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Article *in* Diabetes Care · October 2004

DOI: 10.2337/diacare.27.10.2540

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Diabetic Retinopathy

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Over 135 million individuals are afflicted with diabetes across the world. In the U.S., diabetes affects over 18.2 million people (or 6.3% of the total population) and 800,000 new cases of type 2 diabetes are diagnosed each year (1). Retinopathy is the most common microvascular complication of diabetes, resulting in blindness for over 10,000 people with diabetes per year. Epidemiological studies have described the natural history of and treatment for diabetic retinopathy. There is evidence that retinopathy begins to develop at least 7 years before the clinical diagnosis of type 2 diabetes (2). Clinical trials have demonstrated the effectiveness of photocoagulation, vitrectomy, and control of hyperglycemia and hypertension for diabetic retinopathy (Table 1). The current review will discuss the pathophysiology, screening, medical treatment, and future research for diabetic retinopathy.

PATHOPHYSIOLOGY

Several biochemical pathways have been proposed to link hyperglycemia and microvascular complications. These include polyol accumulation, formation of advanced glycation end products (AGEs), oxidative stress, and activation of protein kinase C (PKC). These processes are thought to modulate the disease process through effects on cellular metabolism, signaling, and growth factors.

Polyol accumulation

Accumulation of polyol occurs in experimental hyperglycemia, which in rats and dogs is associated with the development of basement thickening, pericyte loss, and microaneurysm formation (3,4). High concentrations of glucose increase flux through the polyol pathway with the enzymatic activity of aldose reductase, leading to an elevation of intracellular sorbitol concentrations. This rise in intracellular sorbitol accumulation has been hypothesized to cause osmotic damage to vascular cells (5). Aldose reductase inhibitors (ARIs) have been evaluated for the prevention of retinal and neural damage in diabetes (6). However, three clinical trials of ARIs in humans have not shown efficacy in preventing the incidence or progression of retinopathy (7,8 and S. Feman [St. Louis University, St. Louis, MO], personal communication). The efficacy of new, more potent ARIs remains to be evaluated in clinical trials.

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Received and accepted for publication 9 July 2004.

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Abbreviations: ABCD, Appropriate Blood Pressure Control in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; AGE, advanced glycation end product; ARI, aldose reductase inhibitor; DCCT, Diabetes Control and Complications Trial; DIRECT, Diabetic Retinopathy Candesartan Trial; DME, diabetic macular edema; EDTRS, Early Treatment Diabetic Retinopathy Study; EUCLID, Eurodiab Controlled Trial of Lisinopril in Insulin Dependent Diabetes; FPG, fasting plasma glucose; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PEDF, pigment epithelium–derived growth factor; PKC, protein kinase C; QALY, quality-adjusted life-year; ROS, reactive oxygen species; SSF, seven standard field; SNMDP, single-field digital monochromatic nonmydriatic photography; TGF-β, transforming growth factor-β; UKPDS, U.K. Prospective Diabetes Study; VEGF, vascular endothelial growth factor; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

AGEs

Another well-characterized pathway is damage resulting from accumulation of AGEs. High serum glucose can lead to nonenzymatic binding of glucose to protein side chains, resulting in the formation of compounds termed AGEs (9,10). After 26 weeks of induced hyperglycemia, the retinal capillaries of diabetic rats have marked accumulation of AGEs as well as a loss of pericytes. Furthermore, diabetic rats treated with aminoguanidine (AGE formation inhibitor) have reduced AGE accumulation and reduced histological changes, including microaneurysm formation and pericyte loss (11). An ongoing clinical trial is investigating the effect of aminoguanidine in humans (12). Preliminary results suggest that aminoguanidine reduces the progression of retinopathy but is associated with anemia (13).

Oxidative damage

Diabetes and hyperglycemia can also lead to oxidative stress and formation of reactive oxygen species (ROS), leading to vascular damage. Production of ROS (free radicals) may result from glucose autooxidation, protein glycation, increased flux through the polyol pathway, and prostanoid production (14). Normalization of glucose-stimulated superoxide production has been found to block at least three independent pathways of hyperglycemia-induced vascular damage (15). Furthermore, animal studies suggest that antioxidants such as vitamin E may prevent some of the vascular dysfunction associated with diabetes (16). In one study of patients with diabetes who had no or minimal retinopathy ($n = 36$), treatment for 4 months with high-dose vitamin E (1,600 IU/day) was found to significantly reverse abnormalities of retinal blood flow ($P < 0.001$) (17,18). An 88% normalization of retinal blood flow was seen, despite an unchanged level of glycemic control.

The Heart Outcomes Prevention Evaluation (HOPE) trial is a randomized clinical trial with a 2 × 2 factorial design that evaluated the effects of vitamin E and ramipril in patients at high risk for cardiovascular events (19). Patients were eligible for the study if they were 55 years of age or older and if they had cardiovascular

Table 1—*Outline of 1998 technical review (ref. 40)*

Epidemiology
Impact
Natural history
Causes of visual loss
Providers of eye care for patients with diabetes
Provider of medical care for patients with diabetes
Comprehensive eye evaluation
Initial eye evaluation and minimal follow-up
NPDR levels and disease progression
PDR levels and disease progression
Macular edema levels and disease progression
Treatment objectives
Determination of treatment efficacy
General treatment efficacy
Specific clinical trials outcomes
Management of diabetic retinopathy
Exercise
Aspirin therapy
Ancillary tests
Photography and retinal screening
Conclusions

disease or diabetes with at least one additional coronary risk factor. Patients were randomly allocated to daily treatment with 400 IU vitamin E and 10 mg ramipril or their respective placebos and were followed for an average of 4.5 years. The primary study outcome was the composite of myocardial infarction, stroke, or cardiovascular death. Secondary outcomes included total mortality, hospitalizations for heart failure or unstable angina, revascularizations, overt nephropathy, and laser therapy for diabetic retinopathy. In the 3,654 people with diabetes, vitamin E at this dose had a neutral effect on the primary study outcome (relative risk 1.03, 95% CI 0.88–1.21; $P = 0.70$), on each component of the composite primary outcome, and on all predefined secondary outcomes.

PKC activation

There is increasing evidence that PKC activation is related to hyperglycemia-induced microvascular dysfunction in diabetes (20). Activation of PKC results in numerous cellular changes, including increased expression of matrix proteins, such as collagen and fibronectin, and increased expression of vasoactive mediators, such as endothelin. The changes are seen as thickening of the basement membrane, increased retinal vascular permeability, and alterations in retinal blood flow. Although the activity of multiple PKC isoforms (α, β1, β2, and ϵ) is increased in vascular tissues in the diabetic state, studies suggest that the PKC-β2 isoform preferentially mediates the pathologic complications associated with hyperglycemia (21,22). Moreover, PKC-β has been shown to be an integral component of cellular signaling by vascular endothelial growth factors (VEGFs) (23), important mediators of ocular neovascularization, secondary to retinal ischemia and diabetic macular edema (DME) (24,25). Results from one clinical trial using a PKC inhibitor will be discussed in the section on future directions and PKC inhibitors.

Growth factors

The biochemical pathways described above are associated with production and signaling of growth factors such as VEFG, growth hormone, IGF-I, transforming growth factor-β (TGF-β), and pigment epithelium–derived growth factor (PEDF).

The VEGFs are a family of proteins that are mitogenic for vascular endothelial cells and increase vascular permeability. VEGF is important in fetal vascular development, with VEGF levels diminishing after birth. However, increased expression of VEGF has been demonstrated in diabetic retinopathy (26). In addition, VEGF has been shown to be upregulated by hypoxia, with increasing levels of VEGF in the vitreous associated with increasing retinal ischemia. In a mouse model of hyperoxic retinopathy, soluble VEGF-neutralizing VEGF receptor chimera was shown to suppress retinal neovascularization (27). There is increasing evidence that inhibition of PKC-β can prevent the neovascular and permeability effects of VEGF in animals (28).

Growth hormone and IGF-I have been suspected of playing a role in the progression of diabetic retinopathy. In a previous era, hypophysectomy was shown to lead to regression of proliferative retinopathy in a study of 100 patients (29). Similarly, diabetic dwarfs with low systemic IGF-I levels due to growth hormone deficiency have a reduced incidence of proliferative diabetic retinopathy (PDR) compared with age- and sex-matched diabetic patients. Other evidence includes observations of diabetic retinopathy progression in states of elevated IGF-I, such as puberty pregnancy (30), and upon rapid improvement of metabolic control (31). Such observations have raised interest in the use of growth hormone–inhibitory and antiproliferative somatostatin analogs to treat severe PDR (32,33). In a recent small-scale study of adults with diabetes and PDR, however, a growth hormone receptor antagonist, pegvisomant, failed to induce regression of neovascularization (34). This negative result may have occurred because the treatment was initiated too late; treatment may need to have started prior to the development of PDR. In another small-scale trial (23 patients), octreotide (a somatostatin analog) treatment reduced the requirement for laser photocoagulation compared with conventional treatment in patients with either severe nonproliferative diabetic retinopathy (NPDR) or early PDR (35). Over the 15-month study, only 1 of 22 octreotide-treated patients required photocoagulation compared with 9 of 24 conventionally treated patients. A large clinical trial of octreotide is ongoing. TGF-β is produced by pericytes and may inhibit endothelial proliferation. Active PDR and patients with rubeosis have lower levels of TGF-β (36). Lower levels may promote angiogenesis by removal of an inhibitor. Levels of TGF-β are usually high in the vitreous of normal eyes (37).

PEDF is produced by the retinal pigment epithelium and inhibits neovascularization (38). Systemic injection can reduce the development of retinal neovascularization in mouse retinopathy of a prematurity model (39). It has been postulated that reduced levels of PEDF may contribute to diabetic retinopathy; however, PEDF transgenic knockout mice do not show ocular pathology or altered neovascular responses.

DIAGNOSIS

A previous technical review published in *Diabetes Care* (40) provides an extensive review of the elements of comprehensive eye evaluation and levels of diabetic retinopathy, as well as management for diabetic retinopathy. The current review discusses *1*) techniques for diabetic retinopathy screening, *2*) intervals for evaluating patients without any retinopathy, *3*) a new classification of diabetic retinopathy severity, and *4*) optical coherence tomography.

Many techniques are used in the detection of diabetic retinopathy, including

direct and indirect ophthalmoscopy, fluorescein angiography, stereoscopic digital and color film–based fundus photography, and mydriatic or nonmydriatic digital color or monochromatic single-field photography. Grading of stereoscopic color fundus photographs in seven standard fields (SSFs), as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) group, is a recognized standard for the detection of diabetic retinopathy (41). Although this approach is accurate and reproducible, it is labor intensive, requiring skilled photographers and photograph readers and sophisticated photography equipment, film processing, and archiving.

Ophthalmoscopy is the most commonly used technique to monitor for diabetic retinopathy. However, undilated ophthalmoscopy, especially by non–eye care providers has poor sensitivity compared with stereoscopic seven-field color photography (42). Under typical clinical conditions, direct ophthalmoscopy by nonophthalmologists has a sensitivity of ~50% for the detection of proliferative retinopathy (43).

Various systems using multiple-field photography have been reported. Three groups have reported their results using proprietary systems, and these systems seem to perform well. However, the systems are proprietary and require pupillary dilation and skilled photographers and may therefore be more complex than required for screening purposes.

The Joslin Vision Network (44) compared stereo nonmydriatic digital-video color and three-field fundus photographs in three fields with SSF photography in 54 patients (108 eyes) with type 1 or type 2 diabetes (level 1 evidence). They found substantial agreement ($\kappa = 0.65$) between the two techniques for determination of the clinical level of diabetic retinopathy. Agreement was excellent ($\kappa = 0.87$) for referral to an ophthalmologist for clinical examination. In addition, a retrospective review of a subset of patients that had Joslin Vision Network imaging showed good correlation with an examination by a retina specialist (45).

The Inoveon Diabetic Retinopathy system (46) compared SSF photographs of 290 diabetic patients recorded on 35-mm film and on their proprietary system. The sensitivity and specificity of the digital system in detecting threshold events were 98.2 and 89.7%, respectively. Although Inoveon's diabetic retinopathy-3DT system provides highly accurate diabetic retinopathy referral decisions, the requirement for dilation and the cost both reduce its usefulness as a screening tool.

The DigiScope is a semiautomated instrument that acquires fundus images, evaluates visual acuity, and transmits the data to a remote reading center through telephone lines (47). A pilot study in normal eyes of normal volunteers and 17 consecutive diabetic patients showed that the visualization of many retinal lesions present in diabetic retinopathy can be visualized by the DigiScope. Further studies are needed to evaluate the test characteristics of this technology.

The use of single-field fundus photography has also been used as a detection tool for diabetic retinopathy. Patients with type 1 or type 2 diabetes were sequentially photographed through a nonpharmacologically dilated pupil by single-field digital monochromatic nonmydriatic photography (SNMDP), pharmacologically dilated, examined by ophthalmoscopy by an ophthalmologist, and then had 30° color stereoscopic photographs taken in SSFs (48). There was excellent agreement ($\kappa = 0.97$) between the SNMDP and SSFs for degree of diabetic retinopathy using a "referral" (ETDRS level $\geq$35) or "no referral" (ETDRS level $\leq$20) dichotomization (level 1 evidence). The sensitivity and specificity of SNMDP compared with SSFs were 78 and 86%, respectively. SNMDP was superior to ophthalmoscopy through pharmacologically dilated pupils when compared with SSFs. SNMDP demonstrated 100% sensitivity and 71% specificity when compared with direct ophthalmoscopy. None of the patients identified by ophthalmoscopy for referral were missed by SNMDP. SNMDP demonstrated 25% overcalls (higher retinopathy levels diagnosed by the tested modality rather than by the standard) for referral compared with ophthalmoscopy. However, when adjudicated against SSFs, this difference was due to the reduced sensitivity of ophthalmoscopy. With a sensitivity of 78%, SNMDP did miss some patients requiring referral based on SSFs. The lack of stereopsis also diminishes the ability to diagnose clinically significant macular edema in the absence of hard exudates or retinal hemorrhages and microaneurysms. The authors emphasize that SNMDP is superior to dilated ophthalmoscopy. The effectiveness was confirmed in other studies (49,50).

Single-field photography is not a substitute for a comprehensive ophthalmic examination. However, there is evidence from well-designed comparative studies that single-field fundus photography can serve as an initial evaluation tool for diabetic retinopathy by identifying patients with retinopathy for referral to ophthalmic evaluation and management. The effectiveness is demonstrated by its ease of use (only one photograph is required), cost (the cost of one photograph in most cases), convenience, and ability to detect retinopathy. None of the above approaches, including the proprietary systems, are able to detect other diseases often present in older patients with diabetes. This inability reduces the value of using these approaches when compared with examination by a skilled eye care provider.

Mydriasis and single-field photography

Although most patients can be photographed without pharmacological dilation, lens opacities in older patients can result in photographs that are ungradeable. In the studies previously mentioned, Pugh et al. (50) found that 42 of 50 ungradeable photographs became gradable after dilation. Taylor et al. (49) and Joannou et al. (50a) evaluated only dilated single-field photography. Based on these studies, eyes with ungradeable pictures should have dilation and repeat photography. Eyes with photographs that remain ungradeable after dilation would be considered as screen positives and require referral to ophthalmic evaluation. With the advent of digital photography, the quality of the image taken can be reviewed by the photographer and retakes made if necessary, possibly reducing the high frequency of ungradeable photographs found in older subjects.

Screening interval

Regular dilated eye examinations are an effective approach to detecting and treating vision-threatening diabetic retinopathy (51). They can help prevent blindness and are cost effective (52,53). Guidelines for systematic evaluation have been developed because patients with retinopathy are often asymptomatic and because retinal photocoagulation treatment is more effective at reducing visual loss when ap-

plied at specific, often asymptomatic, but advanced stages of retinopathy (54,55). However, despite the recommendations for regular evaluation and the availability of effective treatment, many patients at risk of visual loss due to severe retinopathy are not receiving dilated eye examinations and necessary photocoagulation treatments (56,57).

Guidelines for the frequency of dilated eye examinations have been based on the severity of the retinopathy (58,59). These recommendations are described in a previously published technical review (40). For patients with moderate to severe NPDR, frequent eye examinations are often necessary to determine when to initiate treatment. However, for patients without retinopathy or with only microaneurysms, the need for annual dilated eye examinations is less clear. For these patients, the annual incidence of either proliferative retinopathy or macular edema is low, suggesting that a reduced frequency of screening would decrease costs without increasing the risk of visual loss (60). Recently, some have suggested that annual screening for some patients may not be cost effective, and in some cases consideration should be given to increasing the screening interval (61). However, for patients where less frequent screening seems appropriate, there should be some oversight by the eye care professional to assure that the patient is not lost to follow-up. Before a less frequent screening schedule should be generally recommended or adopted, a better understanding of the total value of screening eye examinations, the potential indirect effects of less frequent eye examinations, and patient preference is needed.

Eye examinations may include other benefits. Older people often need eye exams for increasing presbyopia and are at higher risk for cataract, glaucoma, age-related macular degeneration, and more, which may result in vision loss. Discussion by ophthalmologists with their diabetic patients about medical as well as ophthalmic conditions certainly has value. For example, most primary care doctors tell their patients that it is important to control blood glucose, blood pressure, and serum lipids. During the eye exam these messages can be reinforced by the ophthalmologist at a time when patients are particularly aware of the implications of vision loss. Patients can also be reminded that controlling these parameters also will reduce the risk of neuropathy and nephropathy. Increased patient compliance will reduce the risks of these secondary complications of diabetes. Prevention of multiple complications is surely better than managing them after they have occurred, both for patient health and because of economic consequences. This value is difficult to measure and is often not incorporated into analyses of the costs and benefits of screening.

Less frequent examinations may also have indirect effects. Long intervals between follow-up visits may lead to difficulties in maintaining contact with patients. Also, patients may be unlikely to remember that they need an eye examination after several years have passed. Finally, a recommendation for follow-up visits at 2- or 3-year intervals may give a patient the impression that visual loss is very unlikely and therefore not a concern. All of these factors may result in longer-than-recommended intervals between examinations. Although automatic reminders from clinics can be helpful, they may be difficult to implement, especially when patients have relocated. Until we have empirical evidence to confirm that lengthening the follow-up interval is not harmful, maintaining an annual frequency seems conservative.

Patient expectations also should be considered. Blindness and visual loss is a major fear of most patients with diabetes. Visual loss leads to emotional distress and reduces functionality in daily life. The magnitude of this fear, the effect of blindness on functionality, and the economic value of these factors are hard to quantify. One way to assess the worth of these factors is to determine the value of blindness in terms of quality-adjusted life-years (QALYs). Investigators have suggested values of 0.48–0.36 (52,62) for blindness, but there are no QALY values for visual impairment that are less than blindness. Changes in QALY values significantly affect the cost-effectiveness of screening. Analyses should include a sensitivity analysis for different values of QALYs before making generalized recommendations.

Physicians may elect to individually reduce the frequency of follow-up for certain patients without retinopathy or nephropathy who are very compliant and have very good control of their blood glucose, blood pressure, and serum lipids. However, they should not assume that aggregate medical care costs can be reduced and efficiency increased by simply decreasing the frequency of screening examinations for entire groups of patients. Until empirical data are available to show otherwise, the general recommendation that individuals with diabetes should have a yearly eye examination seems safe, conservative, and reasonable. Deviations from this guideline are appropriate in certain low-risk groups but with caveats. Even with the current guideline, too many people with diabetes are needlessly losing vision because the opportunity to treat them in a timely fashion was missed. Relaxing the guidelines will not solve this problem. We think the guideline for a regular dilated eye examination should remain at 1 year rather than at 2 or 3 years. It is appropriate for the guideline to be conservative, and deviations from it should only be made after considering all of the risks.

New classification

The ETDRS severity scale was based on the modified Airlie House classification of diabetic retinopathy and was used to grade fundus photographs (63). Although it is recognized as the gold standard for grading the severity of diabetic retinopathy in clinical trials, its use in everyday clinical practice has not proven to be easy or practical. The photographic grading system has more levels than may be necessary for clinical care, and the specific definitions of the levels are detailed, require comparison with standard photographs, and are difficult to remember and apply in a clinical setting. In addition, in the past there has been no common practical clinical standard terminology that has been accepted for the worldwide exchange of information and data (64–66) until a new diabetic retinopathy severity scale was developed by the Global Diabetic Retinopathy Group at the International Congress of Ophthalmology in Sydney, Australia, in April 2002 (67).

The levels in this new diabetic retinopathy disease severity scale are listed in Table 2 and consist of five scales with increasing risks of retinopathy. The first level is "no apparent retinopathy," and the second level, "mild NPDR," includes ETDRS stage 20 (microaneurysms only). The risk of significant progression over several years is very low in both groups. The third level, "moderate NPDR," includes eyes with ETDRS levels 35–47, and the risk of

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