ABSTRACT

The diagnosis of diabetic retinopathy carries several negative implications. The disease may lead to loss of visual acuity and blindness and is often associated with the systemic complications of diabetes (eg, nephropathy and neuropathy), in addition to hypertension and hyperlipidemia. Individually, each of these conditions is detrimental to the patient's health, but they can also worsen retinopathy. Therefore, not only is it important to screen, diagnose, and treat diabetic retinopathy, it is also important to screen, diagnose, and treat the comorbid conditions. The complexity of dealing with these comorbid conditions has led to recommendations for routine, multidisciplinary, team-based diabetes care. Landmark studies have demonstrated the benefit of blood glucose management in preventing and treating diabetic retinopathy. Clinical studies also support the benefit of treating hypertension and hyperlipidemia in reducing progression of the disease. Evidence from the Diabetic Retinopathy Study, the Early Treatment Diabetic Retinopathy Study, and the Diabetic Retinopathy Vitrectomy Study has provided insight into how best to use effective interventions, such as photocoagulation and vitrectomy, in patients with significant diabetic retinopathy, diabetic macular edema, vitreous hemorrhage, and diabetic traction retinal detachments.

Meanwhile, research continues for pharmacologic interventions that prevent or interfere with the pathogenesis of diabetic retinopathy, including vascular endothelial growth factor inhibitors (eg, pegaptanib), protein kinase C-β inhibitors (eg, ruboxistaurin), intravitreal triamcinolone acetonide, pigment-epithelium-derived factor, and growth hormone release inhibition. (Adv Stud Ophthalmol. 2004:18-29)

Diabetes mellitus is a disease with significant negative implications for the patient. Although ophthalmologists are primarily concerned with the ocular complications resulting from macular edema and proliferative diabetic retinopathy, decades of clinical trials and longitudinal studies indicate that people with diabetes are also at higher risk for the systemic complications of nephropathy and neuropathy. In addition, the comorbid conditions of hypertension and hyperlipidemia are common in patients with diabetes and may influence the severity and progression of diabetic retinopathy. Landmark clinical trials have demonstrated the correlation between the severity of retinopathy and elevated levels of serum glucose and hemoglobin A1c. These multicenter clinical studies also indicate that intensive glycemic control can help reduce ocular and systemic complications. Macular edema and proliferative diabetic retinopathy are important indicators of systemic organ involvement, which suggests that a multidisciplinary team-based approach to treatment is needed to reduce ocular and systemic complications. In addition, certain systemic risk factors are thought to independently exacerbate the progression of retinopathy.

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Therefore, treating only ocular conditions without awareness of the myriad systemic implications can lead to reduced efficacy of therapy and increased comorbidity. Intensive multiorgan system therapy is the paradigm on which the multidisciplinary team-based strategy is based.  

The Multidisciplinary Team-Based Approach

What is the multidisciplinary team-based approach? How is it used to prevent and treat patients at high risk for diabetic retinopathy? This treatment strategy is based on frequent patient visits to the internist and the ophthalmologist and increased vigilance in detecting diabetic retinopathy in patients with elevated serum glucose levels, elevated hemoglobin A1c levels, or in patients who have recently been initiated into intensive control that occasionally results in the short-term exacerbation of diabetic retinopathy.  

Furthermore, treatment of coexisting conditions, such as hypertension and hyperlipidemia, by the appropriate specialists reduces the severity of diabetic retinopathy. The appropriate monitoring and referral of patients for diabetic microvascular complications by the ophthalmologist may minimize other significant systemic effects. The multidisciplinary approach to treatment involving ophthalmologists and other specialists starts with maximizing glycemic control. Two landmark studies, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), documented the benefit of aggressive intensification to control of serum glucose levels. The results of these studies form the basis for the strategy of tight control to maintain glucose levels near normal. 

The DCCT, a multicenter prospective study, randomly assigned 1441 patients with type 1 diabetes mellitus to conventional treatment or to intensive treatment. Intensive treatment included the use of an insulin pump or 3 or more insulin injections daily, self-monitoring of blood glucose 4 or more times daily, frequent insulin dosage adjustments, initial hospitalization to implement treatment, and weekly to monthly clinical visits with frequent telephone contact. After 6.5 years, the mean hemoglobin A1c level was 7.2% in the group receiving intensive therapy versus 9.1% in the group receiving conventional therapy. Of the patients receiving intensive therapy, the relative risk for developing diabetic retinopathy was reduced by 27%, the relative risk for developing proliferative diabetic retinopathy or severe levels of nonproliferative diabetic retinopathy was reduced by 47%, the rate of photocoagulation treatment was reduced by 56%, and relative rates of diabetic macular edema were reduced by 23%. Additional endpoints included a reduction in incidences of diabetic nephropathy by 34% to 57% and a lessened clinical risk of other diabetic microvascular complications. Complications of tighter control did not lead to increased death or macrovascular complications. A significant finding in the group receiving intensive therapy was that patients may experience an initial deterioration in diabetic retinopathy that occasionally requires ophtalmologic intervention.

The UKPDS randomly assigned 4209 individuals newly diagnosed with type 2 diabetes mellitus into treatment groups similar to the DCCT, with the intensive therapy cohort receiving oral sulfonylureas and metformin therapy, along with insulin injections as recommended by physicians. Additional randomizations related to blood pressure control. Primary endpoints included rates of development of diabetic retinopathy, diabetic peripheral neuropathy, diabetic nephropathy, and cardiomyopathy. These patients were followed for a median of 10 years. At the conclusion of the study, the relative risk of diabetic retinopathy decreased by up to 76%, laser photocoagulation rates decreased by 29%, and the rate of legal blindness decreased by 16%. Relative risk reduction for diabetic nephropathy rates ranged from 34% to 57%. Better blood pressure control also improved outcomes.

The collective recommendations from these 2 landmark trials (ie, UKPDS-33 and UKPDS-34) indicated that patients diagnosed with type 1 or type 2 diabetes mellitus who made frequent visits to physicians with the goal of maximizing insulin therapy, diet, and exercise significantly decreased ocular and systemic diabetic microvascular complications. Therefore, attempts by ophthalmologists to successfully treat diabetic retinopathy are inextricably linked to control of serum glucose levels (Figure 1). 

Adequate control of serum glucose levels is only one of many therapies that modulate the risks and course of diabetic retinopathy. In addition to increased hyperglycemia as an increased risk factor for progression of diabetic retinopathy, comorbid conditions such as systemic hypertension, nephropathy, pregnancy, anemia, and even gastroparesis may exacerbate diabetic retinopathy. Prevention or better management of these conditions can positively affect the prognosis of diabetic retinopathy.
A significant finding of the UKPDS-38 was the fact that systemic hypertension was an independent risk factor in the progression of diabetic retinopathy. Hypertensive retinopathy can occur even in the absence of diabetic retinopathy and has similar retinal findings, including microaneurysms, flame-shaped hemorrhages, cotton wool spots, and macular exudates.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) also supported the role of hypertension in the progression of retinopathy. Patients with the lowest degrees of systolic and diastolic pressures had a significantly lower risk of progression to proliferative diabetic retinopathy compared to patients with higher levels of hypertension (Figure 2).

The UKPDS-38 evaluated the effects of the treatment of systemic hypertension on diabetic retinopathy. Patients were placed in an intensive control group (maintain blood pressure levels below 144/82 mm Hg) or a less-controlled group (achieve blood pressure levels below 154/87 mm Hg). Individuals in the intensive control cohort had a 34% relative risk reduction in diabetic retinopathy progression, a 47% reduction in deterioration of visual acuity, and a 37% reduction in need for photocoagulation. These benefits were noted regardless of the type of antihypertensive medication used. The Appropriate Blood Pressure Control in Diabetes Trial found a similar lack of significant differences between the efficacy of angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers in the rates of diabetic retinopathy progression. However, with the evidence supporting the benefits of ACE inhibitors in reducing diabetic microvascular complications in patients with renal compromise, additional clinical trials examining their effects on diabetic retinopathy are likely.

The association between diabetic nephropathy and diabetic retinopathy has long been postulated. However, the association between proteinuria and the progression of retinopathy is complex because of multiple confounding factors. Similar to patients with diabetic retinopathy, patients with diabetic nephropathy are likely to have chronic hyperglycemia, elevated hemoglobin A1c levels, and hypertension (independently, each condition can be a cause of retinopathy). The WESDR indicated increased severity of diabetic eye disease as a risk factor for proteinuria. Conversely, studies have suggested that proteinuria is a predictor for future diabetic retinopathy. Severe proteinuria is correlated with a 95% increase in the risk of developing diabetic macular edema. A large percentage of patients with end-stage renal disease who are receiving dialysis have concomitant retinopathy, with most of these cases...
being proliferative diabetic retinopathy. It has been noted that once patients begin receiving dialysis, retinopathy tends to stabilize. The observation that the use of ACE inhibitors reduces renal microangiopathy has spurred increased interest in the use of ACE inhibitors and their potential benefits for reducing diabetic retinopathy.

Other factors are associated with diabetic retinopathy. Hyperlipidemia has been reported to increase the exudation seen in diabetic macular edema. According to analysis from the WESDR, although serum cholesterol levels were not predictive of severity of diabetic retinopathy, they were associated with severity of hard exudates. Other cross-sectional studies in patients with type 1 diabetes mellitus have suggested an association between total serum cholesterol levels and diabetic retinopathy. In the Early Treatment of Diabetic Retinopathy Study (ETDRS), serum levels were measured in 2709 patients. Elevated serum cholesterol, low-density lipoprotein, and triglyceride levels correlated with an increased rate of hard exudation in these patients. The severity of diabetic exudation was also correlated with high-density lipoprotein levels. Although elevated triglycerides at baseline have been reported as a risk factor for proliferative diabetic retinopathy, the WESDR did not confirm any association with serum cholesterol levels and diabetic macular edema.

Studies examining the effects of pregnancy on the progression of diabetic retinopathy have allowed clinicians and investigators an opportunity to examine the complex interactions between diabetes and pregnancy-induced hormonal and metabolic changes affecting serum glucose levels. Progesterone, vascular endothelial growth factors (VEGF), and changes in systemic hemodynamics are hypothesized to contribute to alterations in retinal vasculature. Also, elevations in hemoglobin A1c levels in early pregnancy are associated with an increased risk in progression of diabetic retinopathy. Additional risks for progression in pregnant women with diabetes include increased duration of diabetes, amount of retinopathy at conception, and presence of comorbid conditions, such as hypertension.

Progression of diabetic retinopathy in patients with anemia has also been studied. In the ETDRS analysis, a low hematocrit level was determined to be an independent risk factor for development of high-risk proliferative diabetic retinopathy and severe visual loss. A study that recorded hemoglobin levels in a large population of Finnish patients revealed an increased risk of retinopathy when hemoglobin levels were less than 12 g/dL.

The clinical trials and series discussed earlier in this paper have confirmed the strong correlation between diabetic retinopathy and other systemic complications. However, despite overwhelming evidence that aggressive surveillance and treatment prevent severe visual loss and complications secondary to diabetic retinopathy, the number of patients with diabetes referred for ophthalmic care is far below what it should be, according to the guidelines of the American Diabetes Association (ADA) and the American Academy of Ophthalmology (AAO).

For example, in a series of 2000 patients with diabetes mellitus, 7% to 11% of patients with high-risk proliferative diabetic retinopathy had not been examined by an ophthalmologist within the past 2 years. Complicating the difficulties of appropriate team management is the lack of standardization of terms used to characterize degrees and severity of diabetic retinopathy. Recently, efforts have been made to standardize terminology to a simplified international disease severity scale.

The ADA has established treatment goals based on the evidence showing that glycemic control reduces the risk of diabetes-related complications. The target for patients with diabetes should be a hemoglobin A1c level below 7.0%. Normoglycemia is the ideal goal for most patients, but it is often difficult to achieve.

### Table. American Academy of Ophthalmology Guidelines

<table>
<thead>
<tr>
<th>Diabetes Type</th>
<th>First Exam Recommended</th>
<th>Follow-up Recommended*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>5 years after onset</td>
<td>Yearly</td>
</tr>
<tr>
<td>Type 2</td>
<td>At time of diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Prior to pregnancy (type 1 or type 2)</td>
<td>Prior to conception or early in the first trimester</td>
<td>No retinopathy to mild or moderate NPDR: every 3–12 months; severe NPDR or worse: every 1–3 months</td>
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Glycemic control should be individualized after considering the patient’s medical and social issues. Factors to consider include life expectancy at the time of diagnosis, presence of microvascular complications, ability to understand and administer a complex treatment regimen, and level of social support.

**Current Treatment Strategies in Diabetic Retinopathy**

When diabetic retinopathy is detected, guidelines for intervention to interrupt the natural progression of diabetic retinopathy are derived from the Diabetic Retinopathy Study (DRS), the ETDRS, and the Diabetic Retinopathy Vitrectomy Study (DRVS). These studies form the basis for predicting the natural course of diabetic retinopathy and the foundation for offering photocoagulation and vitrectomy to patients with significant diabetic retinopathy and the foundation for offering photocoagulation and vitrectomy to patients with significant diabetic retinopathy, macular edema, vitreous hemorrhage, or diabetic traction retinal detachments. Additional refinements in surgical technology, surgical techniques, and novel intravitreal pharmacotherapies offer promise in adding to the ophthalmologist's armamentarium in the treatment of diabetic retinopathy.

The DRS and the ETDRS provided clinical outcomes in patients treated with scatter photocoagulation and focal or grid photocoagulation to reduce the risk of long-term severe visual loss. The significance of these studies is based on their empiric, evidence-based study designs. In addition, through these studies, current terminology such as proliferative diabetic retinopathy and severe nonproliferative diabetic retinopathy was introduced.

The DRS included patients with proliferative diabetic retinopathy or bilateral severe nonproliferative diabetic retinopathy. In one eye, patients received photocoagulation with panretinal photocoagulation, direct treatment of neovascularization, or focal treatment (small-sized burns used to seal leaking microaneurysms in the posterior fundus). Photocoagulation was found to reduce the risk of severe visual loss by 50%, with only moderate risk for decreases in visual acuity or constriction in the treatment groups. In patients with high-risk proliferative diabetes, the 5-year rate of severe visual loss was reduced from 50% to 20%.

The ETDRS criteria included patients with mild to severe nonproliferative diabetic retinopathy or non-high-risk proliferative diabetic retinopathy, who had one eye that was treated by early photocoagulation and treatment that was deferred in the other eye. The major endpoints confirmed that focal photocoagulation in the macular area for direct leaks and grid for diffuse diabetic macular edema reduced the risk of doubling the visual angle by 50%. Early scatter and deferred scatter groups experienced similar rates of severe visual loss (2%–6% in the early scatter group vs 2%–10% in the deferred group). The study authors concluded that panretinal photocoagulation was not indicated for mild and moderate nonproliferative diabetic retinopathy but could be considered for severe nonproliferative retinopathy and for patients approaching high-risk proliferative diabetic retinopathy. The benefits of treatments were likely to be more significant in patients with long-standing type 1 and type 2 diabetes mellitus.

In patients with vitreous hemorrhage secondary to proliferative diabetic retinopathy, the DRVS established the benefits of vitrectomy. Patients with vision loss greater than 5/200 secondary to vitreous hemorrhage and no macular retinal detachment were assigned to early vitrectomy or conservative management (vitrectomy only if detachment of the macula was noted or vitreous hemorrhage persisted for 1 year). The chance of significant visual improvement (>10/20) was noted in patients with type 1 diabetes mellitus who were younger, thus they had more severe proliferative diabetic disease. An additional group of patients with extensive, active neovascular proliferative retinopathy was randomly assigned to deferred versus immediate vitrectomy. These patients were also found to benefit from early vitrectomy, specifically in patients with eyes that had severe new vessels. Since the publication of the DRVS in 1990, several innovations in vitrectomy surgery, including bimanual delamination and endolaser, have altered the timing of surgery for many patients, thus a greater number of patients with vitreous hemorrhage may show benefits from early surgical intervention.

In all cases, appropriate detection and treatment relies on appropriate referral to ophthalmologists whenever diabetic retinopathy is a possible diagnosis. These current treatment paradigms of scatter laser photocoagulation for severe nonproliferative diabetic retinopathy and proliferative diabetic retinopathy, focal and grid photocoagulation for diabetic macular edema, and vitrectomy for vitreous hemorrhage and traction retinal detachment serve as the foundation for current photocoagulation techniques and treatment.
The National Eye Institute (Bethesda, MD) is sponsoring a series of additional clinical trials (Diabetic Retinopathy Clinical Research Network) elucidating whether certain changes in laser delivery techniques may benefit patients with diabetic retinopathy. As a comparison to the initial ETDRS grid laser techniques, a pilot study is enrolling patients with a milder intensity but more confluent pattern of laser application to areas of macular edema. In addition to visual acuity, ocular coherence tomography will be used to assess efficacy of treatment. A second trial is investigating the safety and efficacy of intravitreal triamcinolone acetonide (TA) to treat diabetic macular edema.

NEW DEVELOPMENTS IN THERAPY

Several new treatment possibilities are being explored that may prevent the development and progression of diabetic retinopathy. These efforts are based on new understanding of the underlying biochemical processes.

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Growth factors, particularly VEGF, are postulated to be mediators in the development of late-stage diabetic retinopathy. The VEGFs are a family of peptides with several isoforms produced from a single gene by alternative splicing. They are potent mitogenic factors for vascular endothelial cells and induce breakdown of blood-retinal barriers. VEGF plays a critical role in the development of the fetal vascular system, decreasing significantly after birth. However, neural retina, choroid, and retinal pigment epithelium continue to secrete VEGF. In patients with diabetes, hyperglycemia results in a loss of pericytes and endothelial cells, slowing the blood flow and causing progressive hypoxia of the retinal tissues. The localized hypoxia promotes expression and secretion of VEGF, subsequently leading to proliferation of retinal capillary endothelium and neovascularization, in addition to increased vascular fenestrations and macular edema.

In animal studies, exogenous VEGF injected into monkeys’ eyes caused neovascularization of the iris and retina. Other animal studies demonstrated that interventions to block VEGF synthesis with intravitreal injection of anti-VEGF antibodies, VEGF-receptor-binding chimeric immunoglobulin, or antisense VEGF DNA appear to prevent retinal neovascularization. These strategies appear promising for humans. However, therapy must be localized, perhaps by direct intravitreal injection. Systemic anti-VEGF therapy precludes the benefit of angiogenesis to compromised coronary and peripheral circulations, which is less than ideal. Pegaptanib, a VEGF aptamer consisting of a 28-base oligonucleotide that binds to VEGF protein, is being studied in a clinical trial for the treatment of exudative age-related macular degeneration involving choroidal neovascularization. This aptamer may also be a potential treatment for diabetic retinopathy.

Another strategy to prevent the action of VEGF is to block specific VEGF receptors and their subsequent signal transductions. Although 3 VEGF receptors have been identified, VEGF receptor-2 (VEGFR-2) appears to be most important for the mitogenic action in the retinal vascular endothelium. A VEGFR-2 blocker has already undergone preliminary tests as an angiogenesis inhibitor for cancer and may prove useful for diabetic retinopathy.

PROTEIN KINASE C INHIBITORS

The protein kinase C (PKC) family comprises a large group of enzymes that transfer the terminal high-energy phosphate group of adenosine triphosphate to a site on a target protein. This reaction may activate other enzymes, cell membrane receptors, or ion transport channels.

Protein kinase C-β isoform is present at high levels in the retina and is thought to play a crucial role in the pathogenesis of diabetic retinopathy. In patients with diabetes, hyperglycemia triggers an increase in the concentration of diacylglycerol (DAG), an essential cofactor for PKC. This increase in DAG leads to increased activation of PKC. Subsequently, the higher level of PKC acts in concert with hypoxia to upregulate the production of VEGF in retinal tissues. The binding of VEGF to its receptor on a vascular endothelial cell activates a variety of signaling molecules, including PKC β, to initiate angiogenesis or blood-retinal barrier breakdown leading to macular edema. By interfering with the biochemical pathway, PKC inhibitors may prevent the development and progression of diabetic retinopathy. However, because PKC is found throughout the body, a specific inhibitor for the PKC β acting locally in the retina would be preferable.

Recent data from transgenic mouse models support the hypothesis that PKC β is involved in mediating retinal neovascularization. In mice in which PKC is overexpressed, the retinal neovascular response to preproendothelin promoter is substantially increased. In
mice in which the PKC-β gene has been “knocked-out,” exposure to retinal ischemia results in reduced retinal neovascularization.\textsuperscript{111}

In addition, in vivo studies have shown that selective inhibition of the PKC-β isoform prevents VEGF-mediated growth.\textsuperscript{122} In the animal model, selective inhibition of PKC β reduces ischemic retinal revascularization.\textsuperscript{123} Selective inhibition of the PKC-β inhibitor ruboxistaurin has also been shown to block VEGF-induced increases in retinal vascular permeability in animals and humans to normalize changes in blood flow that typically occur as a result of diabetic retinopathy.\textsuperscript{114,115} Preliminary data from animal studies suggest PKC inhibition can normalize diabetes-induced retinal vascular permeability in animals, even if diabetes has been established for as long as 1 month before therapy has been initiated.\textsuperscript{116}

These studies have furthered interest in the PKC-β inhibitor ruboxistaurin, a highly selective dimethylamine analogue.\textsuperscript{117} In the initial testing of the oral form of ruboxistaurin, it appears well tolerated.\textsuperscript{112} Two extensive phase III clinical trials for severe preproliferative diabetic retinopathy and diabetic macular edema are being conducted.\textsuperscript{113}

**Intravitreal Triamcinolone Acetonide**

The ETDRS demonstrated that focal or grid laser photocoagulation is beneficial for treating patients whose eyes have been diagnosed as having clinically significant diabetic macular edema.\textsuperscript{124} However, Lee and O’K reported that despite treatment with grid-pattern laser photocoagulation, 25% of eyes of patients diagnosed with diffuse diabetic retinopathy and diabetic macular edema lost more than 2 lines of vision within 3 years.\textsuperscript{125} Corticosteroids have been used to suppress intraocular inflammation by reducing extravasation from leaking blood vessels and inhibiting fibroblast proliferation. Early research efforts by Macher et al, Graham and Peyman, and Tano et al suggest that an intravitreal injection of corticosteroid can safely and effectively suppress intraocular inflammatory pathologies, such as persistent uveitis and proliferative vitreoretinopathy.\textsuperscript{126-129} Macher also advocated using a crystalline form of cortisone, which has an intravitreal absorption time of 2 months, to provide longer anti-inflammatory effect.\textsuperscript{122} TA, a crystalline corticosteroid suspension, has been shown experimentally to reduce breakdown of the blood-retinal barrier.\textsuperscript{123}

In an uncontrolled study, Mardis et al used an intravitreal injection of 4 mg of TA to treat refractory diffuse diabetic macular edema.\textsuperscript{124} They reported a reduction in macular thickness, which was measured by optical coherence tomography, at follow-up visits of 1 month (55%), 3 months (58%), and 6 months (38%). Follow-up visits also revealed mean visual acuity improvements of 2.4 Snellen lines at 1 month and at 3 months, and 1.3 at 6 months. Jonas et al also reported similar favorable results using a dose of 25 mg intravitreal TA injection.\textsuperscript{125} In both studies, the improvement in visual acuity declined after 3 to 6 months with a recurrence of diabetic macular edema. Therefore, these results suggest that the efficacy of the intravitreal TA injection may be limited in duration and repeated treatments may be required.

Massin et al reported the first prospective controlled trial of intravitreal TA injection versus observation in eyes with diffuse diabetic macular edema that failed previous conventional laser treatment.\textsuperscript{126} They found that one intravitreal injection of 4 mg of TA improved retinal thickness in one eye relative to the untreated eye at 4-week and 12-week follow-up, but there was no statistically significant difference in visual acuity between the treated and untreated eye. By 3 months, there was improved visual acuity in the eyes that had received injections. By 24 weeks, the benefit of the single injection diminished considerably, with a recurrence of diabetic macular edema in 5 of 12 eyes that had been treated; this result was consistent with prior studies.

The safety of intravitreal TA is supported by prior animal studies and by human trials.\textsuperscript{122,127} The main adverse effect observed was intraocular pressure (IOP) elevation, which was reported in 20% to 80% of the patients.\textsuperscript{124,126,130} Most patients with elevated IOP levels were successfully treated with topical antiglaucoma therapy, and pressure levels returned to normal within 6 months without further medication. However, intravitreal TA injection may be contraindicated in the eyes of patients with glaucoma or a history of corticosteroid-induced IOP elevation.\textsuperscript{126} Another potential adverse effect is cataract progression; however, because of the relatively short length of follow-up studies, few cataract formations were reported. Other potential injection-related complications include retinal detachment, vitreous hemorrhage, and endophthalmitis.\textsuperscript{121} In a retrospective multicenter case series, Moshfeghi et al reported 8 of 922 cases of culture-positive, acute, postinjection endophthalmitis, resulting in an incidence rate of 0.87%.\textsuperscript{132} To decrease the risk of some injection-related complications and reduce the need for periodic reinjec-
tion, sustained drug delivery devices containing steroids that maintain a constant intraocular drug level for an extended period are being investigated.133

The mechanism of action of corticosteroids on diabetic macular edema remains unclear. One hypothesis proposes that corticosteroids reduce retinal capillary permeability by increasing the activity or density of the tight junctions in the retinal capillary endothelium.134 Another hypothesis suggests that corticosteroids inhibit the arachidonic acid pathway from producing prostaglandins (known endogenous vascular permeability mediators).135 Also, corticosteroids downregulate the production of VEGF, which may reduce the vascular permeability and macular edema.136

The Diabetic Retinopathy Clinical Research Network, sponsored by the National Eye Institute, is conducting a large prospective, randomized, multicenter clinical trial comparing intravitreal TA injections to macular laser photocoagulation in the treatment of diabetic macular edema. The study is also comparing 1-mg and 4-mg intravitreal TA. The results of the study will help to solidify the role of intravitreal TA injection as a modality in the management of diabetic macular edema.

**Pigment-Epithelium-Derived Factor**

Pigment-epithelium-derived factor (PEDF) was first isolated from fetal retinal pigmented epithelial cells.137 Experimental studies show that it inhibits retinal neovascularization in mice.138 Evidence suggests PEDF and VEGF have a reciprocal relationship that becomes imbalanced with uncontrolled diabetes, as PEDF levels fall and VEGF levels rise.139 VEGF and PEDF play an important role in maintaining the normal anatomy and function of the retinal and choroidal blood vessels.140 In an animal experiment model, the intravitreal injection of adenovirus vector containing the PEDF gene resulted in the inhibition of retinal and choroidal neovascularization,141 suggesting the possibility of using gene therapy to treat diabetic retinopathy in humans. A phase I study of this strategy in patients with advanced neovascular age-related macular degeneration is under way.142

**Inhibition of Growth Hormone Action**

Growth hormones secreted by the pituitary gland are thought to play a part in the pathogenesis of diabetic retinopathy.143 Hypophysectomy, once considered beneficial in inhibiting the production of growth hormone and its action for the treatment of diabetic retinopathy, has been abandoned because of the high rates of mortality and morbidity associated with its use.144 Later studies identified the insulin-like growth factor 1 (IGF-1) as a mediator for the actions of growth hormone in the development of diabetic retinopathy.145 IGF-1 is thought to be a permissive agent necessary for the occurrence of neovascularization, although IGF-1 must be accompanied by other molecules, such as VEGF, to induce neovascularization.146

Octreotide, a somatostatin analogue that inhibits the release of growth hormone, was shown at a high concentration to prevent the progression of diabetic retinopathy to the proliferative stage over a 15-month period.147 A multicenter clinical trial is in progress that may offer a possible treatment to prevent or delay the progression of diabetic retinopathy to proliferative diabetic retinopathy.148

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