Updates in Diabetic Retinopathy & Venous Occlusive Disease

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Personal Introduction:

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Course Introduction: This course primarily reviews the updates in diabetic retinopathy and venous occlusive diseases. We will discuss the common complications of these two retinal diseases based upon clinical findings and diagnostic testing. Appropriate management options are highlighted with an emphasis on knowledge gained from recent relevant clinical trials.

- Global impact of diabetes
  - 347 million worldwide with diabetes
  - 25.8 million with diabetes (8.3%)
  - 183 million persons with diabetes are undiagnosed
  - 15 years after diagnosis of diabetes, approximately 2% become blind and 10% develop severe visual impairment
  - Incidence of diabetic retinopathy is approximately 5-10% per year

- Risk factors for diabetic retinopathy
  - Hyperglycemia
  - Hypertension
  - Hypercholesterolemia
  - Obesity
  - Duration of diabetes
  - Pregnancy
  - Puberty
  - Ethnicity
  - Heritability of diabetic retinopathy

- Prevalence of retinal vein occlusions (RVO)
  - Branch retinal vein occlusion (BRVO)
    - 13.9 million adults with BRVO worldwide
    - 0.9% BRVO in US
  - Central retinal vein occlusion (CRVO)
- 2.5 million adults with CRVO worldwide
- 0.2% CRVO in US

Diagnosis of diabetes and threshold for diabetes in relation to diabetic retinopathy risk

- Symptoms of diabetes plus random plasma glucose >= 200 mg/dl
- Fasting plasma glucose >=126 mg/dl
- 2 hour plasma glucose >=200 mg/dl during an oral glucose tolerance test (OGTT)
- HbA1c >=6.5%
- Preference is to repeat positive diagnostic test; however two different diagnostic tests above threshold confirms diagnosis
- All adults of any age who are overweight (BMI >=25 kg/m² with one or more additional risk factors (inactive, family history, high risk race/ethnicity, hypertensive, low HDL cholesterol, cardiovascular disease) should be screened.
- In no risk factors, initiate screening at age 45 years.

Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22

- Elevated levels doubled the risk of retinal hard exudate at baseline
- 50% increased risk of developing hard exudate during follow up
- 50% increased risk of moderate vision loss at 5 years
- Conclusion: lipid lowering may also decrease the risk of hard exudate formation and associated vision loss in patients with diabetic retinopathy.

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye study Results

- Intensive glycemia and combination of fenofibrate and simvastatin reduced the proportion whose retinopathy progressed by about one-third
- No statistically significant effect of intensive blood pressure

Finofibrate Intervention and Event Lowering in Diabetes (FIELD) Study

- Laser photocoagulation was reduced in the Fenofibrate treated group with high risk diabetic retinopathy
- Conclusion: Fenofibrate use reduced diabetic retinopathy progression.
- Finofibrate activities:
  - Lipid related mechanism
  - Anti-apoptosis
  - Anti-oxidative and anti-inflammatory
  - Anti-angiogenic
Classical classification of diabetic retinopathy: Why Clinically Significant Macular Edema (CSME) is on its way out?

- CSME phrase originated in 1980’s
- Pre-OCT, based on clinical exam or stereo photos, expert skills and subjective
- Defined as edema in the center of the macula or threatening the center
- OCT thickness is now used to manage, monitor response to treatment
- Personal preference!!

Why background diabetic retinopathy is no longer used?

- This term is not as informative as more modern terminology.
- Risk of PDR increases with level of non-proliferative diabetic retinopathy.
  - Mild NPDR: 5% by 1 year, 15% high risk by 5 years.
  - Moderate NPDR: 27% by 1 year, 33% high risk by 5 years.
  - Severe NPDR: 52% by 1 year, 60% high risk by 5 years.

Treatments for diabetic macular edema

- Clinical Trials of anti-VEGF
  - Several recent studies offered insight into the use of anti-VEGF agents.
  - The READ, RISE, and RIDE trials involved the use of ranibizumab in patients with DME.
  - The DA VINCI trial demonstrated the effect of aflibercept therapy in DME patients.
  - The 2-year results of the CATT trial compared use of bevacizumab with ranibizumab therapy in AMD patients.

- Diabetic Retinopathy Clinical Research Network (DRCR)
  - In the DRCR protocol I, investigators compared sham therapy plus prompt focal laser treatment with:
    - Ranibizumab plus prompt laser therapy
    - Ranibizumab plus deferred laser treatment
    - Triamcinolone plus prompt laser therapy
  - Two-year follow-up data recently showed improved visual acuity and central foveal thickness in both ranibizumab groups as compared with those receiving sham plus laser therapy or triamcinolone plus laser therapy.
• **Aflibercept (VEGF-TRAP): Eylea**
  
  o **EYLEA** is a recombinant fusion protein, that acts as a soluble decoy receptor binding to VEGF-A and placental growth factor (PIGF).
  o Inhibits the binding and activation of VEGF receptors.
  o Intravitreal aflibercept injection is a soluble decoy receptor fusion protein that is specifically purified and formulated for intraocular injection.
  o The binding affinity of intravitreal aflibercept to VEGF is substantially greater than that of bevacizumab or ranibizumab.
  o The greater affinity could translate into a higher efficacy or, as a substantially longer duration of action in the eye, allowing for less frequent dosing, as supported by early clinical trials.
  o Indicated for the treatment of patients with neovascular AMD.
  o Indicated for the treatment of patients with Macular Edema following central retinal vein occlusion.
  o Contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in Eylea.
  o DA VINCI study and diabetic macular edema

  o Results from the DA VINCI trial demonstrated improvement in the eyes of patients with DME who used aflibercept as compared with patients who underwent focal laser therapy.

  ➢ **Corticosteroids for diabetic macular edema**

  • Corticosteroid therapy continues to be an option for patients with DME.

    o In patients with DME, Flucinolone Acetonide vitreous inserts provide benefit for at least 3 years.

    • However, it tends to be used now in individuals who do not respond to anti-VEGF treatment.

    • Increased intraocular pressure and cataracts continue to be the main adverse effects related to the use of corticosteroids.

  ➢ **PRP versus PRP plus intravitreal ranibizumab for high-risk proliferative diabetic retinopathy?**

    • Effects of PRP vs. PRP + ranibizumab in high risk-PDR in eyes with no prior PRP
    • Randomized to PRP vs. PRP + ranibizumab
    • 29/40 eyes, 48-week follow up
• Larger reduction in fluorescein leakage, PRP + ranibizumab group with less VA loss and DME

➢ Impact of intravitreal corticosteroids on worsening or improvement of diabetic retinopathy

• Corticosteroid therapy continues to be an option for patients with DME.
• However, it tends to be used now in individuals who do not respond to anti-VEGF treatment.
• Increased intraocular pressure and cataracts continue to be the main adverse effects related to the use of corticosteroids.

➢ Is medical workup indicated for venous occlusive disease?

• Population-based epidemiologic studies are underpowered because of low prevalence and incidence of disease.
• Cardiovascular risk profile is a strong predictor.
  o Hypertension and diabetes increase risk for central vein occlusion.
• All patients with or without retinal venous occlusion should receive general health assessment.
• For young patients without know risk factors, medical consultation with testing for serum homocysteine level and antiphospholipid antibody titers may be reasonable.
• For patients with bilateral simultaneous central retinal vein occlusion, extensive medical and homological evaluation is indicated.

➢ Anti-VEGF or corticosteroids for macular edema from retinal vein occlusion

• Prophylactic PRP to prevent neovascularization inappropriate; therapeutic PRP once neovascularization develops very effective.
• Anti-VEGF drugs being used successfully off label.
• Laser photocoagulation of macular edema not beneficial in cases of CRVO and hence not done.
• Newest treatment: intravitreal injection of steroids and anti-VEGF drugs for macular edema. Stabilizes vascular membranes and reduces vascular permeability.