DIABETIC RETINOPATHY
Didactic lecture in Hotel Krishna main hall by Dr. H. S. Ray M.S., Ophthalmology, FRF (Ahmedabad) - Drishti Eye Hospital, Madan Mahal Main Road, Jabalpur 2.
Session Sponsor:_________

TYPES OF DIABETES MELLITUS
- TYPE -I or IDDM
  - 10% of Diabetics
  - Insulinopenia due to Beta Cell failure
  - Abrupt in Onset & Prone to Ketosis
  - Diagnosed before 40 Years, Majority in Childhood
- TYPE -II or NIDDM
  - Slow Onset & Progression
  - Serum level of Insulin varies- Normal, Above & Low
  - Displays Tissue Resistance to Insulin (Abnormal Insulin)
  - Usually occurs above 40 years (M:F Ratio 2:3)

DIAGNOSIS
Symptoms
- Polyuria,
- Polyphagia,
- Rapid Weight Loss.
Lab findings
- Elevated Plasma Glucose Level:
  * Fasting Plasma Glucose >/= 140mg/dl
  * Post Prandial Plasma Glucose (GTG) >/= 200mg/dl

PATHOGENESIS OF DIABETIC RETINOPATHY
- Hypoxia - Low 2,3 DPG, & High HbA -Lower tissue Oxygen
- Intracellular Sorbitol & Fructose
- Release of Growth hormone, Fibrinogen & Alpha 2 Globulin
- Hyperaggragation of RBCs & Platelets- Sludging of blood flow
- Prostaglandins cause Vascular Insult
- Prostacyclin (PGI 2)
- Thromboxane (TXA 2)
- Leukotrienes inhibits PGI 2 & promotes TXA 2
- Disparity between PGI 2 & TXA 2 plays a role in Diabetic Microangiopathy.

PATHOGENESIS OF POLIFERATIVE DIABETIC RETINOPATHY
- Angiogenic Factors (Peptides)
  - bFGF ( basic Fibroblast Growth Factor)
  - IGF ( Insulin Growth Factor)
  - VEGF ( Vascular Endothelial Growth Factor)
- Role of PVD
- Mechanical effect for developing Proliferative Tissue
- Complete PVD occurs due to Aging
- Partial PVD is more common in Diabetics with PDR
- Scaffolding for Fibro-Vascular Proliferation
- Vitreo-Retinal Traction - TRD
- Precocious PVD before PDR prevents TRD

Anatomic Lesions & Pathogenesis of DR
Microscopic Level Changes
- Capillary Basement membrane thickening, Increases in thickness to 5 Times from 0.5
- Loss of Intramural Pericyte (Pericytes:Endo.Cells= 1:1)
- Capillary Acellularity
- Macroneurysms
- Impairment of Autoregulation

EPIDEMIOLOGY
- Type-1, Males are at higher risk of developing PDR than Maculopathy
- Maculopathy is more common in Type-2
- Retinopathy is a consequence of long term sustained Hyperglycemia, but often modified by Genetics & acquired Systemic factors.
- Tight long term Control of Diabetes, Hypertension, Proteinuria, & Smoking can prevent or retard Diabetic Retinopathy.
**Wisconsin Epidemiologic Study of DR (WESDR)**
- **Younger-Onset group (YOG):** (Before 30 Yrs.)
  - Prevalence of DR: 2% in <2 Yrs. 98% in >15 Yrs.
  - PDR: 0% in <5 Yrs. 25% in 15Yrs. 56% in >20 Yrs.
  - Macular Edema: Rare before 10 Yrs. 21% in >20 Yrs.
- **Older-Onset group (OOG):** (After 30 Yrs)
  - DR: 30% in (IT) & 23% in (NIT) in DM of 2 Yrs.
  - PDR: 20% in (IT) & 4% in (NIT) after 15 Yrs.
- **4-Year Incidence & Progression**
  - YOG: 59% Retinopathy, 41% Progression, & 10.5% to PDR
  - OOG (IT): 47% Retinopathy, 34% Progression, & 7% to PDR
  - OOG (NIT): All incidences are Low, 34% show Retinopathy
- WESDR found an Increase in PDR Risk:
  - Elevated HbA in all group
  - Proteinuria in YOG with DM of 10 Yrs.
  - Elevated Diastolic BP & Male Sex in Younger-Onset.
  - Elevated Systolic BP in Older-Onset group
  - Legal Blindness: 3% in Older-OG, 1.5% in YOG
- **Mortality risk**: Increases in patients of PDR with
  - Diabetic Nephropathy
  - Genetic Factors (Histocompatibility Antigen)
    - HLA-DR Phenotypes 4/0, 3/0, X/X (neither 3 nor 4) have 3 - 4 times higher risk than HLA-DR 3/4, 3/X, 4/X, ones found in DM

**LABORATORY- INVESTIGATIONS**
- **FBS & PPBS (1½ hrs).**
- **Urine**: Sugar, Albumin, M/E
- **Lipid Profile**: Cholesterol, Triglyceride, HDL / LDL / VLDL
- **RFT**: Serum Creatinine & Blood Urea
- **Cardiovascular Workup**: CKP, LDH
- **RA Factor**: If h/o Joint pain.

**Clinical Classification DRS / ETDRS**
- **Background diabetic retinopathy (NPDR).**
- **Pre-proliferative diabetic retinopathy.** (Severe NPDR).
- **Proliferative diabetic retinopathy (PDR).**
- **Advanced diabetic eye disease.**
  - *Persistent New vessels* + Traction RD.
  - *Neovascular glaucoma."
  - 5. *End stage diabetic eye disease.*
  - 6. Maculopathy.
- *Focal* + *Diffuse* + *Ischaemic* + *Mixed.*

**Background Retinopathy (NPDR)**
- **Microaneurysms**
- **Retinal Hemorrhages**
- **Hard Exudates**
- **Retinal Oedema**

**NPDR**

**Pre-proliferative Retinopathy**
**Severe / Very Severe NPDR**

**Proliferative Retinopathy (PDR)**

**PDR with TRD**
Steps of Neovascularization

- Destruction of Basement Membrane
- Extension of Cytoplasmic Bud from Endothelial cells
- Migration & Division of Endothelial cells
- Tubes unite to form Capillaries as Flat Fronds
- NV grows through ILM into Vitreous, accompanied by Proliferative Fibrous Tissue

Types of Neovascularization:

- Epipapillary
- Peripapillary
- Papillo-vitreal a. Columnar b. Arcuate c. Confluent
- Retino-vitreal
- Pre-retinal (Surface)

High-Risk Characteristics of PDR (HRC)

- NVD that is covering ¼ to 1/3 disc area or more in size
- NVD less than ¼ disc area in size with fresh Vitreous or Pre-retinal hemorrhage.
- NVE greater than or equal to ½ DD in size with fresh Vitreous or Pre-retinal Hemorrhage

Glial Proliferation - PDR

Grade 1 : Patchy Gliosis in the Posterior pole or along the Midportion or Distal aspect of the vascular arcades, not involving the Optic Disc. FPE

Grade 2 : Gliosis involving the Optic Disc only. FPD

Grade 3 : Gliosis of the Arcade region & Optic Disc Moderate FPE & FPD

Grade 4 : Circular Band of Gliosis involving the Optic Disc, Vascular arcade, & Temporal Interarcade retinal area. Severe FPE & FPD

Grade 5 : Indicates a Shallow, Circular, Centrally located TRD around the Optic Nerve & Posterior pole caused by traction from a shallow PVD

Grade 6 : Moderately elevated central TRD caused by a highly detached Cone shaped PVD extending to the region of Ora Serrata

Grade 7 : Markedly elevated Total TRD by a highly detached posterior hyaloid adherent to the vitreous base.

Grade 8 : Total TRD caused by excessive traction from a highly detached posterior hyaloid & cyclitic membrane pulling the retina into the Retrolental space. Triangular Syndrome.

Diabetic Maculopathy
Mechanisms of Macular affection in Diabetes

- Collection of interstitial fluid within the Macula with or without lipid exudates or cystoid changes
- Nonperfusion of parafoveal capillaries with or without intraretinal fluid.
- Traction in the Macula by Fibrous Tissue Proliferation causing dragging, surface wrinkling, or detachment of macula
- Intraretinal or Preretinal Hemorrhages in the Macula
- Lamellar or Full-thickness Macular Hole

CSME

- Retinal Thickening at or within 500 micron of the center.
- Hard Exudates at or within 500 micron of the center + Thickening of adjacent retina.
- Area of Retinal Thickening at least 1 Disc Diameter in size. A part of which is at least within 1 DD of the center.
  * Focal * Ischaemic
  * Diffuse * Mixed

CSME Criterion

Levels of Retinopathy

NFDR

- Mild NFDR 5% 15% At least One Microaneurysm
- Moderate NFDR 12-27% 33% Ma, Soft Exudates (CWS), Venous Beading (VB) & IRMAs
- Severe NFDR "4-2-1 rule" 52% 60% Hge / Ma in all 4 quadrants, or V B in 2 or more quadrants, or IRMA in at least 1 quadrant.
- Very Severe NFDR 75% 75% Two or more lesions of Severe NFDR but no NV

PDR Composed of

- NVD, or NVE
- Pre-retinal or Vitreous Hemorrhage
- Fibrous Tissue Proliferation (FPD & FPE)
- Early PDR 75% NVD or NVE (Definition not met for High-Risk PDR)
- High-Risk PDR
- NVD => 1/3 to ½ Disc Area
- NVD less than ½ Disc area with fresh Vitreous or Pre-retinal Hge.
- NVE => ½ DD in size with fresh Vitreous or Pre-retinal Hge.

Progression of PDR

PDR at 1-Year Visit

by Severity of Individual Lesion

Lesion Grade PDR in 1-year (%)

Hge / Ma Present in 2-5 fields 9
Very severe >5 fields 57
IRMAs None 9
Moderate in 2-5 fields 57
VB Absent 15
Present in 2-5 fields 59

Management of Diabetic Retinopathy

- There is No known Cure for Diabetic Retinopathy & Diabetic Maculopathy.
- Laser minimizes the risk of MVL & SVL(<5/60)
- Meyer Schwickerath- Pioneer Photocoagulation in 1955
- Four Major Clinical Trial- DCCT, DRS, ETDRS, & DRVS have largely determined the strategies for management of DR.

Diabetic Control & Complication Trial (DCCT)

- To study Primary prevention & Secondary Intervention
- An average of 3 years Intensive Rx reduction in Risk.
- Rapid Glycemic control in previously uncontrolled Diabetics is detrimental for Diabetic Retinopathy.
- Intensive Rx of DM slowed the development of DR- 9 Yrs Trial
- Benefit of Intensive Rx is more in Early NFDR Stage of DR than in More Advanced Severe NFDR or PDR Stage.
- A 10% reduction of Hb-A level significantly reduced the Risk of Onset & Progression of DR, also reduced the need for Laser Therapy.

DRS (Diabetic Retinopathy Study) Major Conclusions

- Photocoagulation Reduces the risk of severe visual loss by 50% or more (SVL< 5/60)
Modest Risk of decrease in Visual Acuity (usually only 1 line) & Visual Field Following Laser Photocoagulation.

- Treatment benefit outweighs risk for eyes with High-Risk PDR (50% 5-year rate of SVL in such eyes without treatment was reduced to 20% by treatment).

**ETDRS (Early Treatment Diabetic Retinopathy Study)**

**DRVS (Diabetic Retinopathy Vitrectomy Study)**

Major Conclusions:

- Group H: Recent Vitreous Hemorrhage
  - Chances of recovery of Visual acuity > 6/12, increased by 50% in Early Vitrectomy group verses 12% in Conventional Management group at year follow-up in Type-I Diabetes who were younger & had Severe PDR.

- Group NR: Very Severe PDR With Useful Vision
  - Chance of VA > 6/12, increased by Early Vitrectomy (rather than Delayed Vitrectomy) for eyes with Very Severe New Vessels

**Role of Fluorescein Angiography & Fundus Photography**

- **BDR**: Baseline Photo / Maculopathy
- **CSME**: Ischaemia / Extent / Location
- **PPDR**: Extent of CNP / NVD / NVI / IRMAs
- **Angiographic Risk Factors (EDTRS)**
- **Fluorescein Leakage**
- **CNP on FA**
- **Capillary dilatation on FA**
- **Colour Fundus Photo Risk Factors**
- **IRMAs, Venous Beading, Hemorrhage, Ha, Hard & Soft Exudates (CWS)**

Perifoveal Capillary Network
Diabetic Maculopathy - FFA

**Eye Examination Schedule**

- **Age at Onset of Diabetes Time of 1st Ex.** Minimum Follow-up
  - 0-30 yrs 5 yrs after onset Every year
  - 31 yrs or > At Diagnosis Every year
  - During Pregnancy 1st Trimester 3 monthly & for 1styr

**Diabetic Status of Retina Follow-up (Months)**

- Normal or Mild NPDR 12
- NPDR without Macular edema(ME) 6-12
- NPDR + ME (non-significant) 4-6
- NPDR + CSME 3-4
- Severe NPDR 3-4

**General Management Recommendations**

- **General Management Recommendations (Contd.)**

**Laser Management of Diabetic Maculopathy**

- **ETDRS Protocol for CSME**
  - **FA** is done prior to deciding treatable lesion
  - **Discrete points of retinal hyperfluorescence or focal leakage that are >500 micron from the center**
  - **Focal Leaks 300-500 micron from the center of the macula, causing retinal thickening or hard exudates.**
  - **Areas of Diffuse leak within the retina (IRMAs or leaking capillary bed)**
  - **Thickened retinal avascular zones (except normal FAZ).**

**Laser Photocoagulation Technique**

![Laser Photocoagulation Technique](Laser_Photocoagulation_Technique.png)
**Focal photocoagulation:**
Prefebrably Pure Green Laser
Spot size: 50 – 200 micron
Power: 200 – 300 mW
Duration: 0.1- 0.2 sec
Burns: Light to Moderate Intensity
Lesions: focal leaks, MA, IRMAs, or Short capillary segments, Advanced Macular edema- Cystic changes, Patchy NVE< 1DD (1500 micron), Macraoneurysms.

**Grid photocoagulation:**
Pure Green Laser
Spot Size: 50 –200 micron
Power: 200 mW
Duration: 0.1- 0.2 sec
Burns: Light to Moderate
Lesion: Diffuse Macular edema,CME

**Pan-Retinal Photocoagulation:**
<table>
<thead>
<tr>
<th>Spot Size (micron)</th>
<th>Duration (sec)</th>
<th>Power (mW)</th>
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<tbody>
<tr>
<td>100 to 200</td>
<td>0.05 to 0.2</td>
<td>100 to 400</td>
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<tr>
<td>200 to 500</td>
<td>0.05 to 0.2</td>
<td>400 to 500</td>
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Burns of Moderate intensity are placed 2-3 DD away from the macula. 1600 – 2000 burns at 1 burn width apart.

**Standard Therapeutic Approach**
Stage I PRP 2-3 months
Stage II Additional PRP 2-3 months
Stage III Anterior Retinal Cryoautery 2 months
Stage IV Focal Photocoagulation 2 months
Stage V Viterectomy

**EDTRS guidlines for follow up**
Changes in the New Vessel
Appearance of the New Vessel (Calibre, Degree of Network, Extent of Fibrous tissue)
Frequency & Extent of Vitreous hemorrhage
Status of Vitreous detachment
Extent of photocoagulation scar
Extent of TRD & fibrous proliferation

**Additional PC is considered if:**
Active NV (increase in size, fibrous tissue)
Extent of NV is Greater than earlier
Recurrence of Retinal Hemorrhage. Without PVD

“Skip Areas”

Additional PC is less urgent if:
- Decreased Calibre of NV
- Developing Fibrous proliferation
- Extensive or Complete PVD
- Single episode of Vit. Hge. following PVD

Contraindications of Pan-Retinal Laser Photocoagulation

Presence of Grade IV or greater Glial proliferation
- Grade IV or greater Vitreo-Retinal Traction
- Presence of Grade IV or greater Glial proliferation
- Grade IV or greater Vitreo-Retinal Traction
- CNP areas in more than 60% of Macula & Paramacula – Poor Visual prognosis
- Severe Renal Retinopathy with edema, intraretinal yellowish serum accumulates, attenuation & tortuosity of vascular elements and general deterioration of retina.
- Diabetic retinopathy with Advanced Hypertensive retinopathy. Massive edema, exudates, extensive CNP areas, as seen in Renal retinopathy.

Complications of PRP

Field Constriction & Night Blindness
- Fovea / Macular Burn
- Macular Edema & Poor Colour Discrimination
- Serous Retinal Detachment – acute ACG
- Anterior Segment NV
- Post. Synaechia – Iris & Pupillary Abnormality
- Combined Burn & Lens Opacities – Blurred Vision
- Internal Ophthalmoplegia - Transient Myopia - Accommodation Cilioretinal / Choriovitreal NV
- Pain – Younger diabetics & Peripheral Retina – More Painful
- RBH – Due to Retrobulbar Anaesthesia

Peripheral Cryoablation for PDR

Indication:
- Hazy media
- Repeated Vitreous hemorrhage
- Non regressing NVD despite complete PRP

Benefits:
- Accelerated absorption of Vitreous Hemorrhage
- Regression of NVE & NVD

Complications:
- PVR Changes
- TRD- Cryo should be avoided in areas of VR Adhesion

Technique:
- Careful B-scan USG performed to detect areas of TRD
- Transconjunctivally - Two rows of 3 – 4 applications in each quadrant at 12mm & 16mm from the limbus
- After Limbal Peritomy - 20 spots in 4 rows in each quadrant, usually in 2 treatment sessions one week apart.
- Applications are monitored under visualisation with Indirect Ophthalmoscope.
- Otherwise in hazy media application can be for 10 – 15 sec at – 60 degree centigrade

Vitrectomy for PDR

Indications:
- Severe non clearing Vitreous Hemorrhage
- >3 months in Type-I
- >6 months in Type-II
- TRD involving Macula
- Combined TRD & Rhegmatogenous RD
- Severe progressive Fibrovascular Proliferation
- Anterior Segment NV with Posterior segment opacity
- Dense Premacular Hemorrhage
- Ghost Cell glaucoma
- Macular edema with Premacular Traction
- Cataract preventing Laser treatment for severe PDR

Aims of Vitrectomy:
- Removal of all Vitreous opacities & the Scaffolding along which Fibrovascular tissue proliferates
- Division of all membranes & strands
- Treat Retinal Breaks
- Division of Retino-vitreo-retinal bands, ERM Peeling.
- Endophotocoagulation

Complications / Risk:
- Progressive Rubiosis
- Cataract
- Glaucoma
- Recurrent Vitreous Hemorrhage
- RD

Benefits:
- Vitrectomy Prevents or Delays Persistent Intra-gel Hemorrhage
Opaque Membranes
Rubiosis
Burnt out stage

Poor Prognostic Factors:
Age > 40
Preoperative Rubiosis
Cataract
Visual Acuity < 5/60
No previous Laser Photocoagulation

Major modes of visual loss and presentation:

Maculopathy
FA, Control DM,
Grid / Focal Laser
Vitrectomy

Vit. Hemorrhage
PRP after Vitrectomy/
Spontaneous Clearing

PDR + TRD Threatening
Vitrectomy + PRP
or Involving Macula

Involuted Retinopathy
Leave it alone