Diabetic Macular Edema: Current Concepts and Future Therapies

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Overview

- Impact
- Classification
- Pathogenesis
- Treatment
- New potential treatments
Prevalence of DM – the epidemic

- 8.3% of population - 25.8 million people
- 65 years and older - 26.9% have diabetes
- 2020 – 20% of population

*American Diabetes Association, 2010*
Prevalence of DM – the epidemic

- About 1.9 million people ages 20 years or older were newly diagnosed with diabetes in 2010 in the United States.
- Based on hemoglobin A1C (A1C) levels:
  - 35% of adults 20 years or older had pre-diabetes
  - 50% of adults ages 65 years or older are prediabetic
- Prevalence expected to increase by 165% by the year 2050!!!
The problem

- Leading cause of blindness < 65 yrs old
- 30% of those with DM have retinopathy
- 4% with DM have severe visual loss
Population

- African Americans 1.8 times more likely to have DM
- 1:4 over 55 is diabetic
- PDR is 50% more common
- Hispanics 2.5 times more likely to have DM
Pathogenesis

- Diabetes is a disease of small blood vessel damage
- Thickening of BM in vessels
- Loss of pericytes
- Increased permeability of vessels
- Vessel closure
Pericytes

- Elevated blood sugars damage pericytes
- Blood vessels become permeable
- Damage to organs
Hemoglobin A1C

- Chemically modified Hb resulting from high blood glucose levels
- Correlates with blood glucose level over past 3 months
- Correlates with risk of complications
Diabetes Control and Complications Trial
Tight vs Conventional control
Tight control decreased risk of developing retinopathy by 76% and reduced risk of progression of retinopathy by 54%
47% reduction in risk of 3 lines of vision loss at 7.5 yrs with tight control
Hemoglobin A1C

- Reducing HbA1C from 9 to 8 lowers the risk of diabetes related death by 25%, and risk of blindness by 35%

- Rapid change, even rapid improvement, can be associated with worsening of eye findings
Non proliferative DM
Proliferative DM
Rapid Progression of PDR

9/08

6/09
Total RD with LP VA
Slower vision loss with CSDME
Diabetic Macular Edema

Disease State Overview
Diabetic Macular Edema (DME)

- Main cause of mild to moderate vision loss in Diabetic Retinopathy (DR)
  - Will develop in 14% of diabetics over 10 years
  - Incidence of DME increases with increasing DR severity
    - 3% in mild nonproliferative
    - 38% in moderate/severe nonproliferative
    - 71% in proliferative
- 50% of DME patients will lose $\geq 2$ lines of visual acuity within 2 years

Diabetic Macular Edema (DME)

- Characterized by an abnormal collection of extravascular fluid in the macula
- Clinically significant macular edema (CSME) is defined by any of the following:
  - Thickening of the retina at or within 500 microns of the center of the macula
  - Hard exudates at or within 500 microns of the macula center, with thickening of adjacent retina
  - Any retinal thickening, $\geq 1$ disc area in size; within 1 disc diameter of macula center

Focal Macular Edema

- A single or localized cluster of leakage sites
- Hard exudates common

Diffuse Macular Edema

- Generalized breakdown of blood-retinal barrier with leakage from blood vessels throughout the posterior pole of the eye
- Hard exudates less common
Why does this happen?
Diabetes is a disease of small blood vessels
Pathophysiology of DME

- Blood-retinal barrier breakdown with increased vascular permeability in retinal vessels
  - Loss of pericytes surrounding capillaries, leading to capillary wall weakness
  - Development of microaneurysms
  - Endothelial basement membrane thickening leading to focal closure of some capillaries; increased blood flow in other vessels
  - Prostaglandins, interleukin (IL-1), vascular endothelial growth factor (VEGF), and other inflammatory mediators are involved in key steps of this process

Pericytes
Pathophysiology of DME

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Vessel damage/leakage and closure
Ischemia

- Drives production of VEGF
- Makes VEGF
- Stimulates more abnormal vessel formation
Pathophysiology of DME

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Pathophysiology of DME

Primary inflammatory disease

Retinal hypoxia-ischemia

Inflammatory mediators

- Leukocyte invasion-activation
- Increase permeability factors
  - VEGF
  - IL-1
  - TNF-Alpha
  - Prostaglandins
- Increase blood flow

Macular Edema

Healthy vessel

VEGF Receptor Activation

VEGF Receptor Signaling

- Leukocyte / EC adhesion
- Vascular permeability
- Increase blood flow
CSDME

20/40

6 month later

20/200
Factors That Increase the Risk of DR and DME

- Extent of control over diabetes and coexisting conditions affects the risk of DR and DME
  - Blood sugar
    - Maintaining near normal levels can reduce risk of clinically significant DME by 23%
  - Hypertension
    - Increases risk of DME by 3- to 5-fold
  - Hyperlipidemia
    - Correlates with greater severity of retinal hard exudates
  - Renal disease
    - Proteinuria associated with 3- to 5-fold increase in risk of DME

Studies

- UKPDS
  - BS control for DM II decreases DR

- DCCT
  - BS control for DM I decreases DR
Glycemic Control

- DCCT – Diabetes Control and Complications Trial
  - Intensive control - reduced risk by 23% compared to conventional control
  - Long term – 58% reduction in DME development
DME

- Can occur even if BS well controlled
- 29% of patients with DM 20 years or longer

- For the past 30 years – laser and glycemic control
- Patients experience vision loss
Treatment options

- Glycemic control
- Laser
- Pharmacologic agents
- Vitrectomy
Medical Management

- Hemoglobin A1C most important
- Blood pressure
- Lipid, cholesterol
- Cigarette Smoking
- Renal Status
  - Dialysis is effective
- Sleep apnea
Focal/Grid Laser

- ETDRS
  - Laser reduced risk of 2 line loss by 50% - 3 years after initial treatment
  - One line gain in 16%
- Standard of care
- Slows progression
- Damage to retina
- Does not improve VA
- Lower VEGF levels

ETDRS

- Thickening of the retina within 500 μm of the fovea
- Hard exudates within 500 μm of the fovea associated with thickening
- Retinal thickening that is 1DD or larger within 1 DD of the fovea

- ETDRS – do focal laser
Classic Findings of DME
FA guided focal laser
- 56 year old woman with 15 year history of DM
- Hb A1C 8.0
Laser performed

20/40

20/25
What if laser doesn’t work??
What can we do to treat diffuse DME (other than laser)?????
Pharmacologic Agents

- Subtenon Kenalog
- Intraviteal Kenalog
- Anti-VEGF agents
  - Avastin
  - Lucentis
Steroid mechanism of action
Pathophysiology of Macular Edema and Corticosteroid-based Therapies

- Vascular Disease
  - Diabetes
  - CRVO

- Healthy Retinal Microvessel

- Primary Inflammatory Disease
  - Uveitis

- Inflammatory Mediators
  - IL-1
  - TNF-

- VEGF

- Corticosteroids

- Vasodilation
- Leukostasis

- Diapedesis
- Permeability

- Inflammatory proteins

- Macular Edema
Steroids

- Inhibit the expression of VEGF through downregulating PDGF and PAF
- Stabilize cell membranes
- Reduce macular edema
- Reduce inflammation

Administration
- Systemically
- Periocular
- Intravitreal
Periocular Triamcinolone

- Supporting evidence
  - Few small studies – reduced edema

- Opposing evidence for monotherapy
  - DRCR.net
  - Retreatment rates:
    - 64-71% steroids alone
    - 58% laser alone
    - 38-43% laser + steroids
Periocular Triamcinolone

- Theoretical Advantages
  - Low risk IOP elevation
  - Few complications
    - Ptosis
    - Orbital fat prolapse
    - Elevated IOP
Intravitreal Steroids

- Triamcinolone acetonide
  - Depot steroid
  - Effect for 3-6 months
  - Side effects
    - Glaucoma
    - Cataract
    - Endophthalmitis
    - Psuedoendophthalmitis
Laser vs IV Triamcinolone

- Randomized Trial DRCR.net
  - Laser vs 1mg IVTA vs 4mg IVTA
  - Compare vision & mac thickness (OCT)
  - 4 months – IVTA better
  - 1 yr – laser better
  - 2 year – laser better

- Conclusion - laser better long term
- Combo treatment not evaluated
Intravitreal Triamcinolone

- Short term gain, but.....
  - Cataract – 33% vs 4% in 2 years
  - Glaucoma – 51% vs 14% in 2 years
  - Endophthalmitis –0% in 2 years
    - Historically 0.1% and 0.6% pseudoendophthalmitis

Retina, 2008 Jan;28:66-70
Role on IVTA

- Severe diffuse DME refractory to laser
- An adjunct, not an alternative to laser
Intravitreal anti-VEGF agents

- Bevacizumab (Avastin) and Ranibizumab (Lucentis)
Ranibizumab (Lucentis™)
Bevacizumab (Avastin®)

Anti-VEGF-A Murine Mab (~150 kDa)

Humanization

Insertion of murine anti-VEGF-A sequences into a human FAb framework

rhu Fab V1

Affinity maturation (140x)

Insertion of murine anti-VEGF-A sequences into a full-length human IgG framework

Humanization

Lucentis (ranibizumab) (48 kDa)

Avastin (bevacizumab) (149 kDa)

VEGF in Diabetic Retinopathy

- Retinal VEGF levels elevated in experimental diabetes
- Increased VEGF levels found in vitreous of eyes with proliferative DR
- DR patients have higher VEGF levels in the aqueous

Qaum et al, IOVS 2001; Adamis et al, AJO 1994; Aiello et al, NEJM 1994
Anti-VEGF

- Rapid onset to reduce macular edema
- Temporary fix
- May improve response of laser alone
Avastin for DME

- Targets all isoforms of VEGF
- Reduces vascular permeability
- Avastin alone (monthly injections)
  - 6 months - 55% of patients with normalization of OCT
  - No glaucoma, cataract formation
Lucentis and DME READ2

- Lucentis injections result in significantly better visual outcomes than focal/grid laser in diabetic macular edema (DME) at 6 months

- ETDRS has shown that focal/grid laser reduces the risk for moderate visual loss in eyes with DME
  - 22% improved 3 or more lines- laser 0%
  - 46% improved 2 or more lines- 5%

- Long term results with IVK show laser is better long term
Patient 1
67 year old woman
40 year history of DM

Monocular OD
Phthisis OS-TRD

Current VA 20/80
Avastin injected

20/80

20/40
Maintain 20/40 VA with q3month Avastin injections
Patient 2
66 year old man
30 year history of DM

Previous dense laser OU
OD- ischemia HM VA
OS- 20/60

Pale optic nerve - GS
Maintain 20/40 with q2-3 monthly injection of Avastin
Avastin for DME

- Patients with dense laser
- Residual DME
- Diffuse DME
- Use if not a candidate for steroid injection
Lucentis for DME

- Clinical Trials – RESTORE, READ, RISE
- Rapid decrease in macular edema
  - “Better” than laser at 6 months (faster)
  - Monthly injections for 2 years
  - Lucentis recommended for central edema

- Fluid often returns within 9 months

- Improved long-term outcomes with combination therapy?
Why is pharmacologic therapy alone, not as effective as laser?

- **DME** – result of damaged, leaking blood vessels
- **Laser** – seals blood vessels and permanently treats areas of damaged retina which produces VEGF
- **Avastin/Lucentis/Steroids** - reduce VEGF transiently, doesn’t address the source of VEGF
Surgical Treatment
Surgical Treatment for DME

- Studied support surgery for:
  - Taut posterior hyaloid
  - Diffuse DME
  - DME and ERM
  - Non responsive to laser, IVTA, Avastin

- Decreased macular thickness, but VA unchanged
DME and VMT
Pars Plana Vitrectomy

Vitreous

Vitrector

Light pipe

Floaters / debris
If DME is resistant to Laser and Pharmacologic agents =

Look for VMT!
DME Treatments

Current Treatments

- Laser (still first-line treatment)
- Pharmacologic therapy (Steroids and Anti-VEGF agents)
- Vitrectomy Surgery
Treatment of DME

- Optimize medical care
- Laser is primary treatment
- Add pharmacotherapeutic agents
- Surgery if needed
Therapies Under Investigation...
Implantable Devices

- Sustained steroid release
Ozurdex
After 180 days
- Ozurdex - 32.4% gained 2 or more lines
- Control - 21%
- Ozurdex - 18.1% gained 3 or more lines
- Control - 7.6%
Available, expensive
Retisert

- Reduces DME but,
  - more than 90% of patients receiving a Retisert implant require cataract surgery
  - 40% of patients require glaucoma surgery within 3 years.\textsuperscript{29}
Small molecule targets of VEGF

- **VEGF Trap (Regeneron)** - The VEGF Trap-Eye is a fully human, soluble VEGF receptor fusion protein that binds all forms of VEGF-A
  - DAVINCI trial
    - Monthly injections and prn dosing vs laser
    - At week 24 – approximate 10 letter gain compared to 2.5 letters with laser
THANK YOU!