Control of Systemic Factors Can Preserve Vision in Diabetic Retinopathy

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STATEMENT OF NEED

About 18.2 million Americans have diabetes. Type 2 diabetes accounts for up to 95% of all diabetes cases, according to the National Institutes of Health. About 40% of US adults aged 40 to 75 years have abnormal blood glucose levels without having diabetes. Many of these will develop type 2 diabetes in the next 10 years.

Diabetic retinopathy is the leading cause of blindness in people ages 20 to 65 in the United States. Studies have shown that routine screening and early treatment are cost-effective and can preserve sight.

TARGET AUDIENCE

This activity is designed for primary care physicians, endocrinologists, ophthalmologists and other clinicians who treat patients at risk for and with type 2 diabetes.

LEARNING OBJECTIVES

After successful completion of this program, the participant should be able to:

- discuss diabetic retinopathy as the leading cause of blindness in patients aged 20 to 65 in the United States;
- review the origins of pending vision loss in proliferative and nonproliferative diabetic retinopathy; and
- cite the systemic factors that affect the severity of diabetic retinopathy.

METHOD OF INSTRUCTION

Participants should read the learning objectives and CME program in their entirety After reviewing the material, they must complete the self-assessment test, which consists of 10 multiple-choice questions.

Participants have a choice of either completing this activity online, either by visiting www.CMEToday.net to get real-time results or by visiting the *Diabetic Microvascular Complications Today* Web site at www.DiabeticMCToday.com. Participants may also use the print forms following the activity.

ACCREDITATION

This activity has been planned and implemented in accordance with standards of the ACCME through the joint sponsorship of The Dulaney Foundation and *Diabetic Microvascular Complications Today.*

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material or the commercial contributors of this activity; and 2) identification

TABLE 1. CHARACTERISTICS OF DIABETIC RETINOPATHY AND SYSTEMIC AND LOCAL TREATMENT OPTIONS

Type	Ophthalmoscopic Characteristics	Systemic Treatments	Local Treatments
Nonproliferative	Macular edema, hard exudates macular hemorrhage, macular ischemia	Diabetes control, hypertension control (eg ACE inhibitor), lipid control, nephropathy treatment, anemia treatment	Focal laser, intravitreal/periocular corticosteroids, pars plana vitrectomy, anti-VEGF therapies
Proliferative	Nonproliferative findings *plus* IRMA,* retinal neovascularizaton, vitreous hemorrhage, tractional retinal detachment	Diabetes control, hypertension control (eg ACE inhibitor), lipid control, nephropathy treatment, anemia treatment	Nonproliferative treatments *plus* panretinal laser, treatment of vitreous hemorrhage, membrane delamination to treat retinal detachment, panretinal endolaser

* IRMA, intraretinal microvascular abnormalities

of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATIONS

None.

FACULTY CREDENTIALS

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INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of loss of vision among working age adults in the United States. Vision loss from DR can be prevented with timely local and systemic interventions. Routine screening for DR is well established and cost-effective.

According to a 1989 study, the estimated cost of screening and laser treatment per person per year for vision saved from proliferative retinopathy was $966 and $1,118 per person for visual acuity saved from macular edema.[1] This compares favorably to the $6,900 average Social Security costs of that time of 1 year in payments for a person disabled by loss of vision. In another study, the average 30-year cost for management of DR in a patient with type 2 diabetes was found to be about $4,724.[2]

It is imperative that primary care physicians identify patients at risk for developing DR and educate them about its consequences. They need to work with patients to control the systemic factors that contribute to poor outcomes and refer patients for screening and treatment when appropriate (Table 1).

Exams with a dilated pupil are required at least yearly, even in asymptomatic patients.[3]

In nonproliferative DR, manifest or pending vision loss is caused by macular edema, hard exudates, ischemia or hemorrhage. In proliferative DR, vision loss can also be caused by vitreous hemorrhage or tractional retinal detachment associated with retinal neovascularization.

NONPROLIFERATIVE DR

Clinical presentation of nonproliferative DR can include microaneurysms, macular exudation and ischemia.

Among patients who have had diabetes for 15 years, >80% also have evidence of DR, the hallmark of which is retinal capillary microaneurysms. Microaneurysms in DR are caused by the loss of retinal capillary pericytes associated with the accumulation of advanced glycation end products. This accumulation occurs upon glycation of biomolecules which occurs

in the setting of elevated blood glucose levels.[4]

In nonproliferative DR, exudation from microaneurysms can cause macular edema. Exudation of lipids leads to hard exudates in the macula. This is especially likely to occur is if cholesterol, triglyceride or both levels are raised. Blood exudation leads to the development of a superficial flame-shaped nerve fiber layer or a deeper "dot-and-blot" intraretinal hemorrhage. Macular edema, hard exudates, and hemorrhage can be identified upon examination with an ophthalmoscope. Macular edema and retinal thickness can be identified using by optical coherence tomography.

ISCHEMIA

The progression of DR is marked by thrombosis of microaneurysms, which in turn leads to ischemia and worsening vision. Macular exudation, edema and ischemia can all lead to gradual, progressive vision loss. Areas of microvascular occlusion manifest as cotton-wool spots. They appear opaque and white because of the interruption of axoplasmic flow in the retinal nerve fiber layer. Fluorescein angiography, an important tool in the evaluation of vision loss in diabetic patients, is used to assess retinal circulation.

The release of vascular endothelial growth factor (VEGF) from the retina accompanies increasing ischemia. VEGF release results in intraretinal microvascular abnormalities, retinal neovascularization on the vitreous cortex and increased retinal vascular permeability. Vascular endothelial growth factor is 10,000 times as potent as histamine in the induction of vascular permeability. This increased vascular permeability contributes to worsening macular edema.

SYSTEMIC FACTORS

Poor control of blood glucose levels, hypertension, high cholesterol and triglyceride levels, anemia, and diabetic kidney disease all increase the risk of macular exudation, edema, and ischemia.

Microvascular complications like DR, neuropathy and nephropathy are caused by prolonged exposure to hyperglycemia. The Diabetes Control and Complications Trial[5] showed that intensive insulin therapy effectively delays the onset and slows the progression of DR in type 1 diabetic patients. In the primary prevention cohort of DCCT, intensive therapy reduced the adjusted mean risk for the development of DR by 76% versus conventional therapy. In the secondary intervention cohort, intensive therapy slowed the progression of DR by 54% and reduced the development of proliferative or severe nonproliferative DR by 47%.

The UK Prospective Diabetes Study found that improved control in patients with type 2 diabetes led to a reduction in DR as well as an overall reduction in microvascular complications by 25%.[6] A one-point decrease in HbA1c was associated with a 35% reduction in risk of microvascular complications.

Of course diet and exercise are important in the care of diabetic patients. In fact, exercise alone reduces the concentration of HbA1c by about 0.65 point and should be strongly encouraged.

> Poor control of blood glucose levels, hypertension, cholesterol and triglycerides increase the risk of macular exudation.

The choice among insulin, metformin HCl (Glucophage, Bristol-Myers Squibb), sulfonylureas, meglitinides such as repaglinide (Prandin, Novo Nordisk) and nateglinide (Starlix, Novartis), thiazolidinediones, and alpha-glucosidase inhibitors should be tailored to the individual needs of the patient.

In both the Wisconsin Epidemiologic Study of Diabetic Retinopathy[6] (WESDR) and the UK Prospective Diabetes Study, DR progressed significantly more slowly with more tightly controlled blood pressure.[7]

In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus,[8] the angiotensin-converting enzyme inhibitor lisinopril reduced progression of DR in nonhypertensive patients with type 1 diabetes by 50% in 2 years.[9]

Evidence suggests that hyperlipidemia contributes to the progression and morbidity of DR. In the WESDR, the presence of retinal hard exudates was significantly associated with increased serum cholesterol levels in patients taking insulin. In the Early Treatment Diabetic Retinopathy Study,[10] patients who had elevated total cholesterol or LDL were significantly more likely than those with normal levels to have retinal hard exudates. Accumulation of retinal hard exudates can lead to vision loss either from a foveal lipid plaque or from the development of fibrosis.

LOCAL TREATMENTS

Timely focal laser treatment of microaneurysms identified by angiography and associated with clinically significant macular edema is essential in preventing severe vision loss in patients with nonproliferative

DR.[4] Likewise, management of blood glucose levels, blood pressure, lipid levels, renal function and anemia is crucial.

Patients who have clinically significant macular edema have a 62% chance of developing moderate vision loss over 3-year follow-up. Focal laser treatment of microaneurysms reduces this to 28%.[8] Local corticosteroid therapy with periocular or intravitreal administration of triamcinolone has been shown to reduce macular edema, perhaps by stabilizing the blood-retinal barrier. Triamcinolone injections may need to be repeated if macular edema persists or recurs.

Surgical pars plana vitrectomy of the posterior vitreous cortex has been shown to be beneficial in the treatment of refractory diabetic macular edema associated with a taut, opaque posterior vitreous cortex. Anti-vascular endothelial growth factor therapies (eg, injections, implants) are also being developed to treat macular edema.

PROLIFERATIVE DR

VEGF elaborated by an ischemic retina induces retinal neovascularization. These newly formed vessels then erupt through the surface of the retina and grow on the vitreous cortex scaffold. They have a tendency to bleed with vitreous movements and the synchysis (vitreous shrinkage) that occurs normally with age, causing vitreous hemorrhage.

This hemorrhage causes subacute and acute loss of vision and visual field; patients may complain of floaters, veils or both across their central or peripheral field of vision. Organization of hemorrhage on the vitreous cortex or formation of fibrovascular tissue on the vitreous cortex and retina can cause tractional retinal detachment and permanent vision loss. As in nonproliferative DR, macular edema and ischemia can also lead to vision loss.

Just as with nonproliferative DR, the risk of progressive proliferative DR can be reduced by improving control of blood glucose, blood pressure, lipid levels and anemia.

LOCAL TREATMENTS

When retinal or iris neovascularization is noted, multiple (about 1,000) 200-micrometer applications of extramacular panretinal laser photocoagulation can allow for regression of the neovascularization. This reduces the risk of new vitreous hemorrhage and neovascular glaucoma and decreases the risk for severe vision loss by 50% to 60% over 2 years.

Panretinal photocoagulation reduces the neovascular response via one or more of the following factors: inducement of a decrease in VEGF levels by converting a hypoxic retina to an anoxic retina; release of antiangiogenic pigment epithelium-derived factor; thinning of the extramacular retina that allows for improved oxygenation from the underlying choriocapillaris; and/or a reduction in the metabolic demands of the retina.

Vitreous hemorrhage and tractional retinal detachment due to proliferative DR may be treated with surgical pars plana vitrectomy. Locally administered anti-vascular endothelial growth factor therapies are under development to prevent further neovascularization and allow for regression of existing neovascularization.

CONCLUSION

DR is the main cause of vision loss in the working age population in this country. Annual dilated-pupil retinal examinations are an essential and cost-effective measure for people with diabetes. Ophthalmoscopy results can serve as markers for effective control of the risk factors that lead to this retinal microangiopathy. Routine examinations allow identification and local and systemic treatment of DR that could lead to progressive vision loss.

Primary care physicians play a crucial role in the prevention of blindness associated with DR through patient education, treatment of systemic factors associated with poor outcomes, and referral to an ophthalmologist who provides comprehensive care or a retinal specialist for screening and local treatment. ■

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10. Chew EY, Klein ML, Ferris FL 3rd, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. *Arch Ophthalmol.* 1996;114:1079-1084.

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. What is the leading cause of blindness among working age Americans?
a. glaucoma
b. diabetic retinopathy
c. diabetic nephropathy
d. macular degeneration

2. Asymptomatic patients with diabetes do not need yearly dilated eye exams.
a. true
b. false

3. Which of the following is not associated with the clinical presentation of nonproliferative diabetic retinopathy?
a. microaneurysms
b. macular exudation
c. vitreous hemorrhage
d. ischemia

4. What percentage of patients who have had diabetes for 15 years have been shown to have diabetic retinopathy?
a. 10%
b. 25%
c. 50%
d. >80%

5. How are macular edema and retinal thickness identified?
a. x-rays
b. optical coherence tomography
c. MRI
d. fluorescein angiography

6. The release of vascular endothelial growth factor from the retina accompanies increasing ischemia.
a. true
b. false

7. Which of the following systemic factors increase the risk of macular exudation, edema, and ischemia?
a. poor blood glucose control
b. high blood pressure
c. high lipid levels
d. anemia
e. all of the above

8. The Diabetes Control and Complications Trial showed that intensive insulin therapy does not affect the progression of DR in type 1 diabetes.
a. true
b. false

9. Exercise alone is not enough to improve HbA1c levels.
a. true
b. false

10. Focal laser treatment of microaneurysms can reduce vision loss from 62% in patients with clinically significant macular edema to:
a. 28%
b. 50%
c. 22%
d. 38%

REGISTRATION/EVALUATION FORM: DIABETIC RETINOPATHY

To obtain AMA/PRA category 1 credit, you must:

- Read the learning objectives and the CME article and complete the self-assessment test.
- Photocopy and complete this registration/evaluation form and record your test answers in the Answer Section below.
- Send the Registration/Evaluation form to **The Dulaney Foundation, PO Box 44408, Phoenix, AZ 85064, or fax to 602-508-4893.**
- Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 42.

1. A B C D	2. A B	3. A B C D	4. A B C D	5. A B C D
6. A B	7. A B C D E	8. A B	9. A B	10. A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

Telephone _____ Fax _____ E-mail address _____

The processing fee has been underwritten by an educational grant from Eli Lilly and Company.

I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until July 31, 2006.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation.

OBJECTIVES

After successful completion of this program, you should be able to:

• Discuss diabetic retinopathy as the leading cause of blindness in patients aged 20 to 65 years in the United States	5	4	3	2	1
• Review the origins of pending vision loss in proliferative and nonproliferative diabetic retinopathy	5	4	3	2	1
• Cite the systemic factors that affect the severity of diabetic retinopathy	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

OVERALL EVALUATION

• The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
• The information presented will influence how I practice.	5	4	3	2	1
• The information presented will help me improve patient care.	5	4	3	2	1
• The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
• The program was educationally sound and scientifically balanced.	5	4	3	2	1
• The program avoided commercial bias or influence.	5	4	3	2	1
• Overall, the program met my expectations.	5	4	3	2	1
• I would recommend this program to my colleagues.	5	4	3	2	1

(Please circle the number that is most accurate; 5 represents strongly agree and 1 represents strongly disagree.)

- If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____
- Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____

_____

- Please list any topics you would like to see addressed in future educational activities: _____