Diagnosis Diabetes: The Optometric Management Guide

Course Outline

Carolyn Majcher, OD, FAAO, FORS
Associate Professor & Director of Residency Programs
Oklahoma College of Optometry Tahlequah, OK
Majcher@nsuok.edu

Mary Beth Yackey, OD, FORS
Cincinnati Eye Institute
dr.marybethyackey@gmail.com

1. **Introduction**
    a. Diabetes Mellitus (DM)- A state of absolute or relative insulin deficiency, characterized by hyperglycemia and the risk of microvascular and macrovascular complications
    b. DM is a worldwide epidemic- 10.5% of the U.S. population have DM (34.2 million)
        i. Expected to increase to nearly 1 billion by 2050
    c. Diabetic retinopathy (DR)
        i. Epidemiology
            1. Affects approximately 30% of diabetics over age 40 in the US (4.2 million, 2.5% of the population) and approximately 35% worldwide
                a. Number of Americans with DR is expected to triple by 2050
                b. ~ 20-40% of individuals with type 2 diabetes (T2DM) have some DR at time of diagnosis
            2. Global Prevalence of DR among adults with DM in 2020 was 22.3%
                a. 8% have vision threatening DR
                b. 5% CSME
        ii. Visual impairment/blindness
            1. Leading cause of moderate and severe vision loss among working aged adults
            2. Leading cause of new cases of blindness among adults aged 20-74 years in the US
        iii. Barriers to DR screening services:
            1. Lack of knowledge/awareness that DM could affect vision
            2. Asymptomatic nature of condition (often asymptomatic until moderate NPDR is present)
            3. Time and priority issues
            4. Financial barriers
        iv. DR risk factors
            1. Longer duration of DM, Poor glycemic control (and less time in range), Uncontrolled systemic HTN, Hyperlipidemia, Insulin use and duration of insulin use, Sleep apnea, Pregnancy, Puberty, Nephropathy (proteinuria), Cataract surgery, Vasculitis, Vitamin D deficiency, Smoking
            2. Complete PVD protective against proliferation and tractional effects
        v. Introduction to multimodal imaging modalities for DR evaluation
            1. Wide field (WF)/ultra wide field (UWF) fundus imaging
            2. OCT structural
            3. OCT angiography (OCTA)
                a. Non-invasive “flow” imaging that allows for high resolution imaging of neovascular membranes, absence of leakage since no dye injection is done
                b. Focus on the preset enface displays: vitreoretinal interface, superficial & deep capillary plexuses
                c. Can be used to differentiate IRMA from small size neovascularization elsewhere
                d. OCTA montage valuable for visualizing midperipheral nonperfusion
            4. B scan ultrasound

2. Non-proliferative diabetic retinopathy (NPDR)

i. Definition- Absence of neovascularization, changes only occurring within the retina

ii. Signs - Microaneurysms (MAs), Dot and blot hemorrhages, Roth spot hemorrhages, lipoprotein exudates, Cotton wool spots (CWSs), Venous beading, Intraretinal microvascular abnormalities (IRMA), Retinal capillary non-perfusion, Retinal edema/thickening

iii. Sub-classification (American Academy of Ophthalmology)

1. Mild- At least 1 microaneurysm (microaneurysms only), 5% risk of progressing to PDR in 1 year
2. Moderate- More than just microaneurysms but less than severe NPDR (CWSs, blot/dot hemes, or minor venous beading which do not meet the requirements for severe NPDR may be present), 12-27% risk of progressing to PDR in 1 year
3. Severe- Any one of the 4-2-1 rule in the absence of neovascularization, 52% risk of progressing to PDR in 1 year
    a. 4-2-1 Rule:
        i. Severe retinal hemorrhages ≥standard photograph 2A in 4 retinal quadrants
        ii. Definite venous beading > standard photograph 6B in at least 2 quadrants
        iii. Prominent IRMA > standard photograph 8A and present in at least 1 quadrant
4. Very severe- Two or more criteria of the 4-2-1 rule in the absence of neovascularization

3. Diagnosis and management of mild NPDR without DME

1. Standard of care recommendations
    b. American Academy of Ophthalmology Preferred Practice Pattern (AAO PPP)- observation (12 month follow-up if no DME)

4. Diagnosis and management of moderate NPDR without DME

1. Standard of care recommendations
    c. AAO PPP- observation (6-12 month follow-up if no DME or sooner if signs approaching severe are present)
    d. (American Optometric Association Clinical Practice Guidelines) AOA CPG- observation (6-9 month follow-up if no DME or sooner if signs approaching severe are present)
2. Role of multimodal imaging
    a. Ultra-widefield photography detects & documents retinopathy lesions. Identifies predominately peripheral DR defined as majority of DR lesions outside the 75° ETDRS standard 7 fields
        i. Compared to eyes without, eyes with predominately peripheral DR had a 3.2-fold ↑ risk of ≥2-step DR progression (11% vs. 34%), and a 4.7-fold ↑ risk for progression to PDR (6% vs. 25%).
3. Case discussion

6. Diagnosis and management of severe NPDR without DME

1. Standard of care recommendations
    a. AAO PPP- start considering referral to retina specialist for PRP and/or anti-VEGF therapy at this stage (vs observation). If observing 3 month follow-up if no DME, 2-4 month follow-up if NCI-DME present.
2. Guiding evidence for intravitreal anti-VEGF therapy
        3. DRCR.net protocol W (Anti-VEGF Treatment for Prevention of PDR/DME)
            1. Randomized eyes with moderate to severe NPDR without CI-DME to sham (tx deferred until CI-DME or high risk PDR developed) vs periodic intravitreal aflibercept
            2. Lower rates of developing CI-DME with vision loss (11% vs 19%) or PDR (28% vs 49%) in treated eyes vs sham at 2 years
            3. Change in VA at 4 years: -2.7 letters vs -2.4 letters (not significant)
    ii. PANORAMA
4. Clinical considerations/practical approach
    a. Consider refer to retina for consideration of early anti-VEGF/ PRP, then follow at least every 2-3 months
        i. Referral depends on comfort/confidence level in accurate staging of DR
        ii. Ranibizumab and alibercept both FDA approved to treat DR without DME

5. Role of multimodal imaging
    a. Aids in confidently differentiating severe NPDR from early PDR (IRMA vs NVE)
    b. OCTA highlights and localizes subtle vascular abnormalities such as IRMA
    c. OCTA allows for visualization of vascular abnormalities within the deep plexus
    d. Detection, localization, and quantification of nonperfusion to determine risk of progression to PDR
    e. Determination of PVD status (complete PVD = lower risk for progression vision threatening PDR)
6. Discussion of case examples

7. Proliferative diabetic retinopathy (PDR)

i. Definition- Characterized by neovascularization of the disc (NVD, within 1DD of the disc margin), neovascularization elsewhere (NVE) or extraretinal fibrovascular tissue, Vitreous or preretinal hemorrhage may be present that resulted from vitreous traction on neovascularization

ii. Classification- inactive vs active, active divided into non-high risk or high risk
    1. Non-high risk- Does not meet high-risk criteria
        a. Ex: Any size NVE without vitreous heme, or NVD <1/4 in size without vitreous heme
    2. High risk- Criteria for high-risk PDR were established by the the Diabetic Retinopathy Study (DRS), one or more high risk characteristics are present:
        a. NVD ≥1/4-1/3 (standard photo 10A) of a disc area in size with or without vitreous/pre-retinal hemorrhage
        b. Any size NVD with associated with vitreous/pre-retinal hemorrhage
        c. NVE at least ½ of a disc area in size with pre-retinal/vitreous hemorrhage

iii. **Diagnosis and management of low-risk PDR without DME**
    1. Standard of care recommendations
        a. AAO PPP- Same as those for severe NPDR
        b. AOA CPG- "Eyes in which PDR has not advanced to the high-risk stage should also be referred for consultation with an ophthalmologist experienced in the management of diabetic retinal disease."
    2. Role of OCT & OCTA
        a. OCT and OCTA (esp wide field) allows for earlier detection of PDR
        b. OCT can demonstrate cells in the posterior vitreous in even subtle vitreous hemorrhage
        c. OCTA allows for precise definition and quantification of neovascular membranes
            i. Track regression of neovascularization following treatment
    3. Discussion of case examples

iv. **Diagnosis and management of high-risk PDR without DME**
    1. Standard of care recommendations
        a. MUST refer for consideration of treatment (PRP and/or anti-VEGF)
        b. AAO-PPP- Prompt PRP recommended. Anti-VEGF considered a possible alternative/adjunct
        c. AAO-CPG "Patients with high-risk PDR should receive referral to an ophthalmologist experienced in the management of diabetic retinal disease for prompt PRP."
    2. Guiding evidence
        a. PRP- DRS - The risk of developing severe vision loss outweighed the risks of treatment (PRP) side effects for eyes with PDR exhibiting high risk characteristics
            i. PRP reduces the risk of severe vision loss by approx 50% or more
            ii. Prompt PRP is recommended for eyes with high-risk PDR
    3. Role of OCT, OCTA, B scan ultrasound, widefield and ultra-widefield photography
    4. Discussion of case examples

8. Diabetic macular edema

i. Definition-
    1. Collection of fluid in the macular area with or without lipid/exudate
    2. Retinal thickening within 2 DD of the center of the macula
    3. Can occur at any stage of NPDR or PDR, most common cause of decreased vision in DR

ii. Classification- center involved vs non center involved
    1. Center involved DME defined as thickening within the central subfield zone (1mm diameter)
iii. **Management of DME**
    1. Standard of care recommendations
        a. Who should be treated?
            i. CI-DME with VA 20/32 or worse- referral within 2-4 weeks (AOA-CPG 2019)
        b. Who can usually be observed?
            i. CI-DME with VA 20/25 or better – may defer treatment until VA is 20/30 or worse (DRCR.net Protocol V)
                1. Re-examine every 2-4 months
            ii. NCI-DME with VA 20/25 or better
    2. Clinical considerations/practical approach
        a. Consider referral for early treatment (usually anti-VEGF agent) if DR stage is severe NPDR or worse, planning PRP, planning cataract extraction systemic risk factors exist (HTN, renal failure, pregnancy), patient is uncompliant
        b. Additional benefits of anti-VEGF include lower risk of vitreous hemorrhage/PDR development and DR stage improvement
        c. Anti-VEGF therapy is beneficial alone or as an adjunct to PRP when CI-DME + PDR are present
            i. When PRP also needs to be performed usually combo with anti-VEGF since DME is exacerbated by PRP
        d. Avoid anti-VEGF agents or use caution if vitreoretinal traction/TRD is present
    4. Role of OCT & OCTA in diagnosis/management
        a. Identification of subclinical DME
        b. Aids in the classification of DME as center involved vs non-center involved
        c. Monitor response to treatment /determine when retreatment is necessary
        d. OCTA allows for detailed evaluation of the foveal avascular zone (detection of concurrent macular ischemia)
            i. Significant macular ischemia = guarded prognosis following treatment of DME
        e. OCTA may aid in identifying sources of DME such as MAs or IRMA

5. Management updates:

i. Newly approved extended duration anti-VEGF agents: faricimab Jan 2022 & high dose aflibercept Aug 2023
ii. Oral fenofibrate
iii. Nutritional supplementation and medical foods for DR
iv. Autonomous artificial intelligence screening systems for diabetic retinopathy

References

Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020.

(AAO PPP) American Academy of Ophthalmology Preferred Practice Patterns Retina/Vitreous Panel, Hoskins Center for Quality Eye Care. Diabetic Retinopathy PPP – Updated 2024. Available at: https://www.aao.org/preferred-practice-pattern/diabetic-retinopathy-ppp

(AOA CPG) AOA Evidence-Based Optometry Guideline Development Group. Eye Care of the Patient with Diabetes Mea.org/optometrists/tools-and-resources/evidence-based-optometry/evidence-based-clinical-practice-guidlines/cpg-3--eye-care-of-the-patient-with-diabetes-mellitus, Second Edition; Evidence-based Clinical Practice Guideline. Updated 2019.

Teo ZL, et al. Global Prevalence of DR and Projection of Burden through 2045: Systematic Review and Meta-analysis. Ophthalmology 2021.

Los Angeles Latino Eye Study Group. Severity of DR and health-related QOL. Ophthalmology. 2011

Piyasena MMPN, et al. Systematic review on barriers and enablers for access to DR screening services in different income settings. PLoS One. 2019;14(4):e0198979.

The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. Ophthalmology. 1981 Jul;88(7):583-600.

Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985 Dec;103(12):1796-806.

The Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report no. 4. Int Ophthalmol Clin 1987 Winter;27(4):265-72.

Bressler SB, Liu D, Glassman AR, et al. Change in Diabetic Retinopathy Through 2 Years: Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab. JAMA Ophthalmol. 2017 Jun 1;135(6):558-568.

Wells JA, Glassman AR, Ayala AR et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016 Jun;123(6):1351-9.

Baker CW, Glassman AR, Beaulieu WT, et al. Effect of Initial Management With Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss Among Patients With Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity: A Randomized Clinical Trial. JAMA. 2019 May 21;321(19):1880-1894.

Stewart S, Lois N. Fenofibrate for Diabetic Retinopathy. Asia Pac J Ophthalmol (Phila). 2018 Nov-Dec;7(6):422-426.

Chous AP, Richer SP, Gerson JD, Kowluru RA. The Diabetes Visual Function Supplement Study (DiVFuSS). Br J Ophthalmol. 2016 Feb;100(2):227-34.

Wong TY, Simó R, Mitchell P. Fenofibrate - a potential systemic treatment for diabetic retinopathy? Am J Ophthalmol. 2012 Jul;154(1):6-12.

Shi C, Wang P, Airen S, et al. Nutritional and medical food therapies for diabetic retinopathy. Eye Vis (Lond). 2020;7:33.

Wang J, et al. Improving DM and hypertensive retinopathy with a medical food containing L-methylfolate: a preliminary report. Eye Vis (Lond) 2019;6:21.

Witkin AJ, et al. Occlusive Retinal Vasculitis Following Intravitreal Brolucizumab. J Vitreoretin Dis. 2020.

Maturi, R. , et al. Effect of Intravitreous Anti–VEGF vs Sham Treatment for Prevention of Vision-Threatening Complications of DR. JAMA Ophthalmology, 139 (7), 701-712.

Brown DM, Wykoff CC, Boyer D, et al. Evaluation of Intravitreal Aflibercept for the Treatment of Severe NPDR: Results From the PANORAMA Randomized Clinical Trial. JAMA Ophthalmol. 2021;139(9):946–955

Silva PS, et al. UWF Peripheral Lesions Predict DR Progression. Ophthalmology 2015.

Maturi RK, et al. 4-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreous Aflibercept for Prevention of Vision-Threatening Complications of DR. JAMA Ophthalmology 2023.