Epidemiology and Pathophysiology of Diabetic Retinopathy

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Epidemiology and Pathophysiology of Diabetic Retinopathy

- Overview
  - Costs to society
  - Epidemiology of diabetes mellitus
  - Prevalence of diabetic retinopathy, macular edema & proliferative retinopathy
  - Pertinent DR Studies
  - Pathophysiology of diabetic retinopathy
Managing Diabetic Eye Diseases

Prevalence Continues to Increase

- Prevalence of DM in Medicare population increased from 14.5% in 1991 to 25.6% in 19991
- Diabetic retinopathy (DR) among persons with DM increased from 6.9% to 17.4%1
- 25 years after diagnosis of DM, DR occurs in 97% of patients2,3
- 20+ years after diagnosis of DM, diabetic macular edema (DME) occurs in almost 30% of patients2,3
- Burden of DR on the eye care system continues to increase
- Receiving recommended levels of care substantially reduced low vision/blindness in patients with diabetes4

Managing Diabetic Eye Diseases

Diabetes Mellitus (DM) in 2012

- 29.1 million people (9.3% of the population) have diabetes
- 8.1 million (1 in 4) individuals with DM were undiagnosed
- For those diagnosed with diabetes, medical management is the first line of defense
- Most cases of blindness due to diabetes are preventable

Cost to Society (2002 data)

- 4.2% U.S. population had diabetes
  - 2012 up to 9.3%
- 11% U.S. health care expenditures on diabetes
- $90 billion
  - $176 billion direct cost 2012
  - $67 billion indirect cost 2012
- Per capita annual expenditure
  - $13,000 for person w/ diabetes
  - $5,600 per person w/o diabetes (age adjusted)
- 70% of expenditures for rx of metabolic condition
- 30% of expenditures for rx of chronic complications
## Epidemiology of Diabetes Mellitus Diagnosed

<table>
<thead>
<tr>
<th></th>
<th>2002 (Actual)</th>
<th>2012 (Actual)</th>
<th>2020 (Projected)</th>
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<tbody>
<tr>
<td><strong>Total Population</strong></td>
<td>288</td>
<td>313</td>
<td>335</td>
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<tr>
<td>(millions)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Diagnosed</strong></td>
<td>12.1</td>
<td>21</td>
<td>25</td>
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<tr>
<td>with DM (millions)</td>
<td></td>
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<tr>
<td><strong>Prevalence Rate</strong></td>
<td>4.2%</td>
<td>6.7%</td>
<td>7.4%</td>
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Epidemiology of Diabetes Mellitus

- Leading cause of new cases of legal blindness among working-age patients in US
- Blinds another person every 20 minutes
- 30 million in US with DM or impaired glucose tolerance
  - 33% not aware of diagnosis
  - 4.9 million with retinopathy
  - 990,000 with sight threatening retinal disease
  - Incidence is increasing

Epidemiology of Diabetic Retinopathy

- Prevalence of retinopathy
  - 10 years DM duration: 7%
  - 25 years DM duration: 90-95%
- Retinopathy can accelerate during:
  - Puberty
  - Pregnancy
Prevalence of any macular edema

- 5 yrs DM duration: 5%
- 15 yrs DM duration: 15%
- 20+ yrs DM Duration: 30%
Prevalence of proliferative retinopathy

- Type I DM
  - 15 years duration: 50%

- Type II DM:
  - Receiving insulin:
    - 15 years duration: 15 - 20%
  - Not receiving insulin:
    - 15 years duration: 5 - 10%

DR Studies

- Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR)
- Diabetes Control and Complication Trial (DCCT)
- United Kingdom Prospective Diabetes Study (UKPDS)
- The United Kingdom Prospective Diabetes Study-Hypertension In Diabetes Study (UKPDS-HDS)
- Early Treatment Diabetic Retinopathy Study (ETDRS)
- Diabetic Retinopathy Study (DRS)
- Diabetic Retinopathy Vitrectomy Study (DRVS)
- DRCR Protocol I
Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR)

- **Study Design**
  - Population-based study
  - 11 county area of southern Wisconsin
  - Participants recruited between 1979-1980:
    - 1210 with Type 1 DM
    - 1780 with Type 2 DM
  - Underwent clinical exam, 7-field photos
  - Followed 10–14 years
Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR)

- Prevalence of retinopathy by disease duration
DCCT Trial Type 1 DM

- **Study Question:** will intensive BS control prevent or reduce retinopathy progression in Type 1 DM?
- **Participants**
  - 726 patients with Type 1 DM (1-5 year duration) and no DR
  - 715 patients with Type 1 DM (1-5yrs) and mild-to-mod NPDR
- **Design:**
  - Randomized to conventional vs. intensive (multiple injections or pump)
- **Outcome variables:**
  - Development of retinopathy, or 3-step progression
  - Neuropathy
  - Nephropathy, C-V outcomes
DCCT Results

- Effective randomization: conventional (A1c=9) vs. intensive (A1c=7) glucose control
- Intensive control:
  - Reduced risk of development of DR by 76%
  - Slowed progression of DR by 54%
  - Decreased risk of neuropathy by 60%
  - Decreased albuminuria by 54%
Risk Factors associated with DR

- Longer duration of diabetes
- Poorer glycemic control
- Higher blood pressure
- Presence of diabetic nephropathy
- Higher lipid levels
- Smoking
Pathogenesis

- Exact role of hyperglycemia is unknown
- Microvascular disease ("arterioles & capillaries")
- Pericytes
  - Increased apoptosis early in disease possibly due to accumulation of toxic products such as sorbitol or advanced glycation end products (AGEs)
  - Loss leads to weakening of capillary walls and microaneurysm formation
  - Necessary for proper endothelial cell function so loss can lead to capillary leakage/retinal edema
- Basement membrane thickening also present
  - May lead to capillary occlusion
  - Progressive capillary occlusion leads to ischemia
    - VEGF production → neovascularization → fibrous proliferation → traction → vitreous hemorrhage or retinal detachment
Pathogenesis
NonProliferative Diabetic retinopathy

- Mild retinal capillary damage
  - Outpouchings → microaneurysms
  - Leaky capillaries → swelling, serum lipid exudation
  - Very leaky capillaries → frank bleeding

- Severe retinal capillary damage
  - Capillary occlusion → non-perfusion
    - NFL infarcts (cotton wool spots)
  - Remodeling → intraretinal micro-vascular abnormalities
  - Vascular flow shunting → venous beading
Pathogenesis of PDR

- Inflammation / pericyte loss / basement membrane thickening
- Trauma to the vascular endothelium and capillary wall
- Ischemia (capillary non-perfusion)
- Stimulation of vasogenic process
  - VEGF
  - bFGF
  - PEDF
  - Others
**Pathogenesis PDR**

- Development of new blood vessels
  - In response to ischemia and VEGF
  - Usually near/at border of ischemic areas
  - Usually leaky and fragile → bleed easily
  - Frequently have adherent vitreous
  - Frequently incite fibrocyte proliferation → additional traction → retinal detachment
Diabetic Retinopathy Pathological Mechanisms--Role of VEGF

- In advanced retinopathy, capillary dropout results in relative hypoxia
- Hypoxia stimulates production of vascular endothelial growth factor (VEGF)
- VEGF stimulates growth of new vessels and is implicated in the pathogenesis of PDR
- Intravitreal VEGF levels are high in PDR and are lowered by PRP
Causes of Vision Loss in DR

- **Macular Ischemia**
  - Diagnosed by loss of capillaries on fluorescein angiography

- **Clinically Significant Macular Edema (CSME)**
  - Thickening of the retina at or within 500 µm of the foveal center
  - Lipid within 500 µm of the foveal center with adjacent retinal thickening
  - Large area of retina thickening greater than 1 disk diameter in size within 1 dd of the foveal center

- **Sequelae of Neovascularization**
  - Traction or combined traction/rhegmatogenous retinal detachment
  - Vitreous hemorrhage
Pathophysiology of Diabetic Retinopathy

- Genetic
- Environmental
- Immunological
  - HLA-DR phenotypes 4/0, 3/0, and neither 3 nor 4 all with higher risk of PDR
- Long term hyperglycemia
  - Most important factor at present

Pathophysiology of Diabetic Retinopathy

- Capillary pericyte loss
- Endothelial cell loss
- Nonfunctional acellular capillaries
- Capillary basement membrane thickening
- Microaneurysm formation
- Neovascularization

Pathophysiology of Diabetic Retinopathy

- Capillary pericytes:
  - Pericytes are contractile cells
  - Cultured pericytes stain for smooth muscle actin
  - Regulate flow through capillaries

Pathophysiology of Diabetic Retinopathy

- Loss of pericytes:
  - May alter retinal blood flow

*Pt without diabetes, normal pericytes (P)*

*Ghost pericytes Pt with BDR, degenerated (G)*

Pathophysiology of Diabetic Retinopathy

- Capillary basement membrane:
  - Thickening
  - Vacuolization
  - Fibrillar collagen deposition
- Type III collagen normally not found in vivo

Pathophysiology of Diabetic Retinopathy

● **Microaneurysms**
  – Earliest clinically observable lesion of diabetic retinopathy
  – Can be hypercellular or acellular
  – May form due to pericyte loss
    ● Reduction in ant proliferative effect
    ● Weakness in capillary wall

*Frank RN: Etiologic mechanisms in diabetic retinopathy. In Ryan SJ, ed: Retina, Schachat AP and Murphy RP, eds vol. 2 Medical Retina, St. Louis, 1994, Mosby, p. 1261-1262*
Pathophysiology of Diabetic Retinopathy

- Etiology of blood-retinal barrier breakdown:
  - Opening of tight junctions (zonule occludentes) between adjacent endothelial cell processes
  - Fenestration of the endothelial cell cytoplasm
  - The basal surface of RPE cells develop infoldings of its plasma membrane
  - Increase in endocytic vesicle transport

Frank RN: Etiologic mechanisms in diabetic retinopathy. In Ryan SJ, ed: Retina, Schachat AP and Murphy RP, eds, Medical Retina, St. Louis, 1994, Mosby, p. 1263
Diabetic Retinopathy
Summary

- Diabetic retinopathy is an important and rising cause of blindness in the U.S. and western world
- Knowledge of the risk factors for disease are important in counseling patients and in devising therapeutic approaches
- Accurate diagnosis and staging of disease are crucial for identifying intervention points
- Screening at appropriate intervals is critical
- Systemic management of diabetes and prevention of retinopathy will likely remain the most effective approach for reducing diabetic blindness in the future
Summary

- Diabetic retinopathy remains a significant cause of blindness in the US, especially among those between 20 - 64 years of age.
- Hyperglycemia appears to be the major etiologic factor in the development of diabetic retinopathy and its complications.
- Hypoxia, oxidative stress and VEGF and VEGFR2 appear to play major roles in the progression of diabetic retinopathy.
- As the severity of diabetic retinopathy increases, the risk of progression to high-risk PDR increases.