Current Strategies on Managing Diabetic Eye Disease

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I. The stats: Diabetes Mellitus (DM) affects so many people.
   a. The most current report from the CDC released in 2021 states that 38.4 million individuals in the US have diabetes
      i. Accounts for nearly 12% of the total population.
   b. Diabetic retinopathy (DR) is a common complication of diabetes mellitus (DM), affecting approximately 30% of adults with diabetes
      i. Diabetic Retinopathy is the leading cause of blindness in working-aged Americans.
   c. The optometrist's role as the primary care giver for eye care is more important than ever to prevent vision loss among the growing numbers of diabetic patients.

II. Pathogenesis and Clinical Findings.
   a. Nonproliferative Diabetic Retinopathy (NPDR)
      i. Prolonged hyperglycemia can lead to inner retinal microvascular changes.
      ii. These can be visualized in the retina as microaneurysms, hemorrhaging, leakage and exudation and nonperfusion.
      iii. More advanced features of nonproliferative disease include venous beading, intraretinal microvascular abnormalities (IRMA) that represent dilated telangiectatic capillaries still confined intraretinally and vascular sheathing.
   b. Proliferative Diabetic Retinopathy (PDR)
      i. Retinal ischemia prompts vascular endothelial growth factor (VEGF) release, fueling preretinal neovascular growth
      ii. Neovascularization typically begins within the retina and on the optic nerve head but can eventually infiltrate the iris and angle.
      iii. Tractional retinal detachment (TRD) and neovascular glaucoma are the most advanced complications and can cause severe, irreversible vision loss.
   c. Diabetic macular edema (DME)
      i. Vascular leakage that results in intraretinal fluid cysts and retinal thickening that may be accompanied by spillover of subfoveal fluid in severe cases.
         1. This occurs as increased vasopermeability leads to breakdown of the inner blood-retinal barrier and exudation.
         2. DME can occur at any stage of retinopathy
         3. It is the most common cause of reduced vision in diabetes.

III. The new Diabetic Retinopathy Staging update using International Clinical Diabetic Retinopathy (ICDR) Severity Scale
   a. Mild NPDR is now characterized by microaneurysms only
   b. Moderate NPDR is noted whit the presence of intraretinal hemorrhages
   c. Severe NPDR continues to be defined by one factor of the 4-2-1 rule: four quadrants of severe intraretinal hemorrhaging (approximately 20 hemorrhages per quadrant), at least two quadrants of definite venous beading and at least one quadrant of IRMA.
   d. Very severe NPDR is associated with a higher risk of proliferative conversion and is defined as the presence of two or more factors of the 4-2-1 rule.
      i. Risk for conversion to PDR within 1 year in eyes with severe NPDR is 50% and very severe NPDR is 75%.
   e. PDR is defined by the presence of new vessels with or without hemorrhaging into the vitreous or preretinal/subhyaloid space.
      i. Neovascularization in PDR is preretinal and located on top of the retina.
      ii. It can be classified as neovascularization of the disc (NVD, on or within one disc diameter from the disc margin) or neovascularization of the retina elsewhere (NVE).

iii. Active PDR is still vascularized and blood can be seen within the small, fine vessels of the membrane
    1. High Risk vs Low Risk PDR
    2. Referral to Retina Specialist for Anti-VEGF +/- PRP
iv. Inactive PDR has preretinal tissue that is mostly fibrotic, avascular and opaque in appearance.

f. Diabetic Macular Edema
    i. Historically, the ETDRS also coined the term "clinically significant macular edema" (CSME).
        1. This was defined as either retinal thickening within the central 500µm of the macula, hard exudates within 500µm of the center of the macula with adjacent thickening or zones of retinal thickening one disc diameter or larger within one disc diameter of the fovea.
        2. With the advent of OCT, DME is now more commonly described as either center involved (CI-DME) or non-center involved (NCI-DME).
            a. CI-DME is defined as thickening within the central 1mm diameter or "center subfield zone."

IV. Optometric Management of Diabetic Retinopathy and referral guidelines

a. Type 1 Diabetes
    i. The American Diabetes Association (ADA) and AOA recommend a baseline comprehensive eye exam and follow-up examinations for patients with type 1 diabetes.
    ii. The first follow-up should not exceed three to five years after diagnosis, and patients should be followed at least annually thereafter.

b. Type 2 Diabetes
    i. Should be evaluated at time of diagnosis since diabetes may have gone undetected for years prior, making it challenging to determine the exact duration of the disease.
    ii. Follow-up interval depends upon the level of retinopathy present and analysis of other risk factors for progression, such as degree of glycemic control and duration of the disease.

c. No retinopathy or those with only mild retinopathy can be monitored annually assuming no DME is present.

d. Moderate NPDR
    i. Milder cases of moderate NPDR with minimal retinopathy lesions can be monitored every 9 to 12 months.
    ii. More severe end of the moderate NPDR spectrum, a six-month follow-up interval may be more appropriate.

e. Severe NPDR
    i. Referral to a retina specialist should be considered for patients with severe NPDR even in the absence of DME, and patients should be monitored closely, every three to four months.
        1. When considering whether or not to refer a patient with severe NPDR, factors favoring referral include noncompliance, documented rapid progression, absence of complete posterior vitreous detachment (PVD), monocular status and presence of concurrent DME or multiple risk factors for progression such as poor glycemic control. Provider comfort level and in-office imaging availability also should be contemplated.
        2. ERG and OCTA may be helpful in diagnosis of Severe NPDR

f. Proliferative Diabetic Retinopathy (PDR)
    i. Referral to a retina specialist for cases of active and previously untreated proliferative disease.
    ii. More urgent referral of high-risk PDR (24 to 48 hours for high-risk vs. two to four weeks for low-risk).
    iii. Although treatment of low-risk PDR may or may not be immediately initiated (deferred until it reaches high risk), care with ophthalmology should be established.

iv. Due to the high risk for severe vision loss, the AAOph recommends treatment, usually PRP, in cases of active high-risk PDR.
v. Refer patients with anterior segment neovascularization urgently.

g. Diabetic Macular Edema (DME)
    i. As a general rule, the optometric physician should consider referring DME at any stage, especially if it is center involved, causing reduced best-corrected visual acuity (BCVA) or is progressing.
    ii. 2019 AOA Clinical Practice Guidelines recommends consultation within two to four weeks when CI-DME is present
    iii. Diabetic Retinopathy Clinical Research (DRCR) Network Protocol V suggested that close observation until acuity declines or DME worsens may be a reasonable management option for eyes with CI-DME and BCVA of 20/25 or better.
        1. This study found that vision at two years was no different whether eyes with CI-DME and good acuity were immediately treated with aflibercept, macular laser or if treatment was withheld until acuity worsened.
        2. Patients with DME should be followed every two to four months.

V. Diabetic Eye Exam
a. A thorough history should be obtained including the duration of DM, some indication of glycemic control (HbA1c and/or fasting blood glucose level, glucose time in range) and medications.
b. Visual acuity, entrance test, slit lamp exam and intraocular pressure (IOP) should be obtained, as in a standard eye exam. A magnified slit lamp examination of the entire iris (lids retracted as needed) should be done prior to dilation.
    i. If any neovascularization of the iris is present or IOP is elevated, perform gonioscopy to inspect for neovascularization of the angle.
c. Dilation- funduscopic exam of the posterior pole and the periphery is the standard of care for diabetic eye exams.
    i. Vitreous and preretinal hemorrhages may be subtle in PDR
d. Multimodal imaging technologies often help highlight subtle vascular abnormalities and results in more accurate retinopathy staging and increased exam efficiency.
    i. Color fundus photography (widefield imaging), OCT, OCT-A, ERG, FA, FAF and B scan ultrasonography
    ii. Multiple studies have shown that inspection of fundus photos may actually be superior to ophthalmoscopy for identification of some lesions such as microaneurysms, small intraretinal hemorrhages, IRMA and subtle neovascularization.
    iii. However, at this point in time, imaging is less than a perfect science. The presence of artifacts, lack of stereopsis and poor identification of peripheral lesions are just some reasons why imaging, including ultra-widefield techniques, is often not an adequate replacement for clinical examination.

VI. Patient Education
a. After 15 years of disease duration, 80% of patients with type 1 DM will have some degree of retinopathy.
b. Elevated blood glucose levels and HbA1c values (less than or equal to 7%), as well as less glucose time in range assessed by continuous glucose monitoring devices, are also associated with higher rates of retinopathy.
c. Control of blood pressure, lipids and management of comorbidities, such as sleep apnea, all reduce risk of progression.
d. Pregnancy in diabetics places increase risk of progression to severe retinopathy; however this is not the case in those with gestational diabetes
e. Glucagon-like peptide-1 (GLP-1) receptor analogs are a newer, highly effective category of medication for diabetes management including semaglutide (Ozempic and Wegovy, both Novo Nordisk), and tirzepatide (Mounjaro, Eli Lilly)
    i. Although improved glycemic control is encouraged for promotion of long-term positive outcomes, a transient worsening of retinopathy may be seen initially.
        1. Likely related to VEGF expression, reactive oxygen species production and breakdown of the blood-retinal barrier.

VII. Treatment and Management Considerations for NPDR

a. Fenofibrate - dyslipidemia medication that is a safe and inexpensive fibric acid derivative.
    i. FIELD and ACCORD (large randomized trials) have shown that fenofibrate, when used as an adjunctive treatment to standard of care DR therapies, can slow progression of pre-existing DR and reduce the need for treatment of DME and proliferative DR in patients with type 2 diabetes.
    ii. The DRCR Network is currently recruiting for Protocol AF (Fenofibrate for Prevention of DR Worsening), which is enrolling patients with mild to moderately severe NPDR and no CI-DME at baseline.
        1. Results are expected in 2029.

b. Nutritional supplementation and medical food therapies.
    i. We know that many patients with DR have concurrent vitamin and mineral deficiencies that fuel retinal microvascular damage and inflammation.
        1. The goals of supplementation in DR are to decrease inflammatory mediators, reduce oxidative stress, support retinal metabolism and promote microvascular health.
        2. Supplement components of interest include lutein and zeaxanthin, L-methylfolate, N-acetylcysteine, vitamin E, vitamin D, vitamin C, vitamins B1, B2, B6 and B12 (methylcobalamin) and alpha-lipoic acid.
        3. The role of anti-VEGF therapy in severe NPDR management and its potential benefits continues to be debated.

VIII. Treatment Considerations for Proliferative Diabetic Retinopathy

a. Both PRP and anti-VEGF may be used to treat PDR; however, PRP is generally recommended in high-risk PDR.
b. Vitrectomy may be management options should PRP result in inadequate neovascular involution.

IX. Treatment Considerations for DME

a. First-line therapy for CI-DME involves anti-VEGF therapy, and newer generation agents such as faricimab and high-dose 8mg aflibercept may provide extended duration of action allowing for less frequent injections and reduced treatment burden.
b. Macular photocoagulation remains a viable treatment option for non-center-involved DME, especially when focal areas of noncentral leakage are present.
c. Intravitreal corticosteroid injections and sustained-release implants may be employed when DME is diffuse or unresponsive to anti-VEGF therapies, especially in pseudophakic eyes.