REVIEW

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Diabetic retinopathy: Treating systemic conditions aggressively can save sight

ABSTRACT

To control diabetic retinopathy, we need not only to detect it promptly, but also to manage common systemic comorbid conditions such as hypertension, hyperlipidemia, anemia, obstructive sleep apnea, and smoking—all of which tend to accelerate its course and increase its severity.

KEY POINTS

A target blood pressure of less than 130/75 mm Hg is recommended for any patient with evidence of retinopathy. In these patients, attributing elevated blood pressures to "white coat" hypertension is dangerous, as it may delay intervention.

Anemia often accompanies diabetic kidney disease and is thought to exacerbate the ischemic aspect of diabetic retinopathy. In patients with diabetes, it often occurs during the stage of overt proteinuria but before the onset of even moderate renal impairment.

Once lipid exudates collect in the fovea, treatment does not improve vision. Aggressive treatment of serum lipids and hypertension must be started early in the course of retinopathy.

The nocturnal hypoxemia, hypercapnia, and hypertension of obstructive sleep apnea are thought to aggravate diabetic retinopathy.

AS THE YEARS PASS WITH DIABETES, the risk of microvascular complications (retinopathy, nephropathy, and neuropathy) increases. We now know that care of these patients entails not only tight blood glucose control, but also aggressive treatment of systemic conditions that exacerbate or accelerate the course of diabetic microvascular and macrovascular disease: ie, hypertension, anemia, hyperlipidemia, obstructive sleep apnea, and smoking.

Studies continue to show that a comprehensive and aggressive approach to management significantly slows progression to end-organ failure. We discuss the rationale for aggressive and comprehensive management of diabetic patients and suggest how to implement such a program in primary care practice.

COURSE OF RETINOPATHY ACCELERATES

Within the retina, as in other organs, there is no observable microangiopathy during the first few years of diabetes. The first lesions are usually not seen until about 5 years after the onset of hyperglycemia, although about 20% of patients with type 2 diabetes may have observable microangiopathy at the time of diagnosis. Thereafter, retinal microvascular occlusion and leakage accelerates and progresses, so that after 15 years 80% of patients with type 2 diabetes and 97% of those with type 1 diabetes have some degree of retinopathy. Of those with type 1 diabetes, 14% develop vision problems from macular complications, and 40% develop proliferative retinopathy.[1,2]

The success of laser and surgical treatments[3] depends significantly on when the retinopathy is discovered and treated. Therefore, vigilant screening is needed to detect the retinopathy as early as possible.

Some forms of macular edema cannot be treated by laser because of their extensive involvement of the perifoveal capillaries. In such cases, systemic medical treatment is used in conjunction with local therapies such as retrobulbar steroids, intravitreal steroids, or vascular endothelial growth factor antagonists.

HYPERGLYCEMIA: TIGHT CONTROL IS BEST

Hyperglycemia has been the primary target of diabetes care since two major studies recognized that it accelerates the course of retinopathy, neuropathy, and nephropathy in type 1 diabetes[4,5] and in type 2 diabetes.[6,7] In these studies, every 1% absolute reduction in hemoglobin A_{1C} produced an approximately 35% reduction in the onset of retinopathy and rates of significant progression; the better the control of blood sugar, the slower the course of retinopathy.

Controlling glucose tightly and treating comorbidities can delay organ failure

Although the magnitude of the absolute risk reduction declines with continuing proportional reduction in hemoglobin A_{1C}, there is still meaningful reduction in risk to be gained as the level is reduced toward the normal range (4%–5%).

These studies and others have led to a massive physician and public awareness campaign about the importance of improving blood sugar control, and to a general recommendation by the American Diabetes Association for target levels below 7% for all diabetic patients.

In the Diabetes Control and Complications Trial, early worsening of retinopathy was observed in 13.1% of patients treated intensively and in about 6% of patients treated conventionally.[5] The most important risk factor for early worsening of retinopathy was a higher hemoglobin A_{1C} level at the start of the trial and a large reduction induced during the first 6 months of treatment. Although there was initial concern over such worsening, the long-term outcomes with intensive treatment among these patients were actually more favorable than for the conventionally treated patients.

Furthermore, there was no evidence to support reducing hyperglycemia more gradually. In only a small number of patients did the early worsening actually lead to proliferative retinopathy. However, we recommend that if patients are observed to have retinopathy with severe preproliferative retinal lesions, a prudent course may be to delay starting intensive treatment until panretinal laser photocoagulation is completed (in a few weeks), particularly if the hemoglobin A_{1C} is very high.

BLOOD PRESSURE CONTROL

In the third US National Health and Nutritional Examination Survey, 1988 to 1994, hypertension was found in 65% to 75% of diabetic adults.[8] In multiple studies of both type 1 and type 2 diabetes, hypertension was associated with higher rates of onset and progression of retinopathy and of macular edema, the greatest cause of central vision loss among diabetic patients.

Even modest elevations increase risk

The regulation of blood flow within the retinal microvasculature is impaired in diabetes, leading to increased microvascular hypertension and to increased susceptibility to injury from even modest levels of systemic hypertension[9–11]: even modest elevations of either systolic or diastolic blood pressure that may be within the normal range for nondiabetic people significantly increase the risk for the development and progression of retinopathy compared with diabetic patients with lower blood pressures.[12]

Aggressive control necessary

In multiple trials, aggressive blood pressure treatment was accompanied by improved outcomes in retinopathy and nephropathy without an observed threshold blood pressure below which treatment was not beneficial.[13–15] As a result, the Joint British and American Diabetic Societies have recommend that for both type 1 and type 2 diabetes, hypertension should be aggressively treated to levels less than 130 mm Hg systolic and less

than 80 mm Hg diastolic, and to less than 75 mm Hg diastolic when there is any degree of proteinuria.[16,17] We also recommend these target levels for any patient with evidence of retinopathy.

Furthermore, in these patients, attributing elevated blood pressures to "white coat" hypertension is dangerous, as it may delay appropriate intervention. Blood pressure in diabetic patients is labile and is effectively measured only by 24-hour monitoring or by home blood pressure measurements, with the objective that *all* measured blood pressures should be controlled to the target levels.

Although there have been some concerns that lowering blood pressure below a certain point might increase morbidity and mortality from acute stroke or cardiac ischemia (the "J curve" phenomenon), studies to date show no evidence of this. Rather, with aggressive blood pressure control, stroke and cardiovascular events are reduced.[12–15,18,19]

However, such target levels for hypertension control in diabetic patients constitute a formidable challenge. In the United Kingdom Prospective Diabetes Study, 29% of patients needed three or more antihypertensive drugs to reach these goals, and 60% needed at least two drugs after 9 years.[12,19] In practice, many patients require combinations of treatments from different classes to manage their hypertension, and this should be aggressively pursued.

Choosing an antihypertensive drug

The choice of antihypertensive agent for diabetic patients is still controversial:

Diuretics. A major advantage of diuretics is low cost; however, they modestly raise blood sugar levels, aggravate dyslipidemia, and, at higher doses, cause sexual dysfunction.

Beta-blockers are inexpensive and reduce death and cardiac events after myocardial infarction as well as when used as primary prevention; however, they can produce hypoglycemia unawareness and sexual dysfunction and can worsen asthma and conduction disturbances.

Alpha-receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers appear to be neutral with regard to glycemic control and insulin resistance. Edema and tachycardia limit the use of calcium channel blockers, and an increased risk of adverse cardiovascular events has been shown with alpha-blockers vs diuretics[20] and with calcium channel blockers vs ACE inhibitors[21] in patients with diabetes.

ACE inhibitors and angiotensin II receptor blockers cause dilation of efferent glomerular arterioles, which results in a protective effect with respect to nephropathy. Because of this, these drugs are preferred in the early treatment of hypertension in diabetic patients with microalbuminuria.[19,22] Side effects that limit the use of ACE inhibitors are idiopathic cough and hyperkalemia. (The cough is not observed as often with angiotensin II receptor blockers.) Care should be taken in prescribing these drugs in patients with symptomatic neurogenic orthostatic hypotension.

Blood pressure lability

Peripheral autonomic neuropathy contributes significantly to the lability in blood pressure in diabetic patients.

Neurogenic orthostatic hypotension, in which systolic blood pressure falls by 20 mm Hg or more and diastolic blood pressure by 10 mm Hg upon standing from a supine position, is one of the most bothersome symptoms of autonomic neuropathy. Neurogenic orthostatic hypotension may or may not be symptomatic, and the symptoms are often independent of the magnitude of the blood pressure decrease. Symptoms are usually worse in the morning and may include lightheadedness, blurring of vision, nausea, fatigue, cognitive impairment, and headache.

Hypertension is linked to onset and progression of retinopathy, macular edema

Diagnosis of neurogenic orthostatic hypotension is done in the office, but the patient must remain supine at least 10 minutes before the blood pressure is taken to maximize the decrease upon standing. Blood pressure and heart rate should be measured immediately on standing and again at 1 and 3 minutes, with the arm held at heart level. Sitting blood pressure measurements are not useful, as sensitivity is reduced in patients with a milder condition.

Nonpharmacologic treatments include increasing oral fluid intake, wearing support stockings, and small increases of oral salt

intake (by diet or tablets). Patients should avoid strenuous morning activities, standing rapidly, excessive heat, and drugs that exacerbate neurogenic orthostatic hypotension (eg, beta-blockers, tricyclic antidepressants, and phenothiazines).

Drug treatment may include fludrocortisone, which acts through renal retention of salt and fluid. Pyridostigmine has been found to raise standing blood pressure without affecting supine blood pressure. Midodrine, a peripherally active alpha-1 agonist, may be especially useful when volume expansion is contraindicated because of cardiomyopathy. It should be noted that both fludrocortisone and midodrine may exacerbate supine hypertension.

Nocturnal supine hypertension. Although neurogenic orthostatic hypotension can often be detected during the office evaluation, hypertension in the supine position most often goes unrecognized. Factors that contribute to supine hypertension are an increase in circulating blood volume that occurs during the day in the upright position and the suppression of the renin-angiotensin axis that occurs in the supine position.

Fluids, salt intake, support stockings help relieve orthostatic hypotension

While clinical symptoms of supine hypertension are rare, the problem is of great concern in this population, as there is increasing evidence that it aggravates nephropathy and may contribute to worsened vision upon awakening, a common problem in diabetic patients with retinopathy and macular edema.[23]

Treatment should include elevating the head of the bed 10 to 20 degrees (4–6 inches). This will mechanically reduce blood pressure in the head, activate the renin-angiotensin axis to increase salt and fluid retention, and also ultimately improve the morning symptoms of neurogenic orthostatic hypotension. Also, a short-acting, sodium-sparing agent such as hydralazine (25–50 mg) may be required at bedtime to treat nocturnal hypertension and allow for more aggressive treatment of morning hypotension.

ANEMIA

Anemia often accompanies diabetic kidney disease and is thought to exacerbate the ischemic aspect of diabetic retinopathy.[24] Anemia in patients with diabetes commonly develops during the stage of overt proteinuria but before the onset of even moderate renal impairment. In diabetic patients with glomerular filtration rates greater than 90 mL/minute, the most common causes are iron deficiency or gastrointestinal bleeding.[24] However, at glomerular filtration rates less than 60 mL/minute, the most common cause of anemia is a relative erythropoietin deficiency.[24] The anemia frequently results in hemoglobin levels depressed below 10 or 11 g/dL (hematocrit less than 30% to 33%). Although serum erythropoietin levels may be in the normal range of 10 to 30 μU/mL, such values are relatively depressed for the severity of the anemia.

In a cross-sectional study of 1,691 diabetic patients, those whose hemoglobin levels were lower than 12 g/dL had a twofold higher prevalence of retinopathy after other known factors were controlled for; among those with retinopathy, the severity correlated with the severity of anemia.[25] Among the subjects with retinopathy, the risk of having severe rather than mild retinopathy was five times higher if the hemoglobin level was less than 12 g/dL.

The Early Treatment Diabetic Retinopathy Study evaluated the effect of moderate levels of anemia. A low hematocrit (< 40% in men, < 34% in women) was an independent risk factor for high-risk proliferative retinopathy and severe vision loss (odds ratio 1.52).[26]

Studies of iron supplementation or erythropoietin analog treatment on retinopathy are few and are only small, uncontrolled series.[24,27] They suggest, however, that treatment of anemia is associated with fewer new showers of infarcts, which may result in a slowing of the progression of capillary nonperfusion and the development of proliferative retinopathy.[24] Multicenter studies are being organized to specifically address the correction of anemia and diabetic retinopathy.

Anemia's effects on nephropathy

Although the evidence is sparse for retinopathy, we have significant data on the consequences of anemia on the progression of diabetic nephropathy.[28,29] Treatment with erythropoietin has been shown to slow the progression of nephropathy.[30–32] These data have led

to consistent recommendations from the US National Kidney Foundation, the European Working Group on Anemia Management, the Canadian Society of Nephrology, and the reconvened American Anemia Working Group, to treat anemia aggressively with erythropoietin at any stage of kidney disease in which hemoglobin levels are 11 g/dL or lower, with a treatment target level of 12.5 g/dL.

We recommend aggressive treatment with similar target hemoglobin levels in any diabetic patient with evidence of nephropathy or retinopathy. Such aggressive treatment has additional benefits, including improvements in quality-of-life scales, cognitive function, exercise capacity, and cardiac function, as well as reductions in hospitalization and mortality rates.[31,33–36]

HYPERLIPIDEMIA

Lipids may independently contribute to the microvascular injury observed in diabetes.[37] The multicenter Early Treatment Diabetic Retinopathy Study reported a relationship between total and low-density lipoproteins and the frequency of retinal hard exudates,[38] and the Wisconsin Epidemiologic Study of Diabetic Retinopathy showed a similar trend, along with increased severity of the retinopathy.[39] In patients who were older at the onset of diabetes, this relationship was not observed; however, when hypertension was added, it did correlate with the severity of hard exudates.

Dyslipidemia in diabetic patients causes endothelial dysfunction, which is implicated in the progressive resistance of hypertension to treatment, although treatment of elevated lipids with statins has not been associated with improved hypertension control. However, reports of intensive treatment with statins associated with hypertension control[40] did result in a decrease in intraretinal hard exudates.

Unfortunately, once lipid exudates have collected within the fovea, vision does not improve even if the exudates resolve with treatment. Therefore, aggressive treatment of serum lipids and hypertension must begin early in the course of retinopathy, ie, before the accumulation of lipids causes loss of vision.

OBSTRUCTIVE SLEEP APNEA

We recently suggested an association between obstructive sleep apnea and exacerbations of diabetic retinopathy, with the development of more diffuse macular edema associated with progressive ischemia.[23] Sleep apnea is a documented independent risk factor for systemic arterial hypertension.[41] It contributes to pulmonary hypertension[42,43] and has been reported to be a significant risk factor for nocturnal stroke and myocardial infarction.[44,45] In diabetic patients it is also a risk factor for renal failure.[23,24]

The prevalence and severity of obstructive sleep apnea increase dramatically with obesity, which is also associated with type 2 diabetes. Sleep apnea is present in over 60% of moderately overweight patients (body mass index of 28, or approximately 212 pounds at 6 feet) and rises to over 80% in the very obese.[46]

Deposition of fat in the tissues surrounding the pharyngeal airway narrows the aperture, thereby promoting obstruction. Obstructive sleep apnea is thought to aggravate diabetic retinopathy because of the associated nocturnal recurrent hypoxemia with hypercapnia and hypertension.[23] The same abnormalities of retinal autoregulation that are induced by hyperglycemia[47,48] make the retina susceptible to ischemic injury from hypoxemia and hypertension and are aggravated by hypercapnia.

Once lipid exudates collect in the fovea, treatment does not improve vision

In most cases, obstructive sleep apnea is treated with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (bi-PAP) delivered during sleep through a nasal mask. In a small number of patients, retinopathy was observed to improve with a reduction in nerve-fiber-layer infarcts and a reduction in macular edema.[23] However, compliance with CPAP or bi-PAP is extremely difficult to assess, and there appears to be a wide range of acceptance and usage. Furthermore, successful treatment is most often defined as a subjective improvement in daytime somnolence, which may be related to fewer arousals from snoring but may not reflect an improvement in the severity or frequency of the hemodynamic events associated with the apneic or hypopneic episodes.

Surgical treatment or tongue and mandibular repositioners are less commonly

used, appear to have limited success in obese patients, and have not been studied in diabetic patients.[23]

The association between obstructive sleep apnea and diabetic retinopathy warrants further evaluation. In the interim, because obstructive sleep apnea syndrome is so common in obese patients, it appears prudent to evaluate obese diabetic patients for this syndrome, especially if they snore, have fragmented sleep patterns, or report daytime somnolence.

Furthermore, even though obesity is one of the strongest risk factors for obstructive sleep apnea, the syndrome also occurs in 10% to 30% of people with ideal body weight.[49,50] Therefore, we recommend evaluation for obstructive sleep apnea and aggressive treatment in any patient who has these symptoms (even if the patient is not obese) and who also has chronic hypertension, nocturnal hypertension, or an accelerated course of ischemic retinopathy with diffuse macular edema.

SMOKING

In a few patients, treating sleep apnea may improve retinopathy

Several mechanisms may explain the increased risk of small-vessel ischemic disease among smokers. Circulating activated leukocytes are increased in smokers with platelet activation.[51] Nicotine in tobacco smoke causes severe retinal vasoconstriction.[52] Carboxyhemoglobin in the blood displaces oxygen, further contributing to the smoke-induced ischemic and hypoxic environment of the tissue. Low-density lipoprotein levels tend to be elevated in smokers, and high-density lipoprotein levels are decreased.[53]

Two studies have identified smoking as a risk factor in non-arteritic anterior ischemic optic neuropathy.[54,55] However, the role of smoking in diabetic retinopathy has not been clearly established; while some studies have shown an association,[56,57] others have shown no relationship when controlling for additional risk factors such as age of onset and duration of diabetes or associated hypertension.[58] It is possible, however, that the failure to correlate diabetic retinopathy with cigarette smoking may be due to increased mortality in smokers.

Since the link between cigarette smoking and cardiovascular disease is well established, especially among patients with diabetes, it is imperative that physicians urge their diabetic patients to quit smoking.

CHALLENGES TO LONG-TERM MANAGEMENT

Physicians caring for diabetic patients need not only to maximize blood glucose control, but also to closely monitor and aggressively treat other systemic conditions that exacerbate or accelerate the course of microvascular and macrovascular disease. Screening for and aggressively treating hypertension, hyperlipidemia, anemia, obstructive sleep apnea, and smoking in diabetic patients has been shown to slow progression to end-organ failure.

However, such an aggressive long-term screening and treatment plan can be daunting to implement and follow, given the time constraints of a busy primary care practice. Such an approach requires communication with allied professionals and cooperating subspecialists. Constraints of time and reimbursement present difficulties for even the most organized practice.

One common problem is that there are no mechanisms in place to easily identify when the care for or by a patient is within such guidelines. Frequently the physician must rely on memory or on handwritten notes, which with complex long-term care become impossible to review in the time constraints of the office visit. Chronologic trends, even in the best of circumstances, are difficult to review unless presented in tabular or graphic formats.

Clear practice guidelines are required that promote not only evidence-based medical management but also patient education. Patients must be encouraged to become active partners with their providers in managing their own disease.

Consider a practice redesign

To effectively manage patients with chronic disease, physicians must be able to chronologically track the care of their patients, to highlight problems or deficiencies as they arise, and to promote prevention in order to reduce complications. In many cases, this may mean redesigning one's practice.

Resources to begin the practice redesign

are available from a variety of sources. A number of federal agencies are funding demonstration projects to assist in practice redesign. Also, physician specialty organizations such as the American Academy of Family Practice are involved in such projects to develop systems that assist the physician with the delivery of care. The Medicare Quality Improvement Organizations (**www.medqic.org**) provide an excellent source of free technical assistance with practice redesign. They also can provide many tools to facilitate system changes and promote better patient education and involvement.

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