A DIABETIC RETINOPATHY RISK FACTOR CHECKLIST


In addition to HbA1C, remember to evaluate patients for these 11 other systemic complications.

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Diabetes mellitus is a growing epidemic, affecting an estimated 30 million Americans (~9% of the US population) and 415 million adults globally.[1,2] Patients with diabetes are at an increased risk for myriad systemic and ocular complications, include neuropathy, nephropathy, and diabetic retinopathy (DR). Research shows that diabetic retinal neurodegeneration is associated with the progression of the disease, which is preceded by visible microangiopathy.[3] In fact, all retinal layers are affected before microangiopathy findings are even observed.[4,5]

Because diabetes is a systemic disease, a multidisciplinary approach is needed for the evaluation and treatment of concomitant systemic conditions that influence the progression and outcome of DR. Eye care providers play a crucial role in ensuring patients with diabetes receive the appropriate annual systemic medical evaluation.[6]

A patient's DR is not slowed simply by controlling blood sugar; a multitude of factors influence the onset and progression of DR (Figure 1). Thus, it is incumbent upon physicians to review not only a patient's HbA1C, but also the following other risk factors.

HBA1C

Elevated glycosylated hemoglobin (HbA1C) is a strong risk factor associated with the development and progression of DR (Figure 2). The Diabetes Control and Complications Trial, which included patients with insulin-dependent diabetes, and the

Figure 1. This patient presented with nonproliferative DR and a slew of systemic risk factors, including sleep apnea (without CPAP use), anemia, albuminuria, high blood pressure, vitamin D deficiency, and a HbA1C of 9%. The patient was also a smoker and had gum disease.

United Kingdom Prospective Diabetes Study, which included patients with noninsulin–dependent diabetes, both showed that tight control of blood sugar can reduce the incidence of retinopathy.[7,8] The studies found that for every 1 absolute percentage point decrease in HbA1C the incidences of DR onset and significant progression decreased by approximately 35%.[9]

However, HbA1C may only account for approximately 10% of a patient's risk for complications.[2,10]

HYPERTENSION

Studies show that hypertension is associated with higher rates of the onset and progression of DR and macular edema in both type 1 and type 2 diabetes.[11] A patient with modest elevations of either systolic or diastolic blood pressure may be at an increased risk for the progression of retinopathy compared with a patient with diabetes who has lower blood pressures.[11,12]

CHOLESTEROL

In patients with type 2 diabetes, hyperlipidemia concomitant with hypertension is associated with worse stages of retinopathy and increased accumulation of intraretinal exudation.[2,11] Both the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Wisconsin Epidemiologic Study of Diabetic Retinopathy showed a relationship between total and low-density lipoproteins and the frequency of hard exudates found in the retina.[11] (It can be both an early or late sign of DR, depending on the patient's systemic profile.)

ANEMIA

Diabetic kidney disease, along with anemia, is thought to exacerbate the ischemic aspect of DR. When glomerular filtration rates reach less than 60 mL/minute, the most common cause of anemia is a relative erythropoietin deficiency. Anemia frequently occurs when hemoglobin levels are depressed below 10 g/dL or 11 g/dL (hematocrit less than 30% to 33%).[11,13] The ETDRS evaluated the effect of anemia and found that low hematocrit (< 40% in men and < 34% in women) was an independent risk factor for high-risk proliferative retinopathy and severe vision loss.[11,13]

SMOKING

Nicotine is known to cause severe retinal vasoconstriction, and smoking can cause an increase in circulating activated leukocytes along with platelet activation. Carboxyhemoglobin in the blood eventually displaces oxygen and further contributes to an ischemic and hypoxic environment in the retinal tissue. Patients who smoke tend to have elevated low-density lipoprotein levels and decreased high-density lipoprotein levels.[11,14]

OBSTRUCTIVE SLEEP APNEA

The recurrent nocturnal hypoxemia and the hypercapnia and hypertension associated with obstructive sleep apnea may aggravate DR and may be a driving factor for more diffuse macular edema. Sleep apnea is also an independent risk factor for several systemic conditions, such as systemic arterial and pulmonary hypertension, nocturnal stroke, and myocardial infarction. In patients with diabetes it is also a risk factor for renal disease and eventual renal failure. Most patients with obstructive sleep apnea are treated with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (bi-PAP).[11,15]

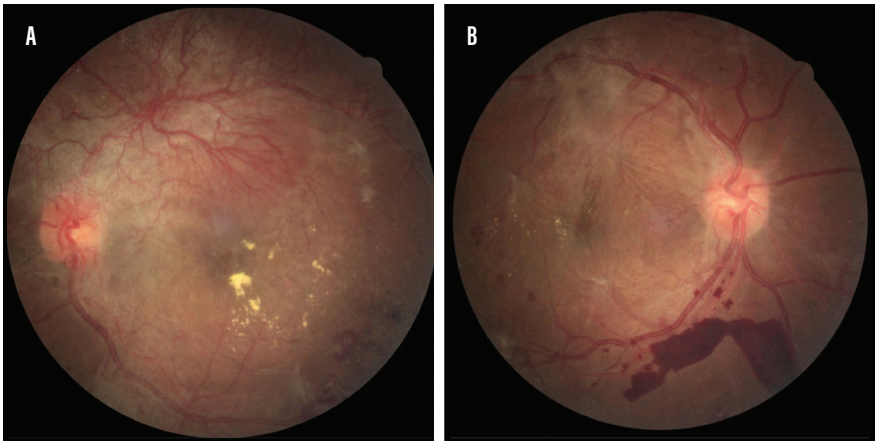

Figure 2. This patient presented with fibrous proliferative DR and a HbA1C of 13%. The left eye (A) shows a large area superiorly of retinal neovascularization and hard exudates in the macular area. The right eye (B) shows a pre-retinal hemorrhage inferiorly.

HOW STRESS AND SLEEP DEPRIVATION ARE LINKED TO DIABETES

Chronic stress has long been associated with complications in the diabetic population. The chronically stressed individual experiences an uptake in release of glucocorticoids and catecholamines due to the improper functioning of the hypothalamic-pituitary-adrenal axis.[14] The increased presence of glucocorticoids within the body leads to insulin resistance and inflammation.[14] Siddiqui et al demonstrated that those with normal glucose tolerance have lower chronic stress and stress responses than patients recently diagnosed with diabetes.[15]

Patients existing on decreased amounts of sleep are at higher risk of developing diabetes due to an increase in insulin resistance, increased hunger, and increased caloric intake.[16] A meta-analysis of studies on diabetes and sleep found that short sleepers (< 7 hours) are at a higher risk for developing type 2 diabetes; in addition, those who sleep for longer periods who develop type 2 diabetes are more likely to have developed the condition through a different mechanism than short sleepers.[17]

VASCULITIS

This subacute inflammatory process plays an important role in the pathogenesis of DR, including increased retinal vascular permeability, vascular occlusion, neovascularization, and retinal neurodegeneration.[2]

METFORMIN AND VITAMIN B12 DEFICIENCY

A meta-analysis showed that metformin use can, in some patients, decrease vitamin B12 levels, which can put a person with type 2 diabetes at risk for developing borderline to complete deficiency.[16] Metformin may also cause a deficiency in folic acid in patients with type 2 diabetes.[17] Any form of anemia can worsen retinopathy because it exacerbates the ischemic retinal process.

OBESITY

Approximately 90% of patients with type 2 diabetes are either obese or overweight.[18] Obese patients tend to have an increase in chemical factors that lead to increased insulin resistance that, coupled with decreased insulin production, facilitate the presence of an increase in blood glucose levels.[18,19] The specific mechanism by which insulin resistance is created stems from the release of cytokines, glycerol, and other fatty acids.[10]

This is particularly concerning because the prevalence of type 2 diabetes is shifting more toward a younger obese population.[18]

PROTEINURIA

A high prevalence of patients with insulin-dependent diabetes have high amounts of protein in their urine, known as *proteinuria*. This condition signals imminent renal failure.[20] In addition to this complication, the presence of microalbuminuria has a direct relationship with kidney function and is often the first sign that the kidneys are becoming negatively affected by diabetes.[21]

For these patients, physicians should ensure they have tight blood pressure control and recommend that they decrease their dietary intake of protein to reduce proteinuria and slow the progression to renal failure.[20,22]

VITAMIN D

Recent research suggests an association between patients with type 2 diabetes who also have a vitamin D deficiency and an increased risk of DR.[23] Animal studies have reported an inhibitory effect of vitamin D

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administration on endothelial cell inflammation and proliferation—a major cause of severe retinopathy. Further studies are required to better understand the causal relationship between vitamin D deficiency and DR in patients with type 2 diabetes.[22,24]

FINAL THOUGHTS

Patients with diabetes have a lot to consider when it comes to their health (see *How Stress and Sleep Deprivation Are Linked to Diabetes*). Eye care providers are essential members of the care team and can help patients review their risk factors and potentially help them avoid developing DR. And if for whatever reason patients do end up with DR, as we all know, the earlier we can catch a problem, the sooner we can recommend a management strategy aimed at protecting the patient's ocular and systemic health. ■

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