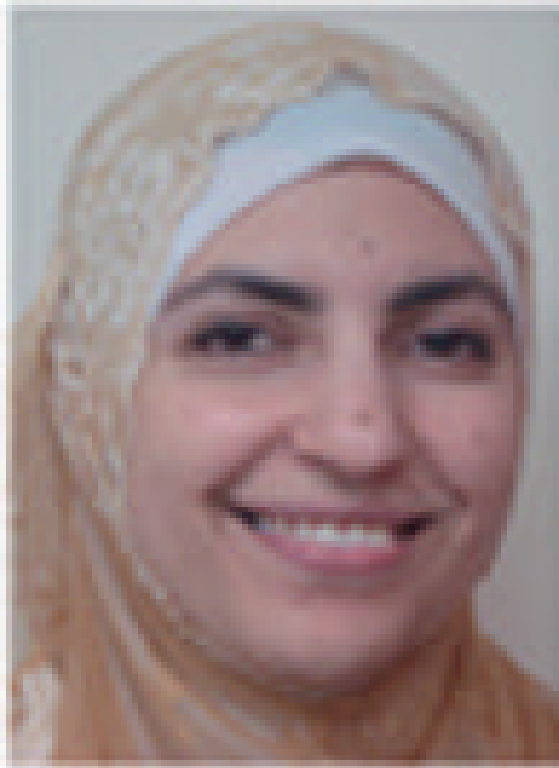
Retinal vascular degeneration and development of acellular capillaries are considered a hallmark of DR where occluded capillaries cause local ischemia that can trigger expression of angiogenic factors and neovascularization. Recent studies demonstrated protective effects of simvastatin in preventing apoptosis and degeneration of retinal capillaries in STZ-diabetic rats and retinal endothelial cells [25,26]. Protective effects were attributed to blocking oxidative stress or inhibiting matrix metalloproteinase (MMP)-9, in part, by inhibiting isoprenylation of H-Ras; a small molecular weight G-protein. The protective role of a statin in preventing retinal neovascularization was first demonstrated in 2002, where cerivastatin prevented an advanced glycation end products-induced increase in VEGF expression and its angiogenic response in endothelial cells [27]. Since rodents do not develop proliferative DR, an ischemic retinopathy mouse model is used to demonstrate the protective effects of statins in reducing ischemia, thereby preventing pathological neovascularization by either improving angiogenic repair or via antioxidant and anti-inflammatory effects [28]. The study by Medina *et al.* highlighted the differential actions of statins with low doses restoring angiogenic repair while high doses might be harmful by inhibiting reparative processes and inducing the premature death of retinal endothelial cells [29]. Similarly low, but not high, doses of pitavastatin prevented choroidal neovascularization [30]. In support of statins' dose-dependent effects, escalating doses of statins can induce apoptosis in pericytes, the cells that surround the capillary endothelial cells and help maintain the BRB [31]. These results suggest a critical role for monitoring the dose of statin in diabetic patients who are at risk of developing proliferative retinopathy.

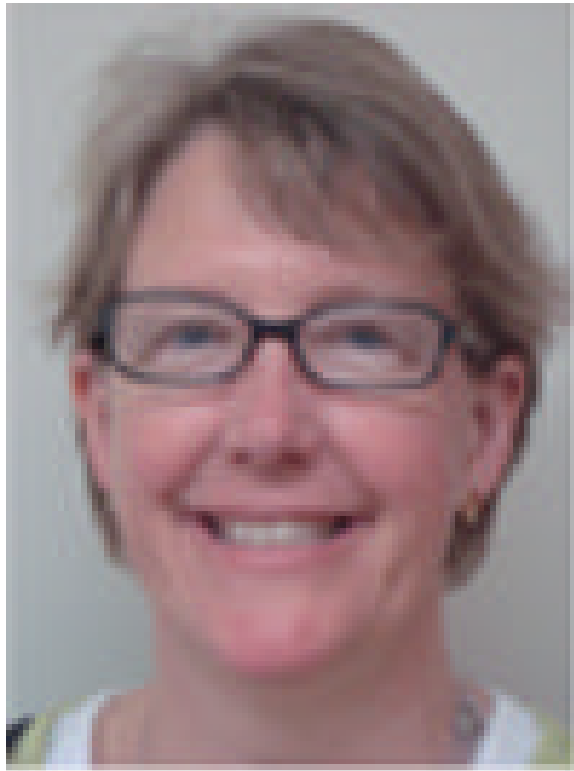
To date, most statin studies in the diabetic retina have focused on tissue-wide and endothelial cell effects, leaving the effects of statins on the neurons and glia relatively understudied. Prior studies demonstrated neuroprotective effects of pitavastatin in nondiabetic models, including *N*-methyl-D-aspartate-induced excitotoxicity and ischemia-reperfusion injury [32,33]. Our recent study demonstrated, for the first time, that atorvastatin blocked diabetes-induced retinal ganglion cell (RGC) death in STZ-diabetic rats and RGC cultures via restoration of the NGF [21]. Although the role of statins in reducing glial inflammation was demonstrated in the CNS [34], relatively little is known about glial cells in the retina. Our studies in Müller cells demonstrated that while both high glucose and peroxynitrite stimulate the proform of NGF (proNGF), they also impair neuronal survival via the inhibition of MMP-7, an enzyme involved in NGF maturation. Treatment with atorvastatin blocked Müller activation and restored activity of MMP-7, thus re-establishing the NGF/proNGF balance of the retina [21]. These effects were associated with preserving BRB function and protecting RGCs from death, two early hallmarks of DR. Given that inflammatory cytokine release and microglia viability are both reduced by statins [35], further investigation of the effects of statins on the microglia and other retinal cell types beyond the endothelial cells in the diabetic retina is needed.

In summary, there is a clear need for medical treatment options in addition to glycemic control for DR. Current management strategies include laser treatment and anti-VEGF therapy, which are effective but do not prevent the development or progression of DR in all patients. Given that the identification of diabetes-induced dyslipidemia as a risk factor for DR, the positive outcome of reduced laser treatment observed in CARDS, and the significant reduction in progression of DR in ACCORD-Eye, statins may be potential options for the management of DR. In addition, elaborate experimental evidence from animal and cell culture models support the possible use of statins as an add-on therapy for DR in clinical settings. Interestingly, while the majority of clinical studies included Type 2

diabetic patients, the majority of experimental studies used an STZ (Type 1) diabetic model. Other important considerations are the statin dosage and end points measured to evaluate beneficial effects. In clinical studies, standard doses of statins that normally control elevated lipids were used and end points were limited to visual acuity or the laser treatment frequency. By contrast, higher levels of statins were mostly used in animal models, which demonstrated pleiotropic effects, such as statin's antioxidant and anti-inflammatory properties. Further studies are needed to evaluate the protective effects of higher statin doses to control oxidative and inflammatory insults in the diabetic retina and eventually stop the progression of DR.

Biographies





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