Complications of Diabetic Retinopathy

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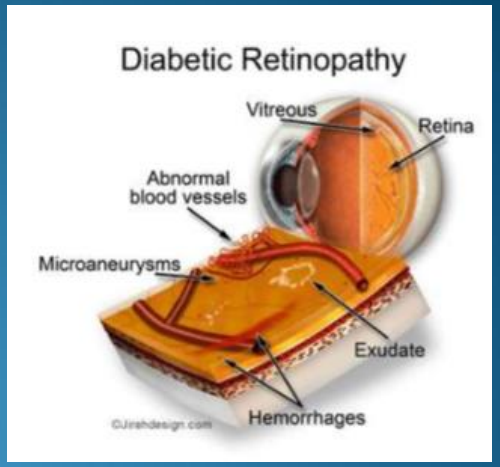
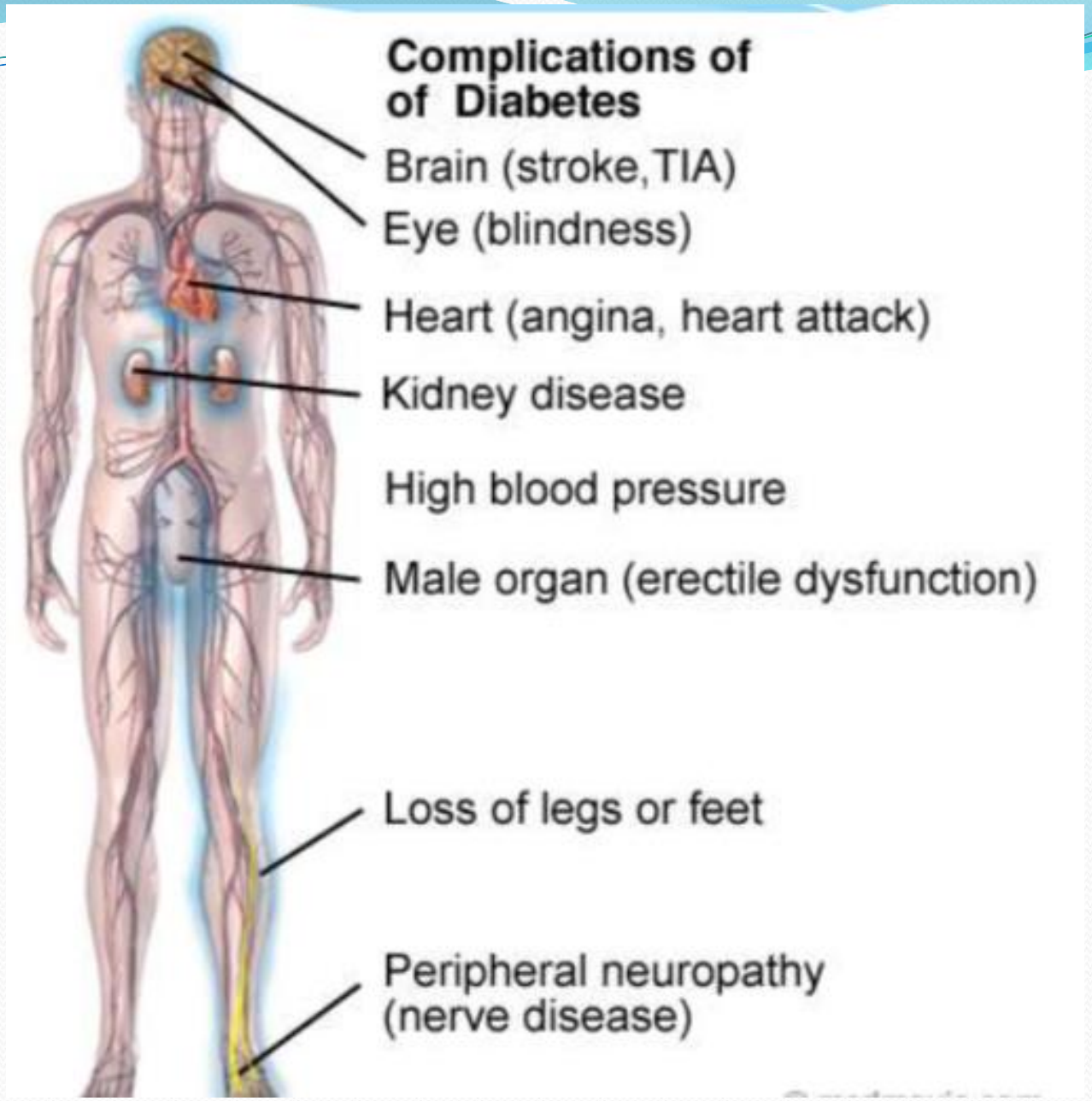


DM is a chronic disorder characterized by persistent hyperglycemia resulting in micro and macrovascular complications.

The 2013 International Federation of Diabetes (IDF) Atlas for Diabetes ranked the Middle East and North Africa (MENA) with the highest worldwide prevalence of diabetes at 10.9%, the national prevalence of diabetes is 11.4% of the adult population in Iran.

Based on the current data, 37% and 29.6% of diabetic cases have some degrees of DR in Tehran and Yazd provinces, respectively.


Complications of
of Diabetes
Brain (stroke, TIA)
Eye (blindness)
Heart (angina, heart attack)
Kidney disease
High blood pressure
Male organ (erectile dysfunction)
Loss of legs or feet
Peripheral neuropathy
(nerve disease)

Ocular complications of DM

1-Diabetic Keratopathy

2-Glaucoma

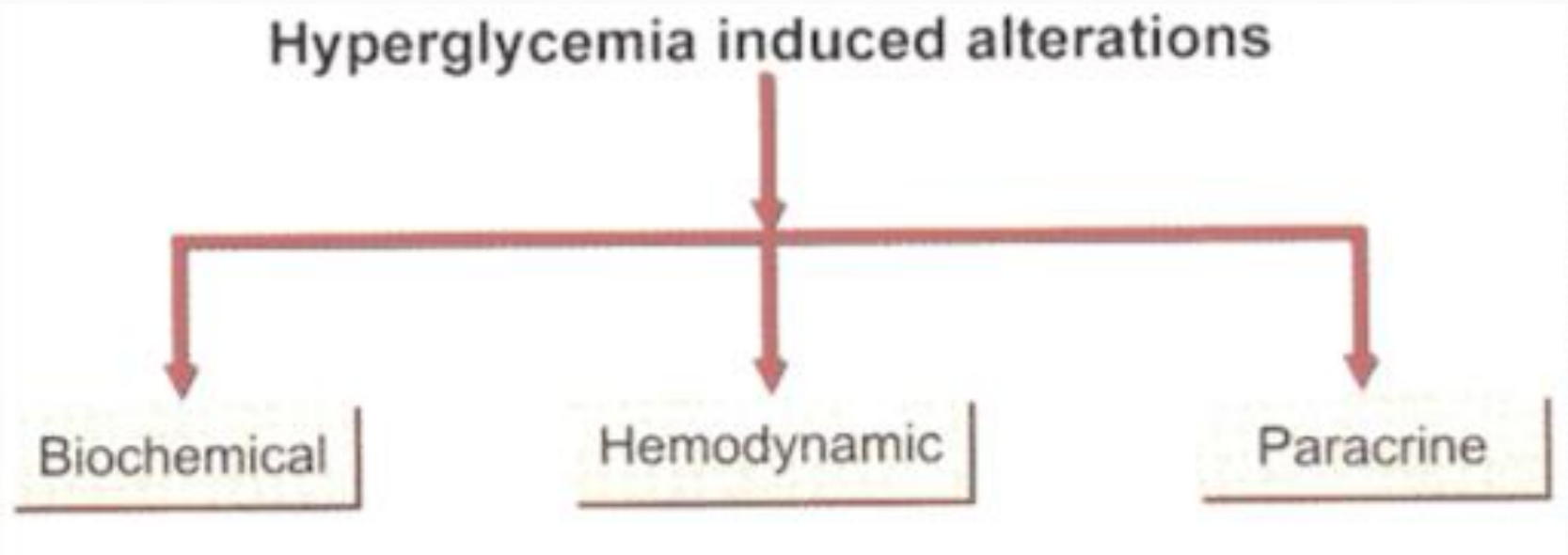
3-Cataract

4-Optic Neuropathy

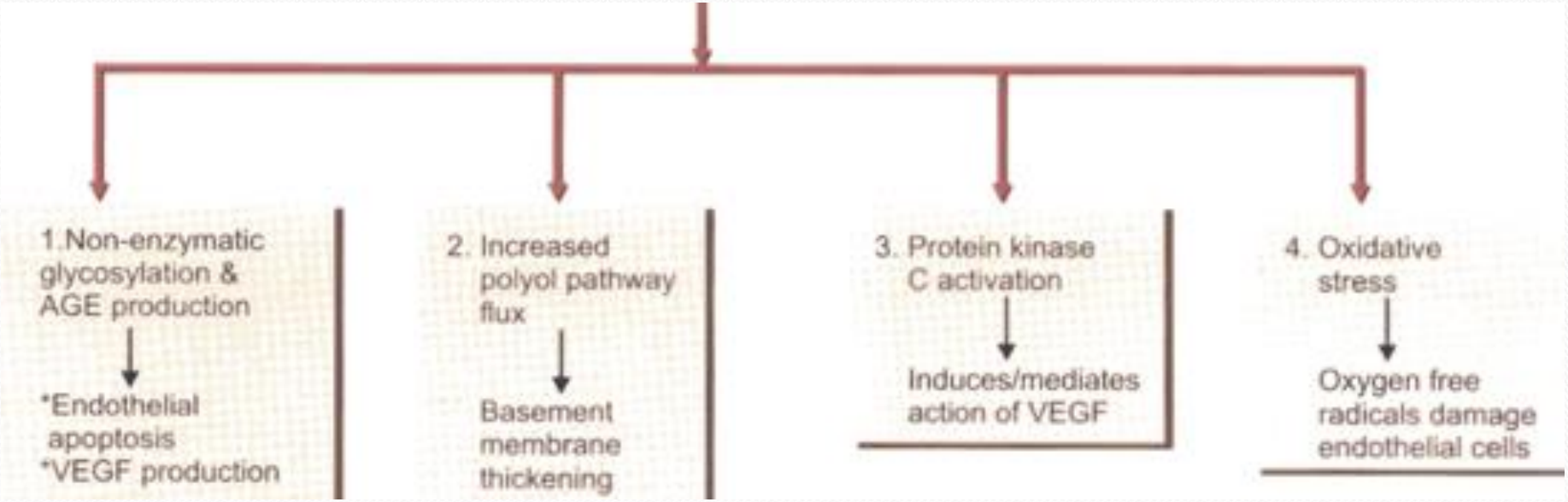
5-Oculomotor palsy (3,4, 6)

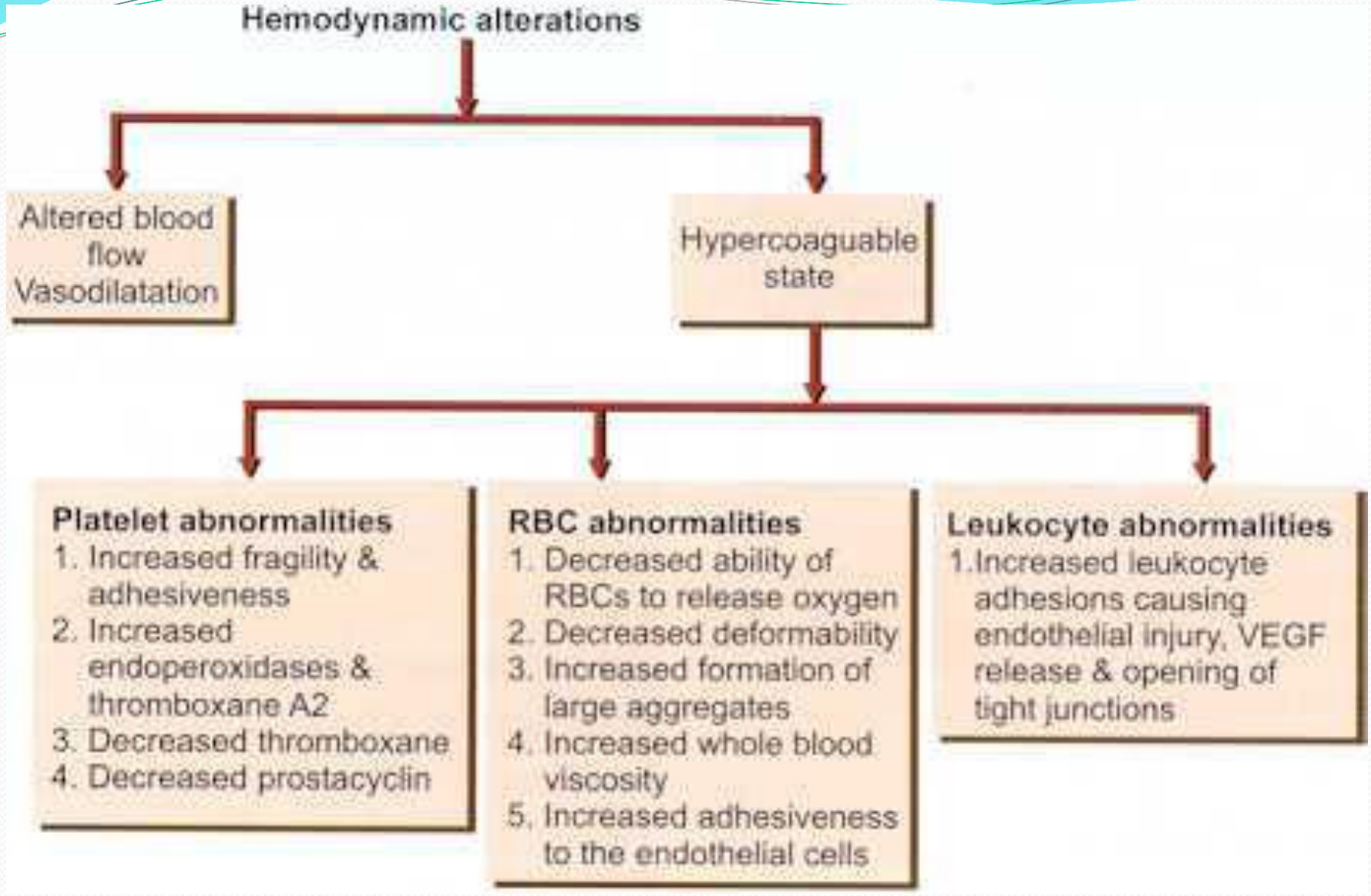
6-Diabetic retinopathy

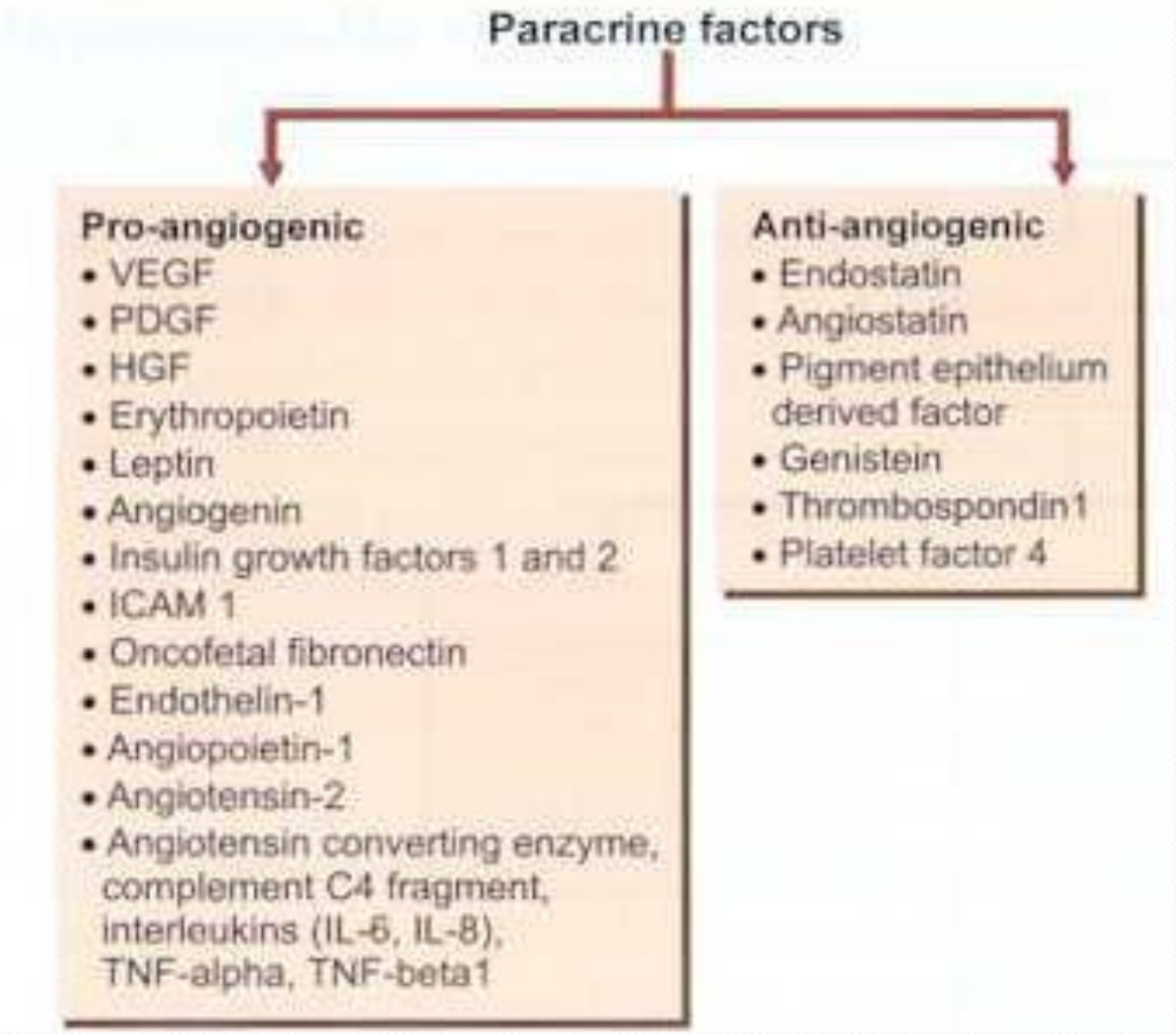
Pathogenesis of DR



Biochemical alteration




Hemodynamic alterations
Altered blood flow Vasodilatation
Hypercoaguable state
Platelet abnormalities
1. Increased fragility & adhesiveness
2. Increased endoperoxidases & thromboxane A2
3. Decreased thromboxane
4. Decreased prostacyclin
RBC abnormalities
1. Decreased ability of RBCs to release oxygen
2. Decreased deformability
3. Increased formation of large aggregates
4. Increased whole blood viscosity
5. Increased adhesiveness to the endothelial cells
Leukocyte abnormalities
1. Increased leukocyte adhesions causing endothelial injury, VEGF release & opening of tight junctions


Paracrine factors
Pro-angiogenic
• VEGF
• PDGF
• HGF
• Erythropoietin
• Leptin
• Angiogenin
• Insulin growth factors 1 and 2
• ICAM 1
• Oncofetal fibronectin
• Endothelin-1
• Angiopoietin-1
• Angiotensin-2
• Angiotensin converting enzyme, complement C4 fragment, interleukins (IL-6, IL-8), TNF-alpha, TNF-beta1
Anti-angiogenic
• Endostatin
• Angiostatin
• Pigment epithelium derived factor
• Genistein
• Thrombospondin1
• Platelet factor 4

Theories proposed for pathogenesis of DR

increased platelet adhesiveness

increased erythrocyte aggregation

abnormal serum lipids

defective fibrinolysis

abnormal levels of growth hormone

upregulation of VEGF

abnormalities in serum and whole blood viscosity

Microvascular occlusion

Endothelial cell damage and proliferation

Capillary basement membrane thickening

Increased plasma viscosity
Deformation of RBC
Increased platelets stickiness

Decreased capillary blood flow and perfusion

Retinal hypoxia

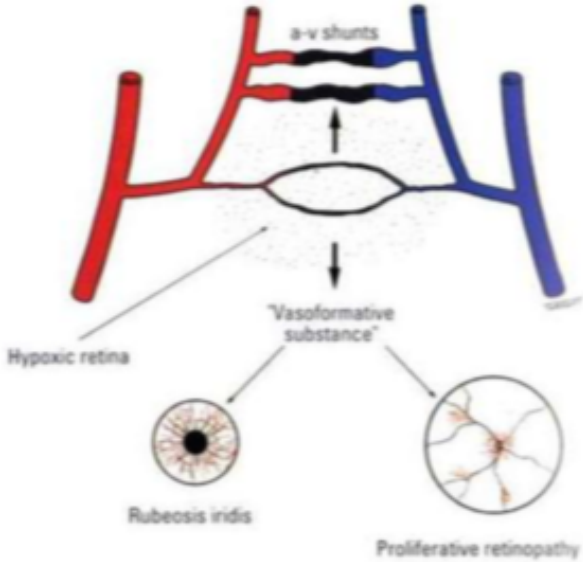
VEGF

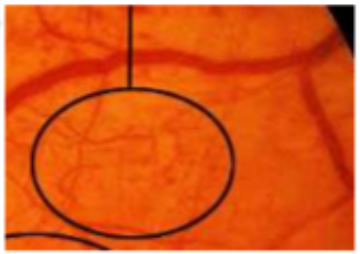
A-V shunt
IRMA*

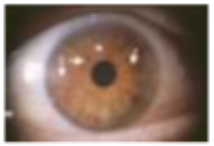
Neovascularization and fibrovascular proliferation

Rubeosis iridis

Proliferative retinopathy



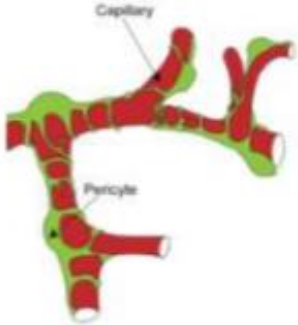


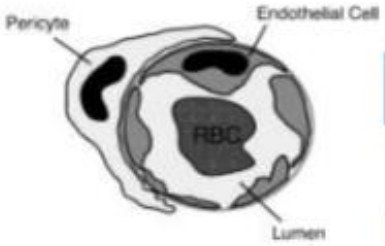


*intraretinal microvascular abnormalities

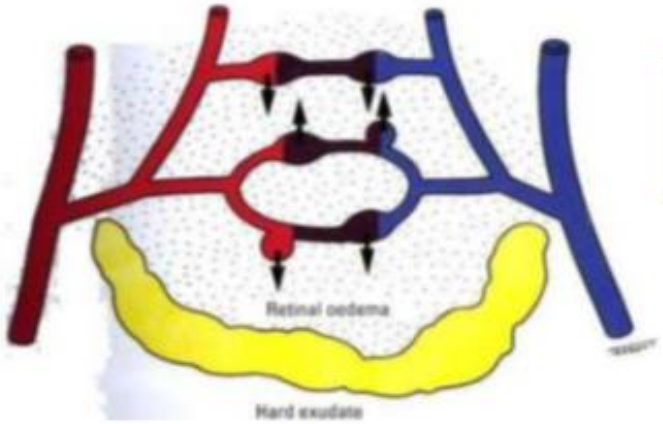
Microvascular leakage

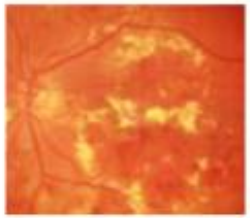
Degeneration and loss of pericytes → Capillary wall weakening



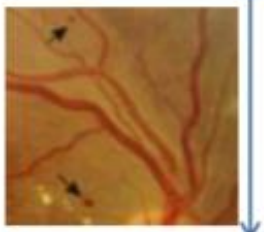


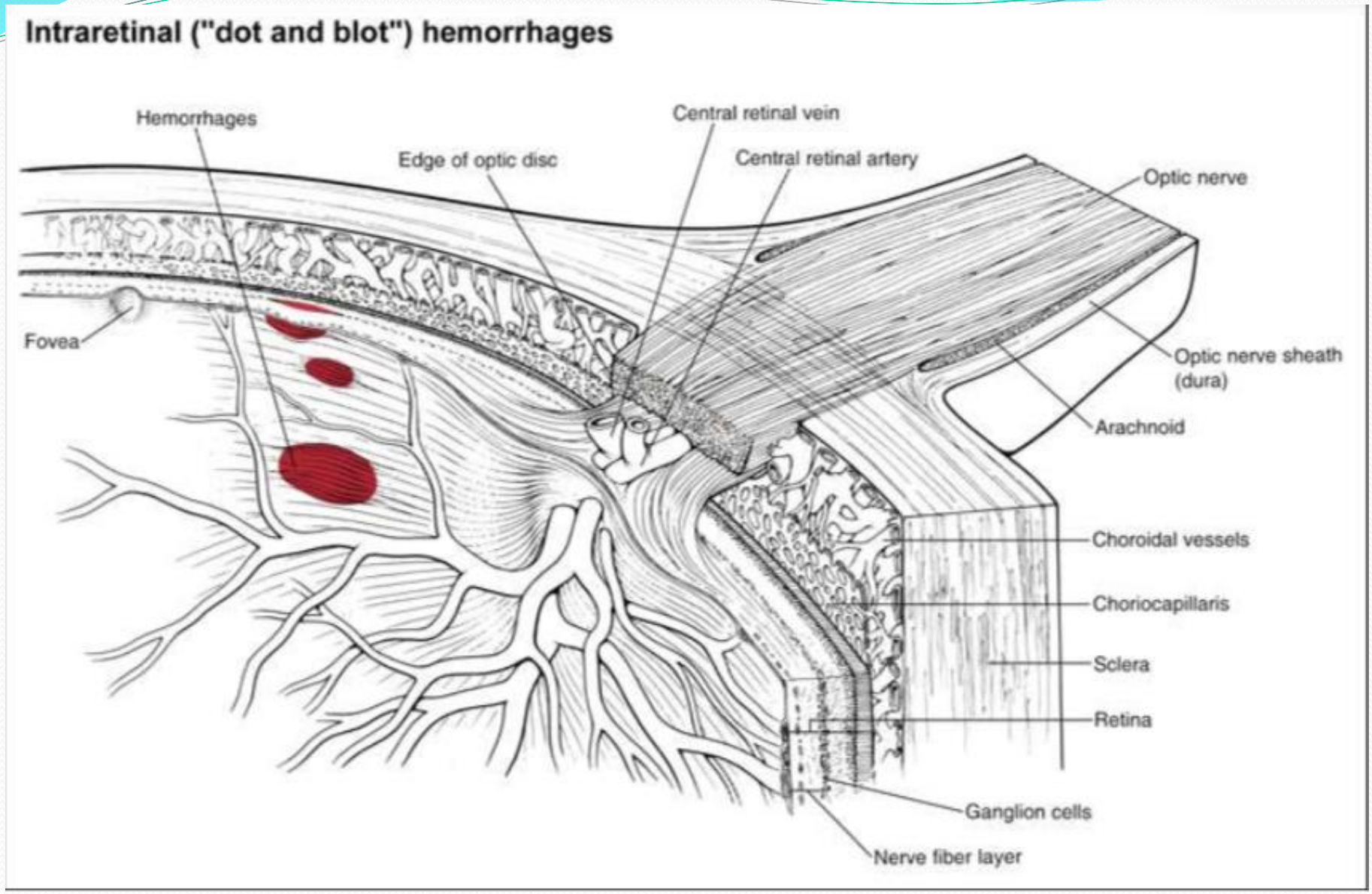
Capillary wall weakening → Plasma leakage → Retinal edema → Hard exudate (Circinate pattern)





Capillary wall weakening → microaneurysm → Intraretinal hemorrhage




Intraretinal ("dot and blot") hemorrhages
Hemorrhages
Central retinal vein
Edge of optic disc
Central retinal artery
Optic nerve
Fovea
Optic nerve sheath (dura)
Arachnoid
Choroidal vessels
Choriocapillaris
Sclera
Retina
Ganglion cells
Nerve fiber layer

Risk Factors for Diabetic Retinopathy

- **1. Duration of diabetes**
- **IDDM:**
- Do not develop diabetic retinopathy for 5 years after
- diagnosis. After 20 years, 50% of these patients would develop PDR
- **NIDDM**:
- The time of onset and therefore duration are
- difficult to predict precisely and approximately 3% to 4%
- would have changes of diabetic retinopathy at the time of presentation. The prevalence of PDR after 20 years of onset is expected to be only 5 to 10 percent.

- **2. Control of blood glucose**
- **3. Puberty**
- **4. Type of diabetes**
- PDR is more prevalent in type 1 than in type 2 diabetes. The incidence of macular edema over a period of 10 years follow-up has been found to be 20.1 % in the younger onset group, 25.4 % in the older onset group taking insulin and 13.9% in the older onset group not taking insulin.

5. Nephropathy

A diabetic patient with retinopathy is at a moderate risk of having nephropathy but the patient who has nephropathy, is at a much higher risk of having retinopathy.

6. Hypertension

7. Pregnancy

8. Genetic factors

Clinical Course of DR

Non-proliferative Diabetic Retinopathy

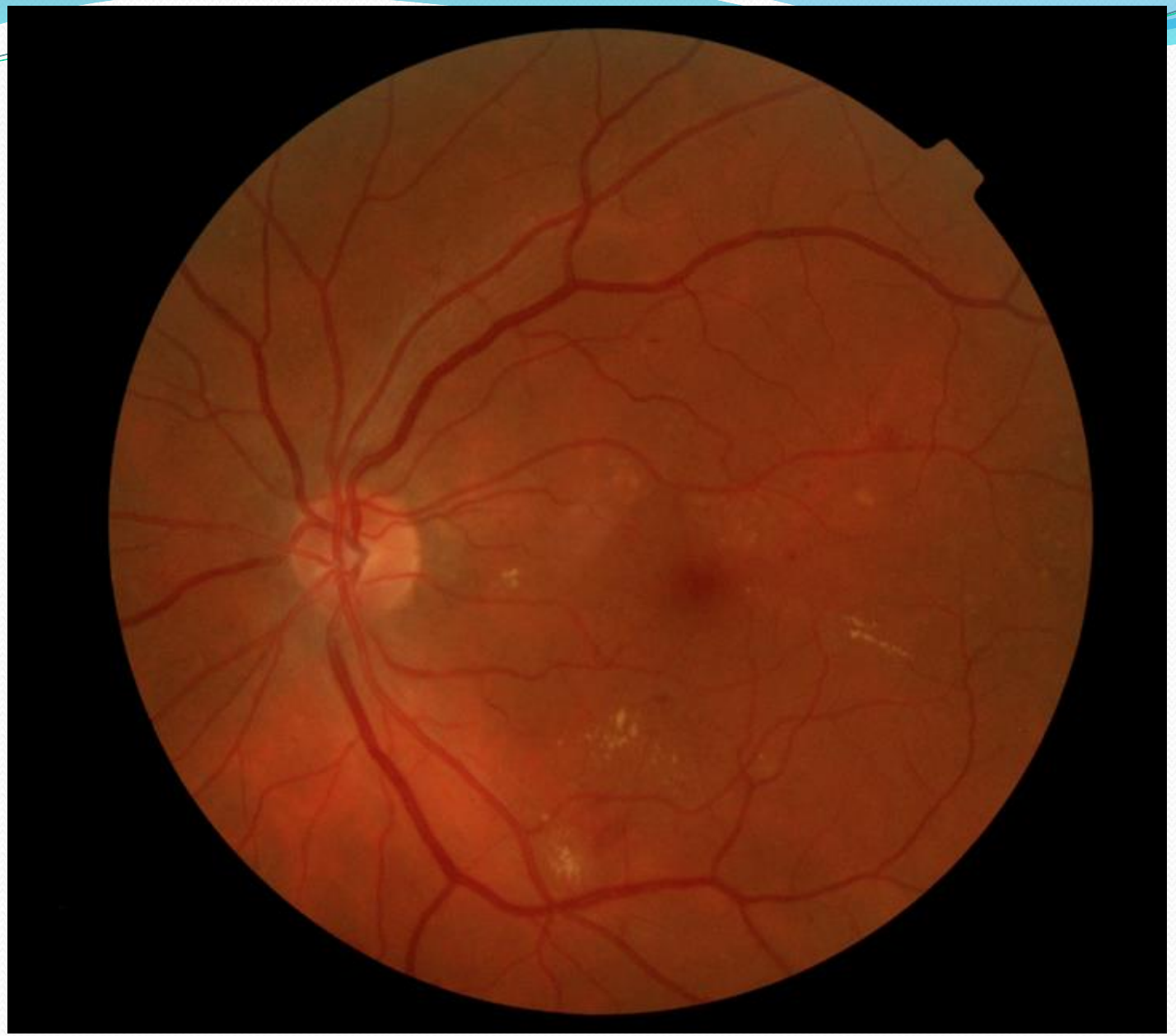
NPDR is characterized by the intraretinal abnormalities.

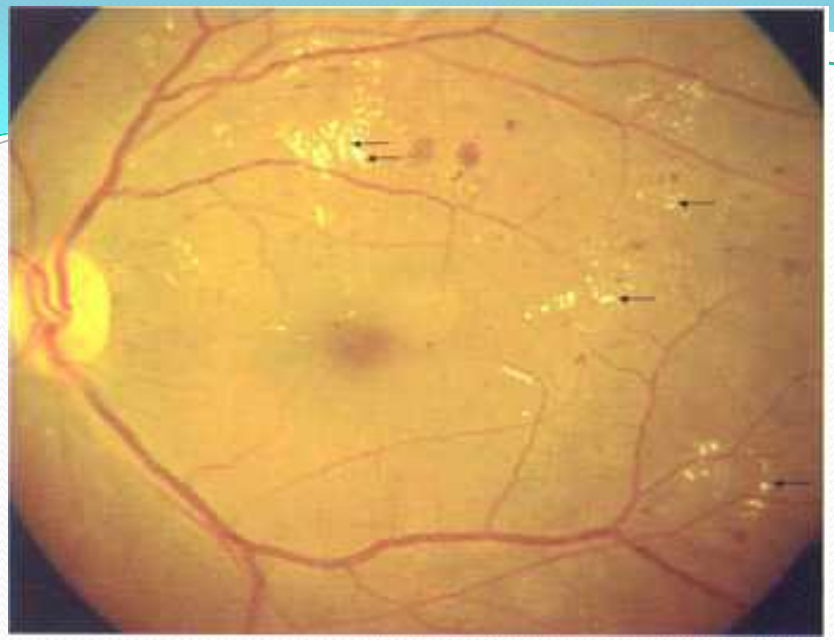
Microvascular occlusion is the hallmark of NPDR.

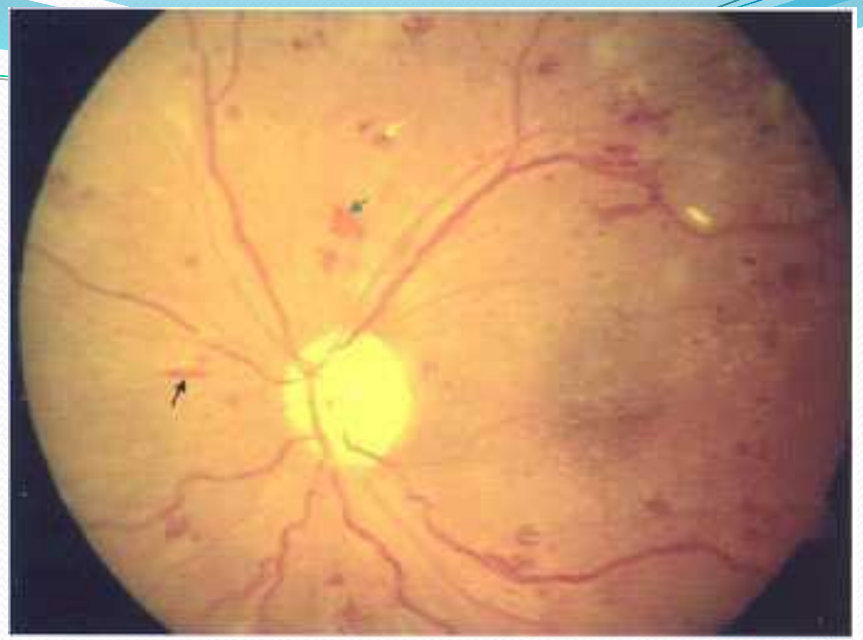
Capillary and arteriolar occlusions result in **microaneurysms, intra-retinal hemorrhages, HE , CWS and venous abnormalities**.

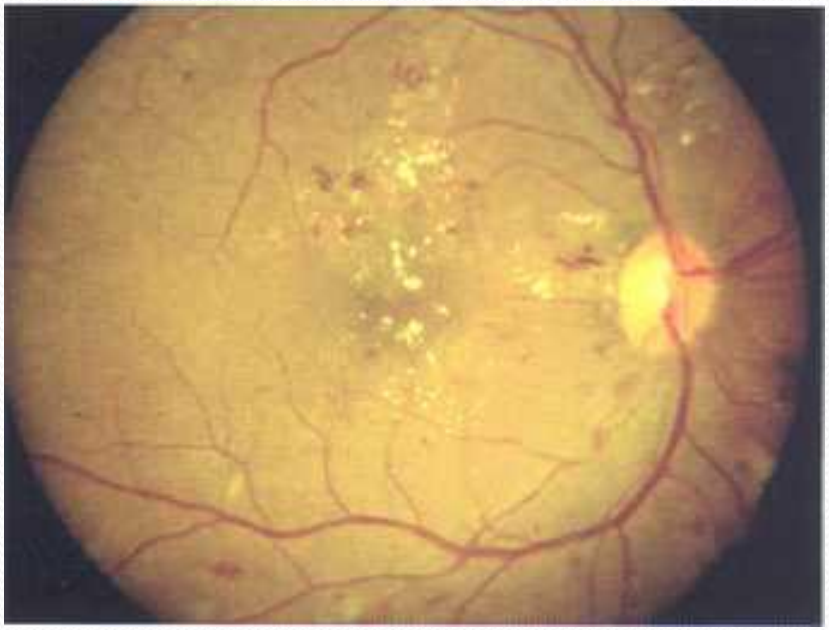
Microaneurysms are the first clinical sign of DR.

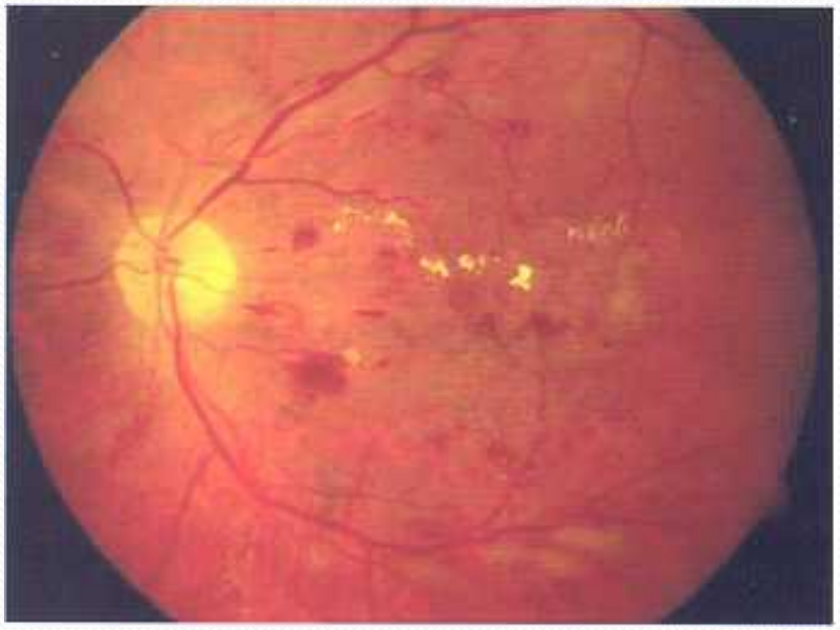
Venous beading, IRMAs, hemorrhages in all the four quadrants indicate disease severity and increased chances of progression to PDR.

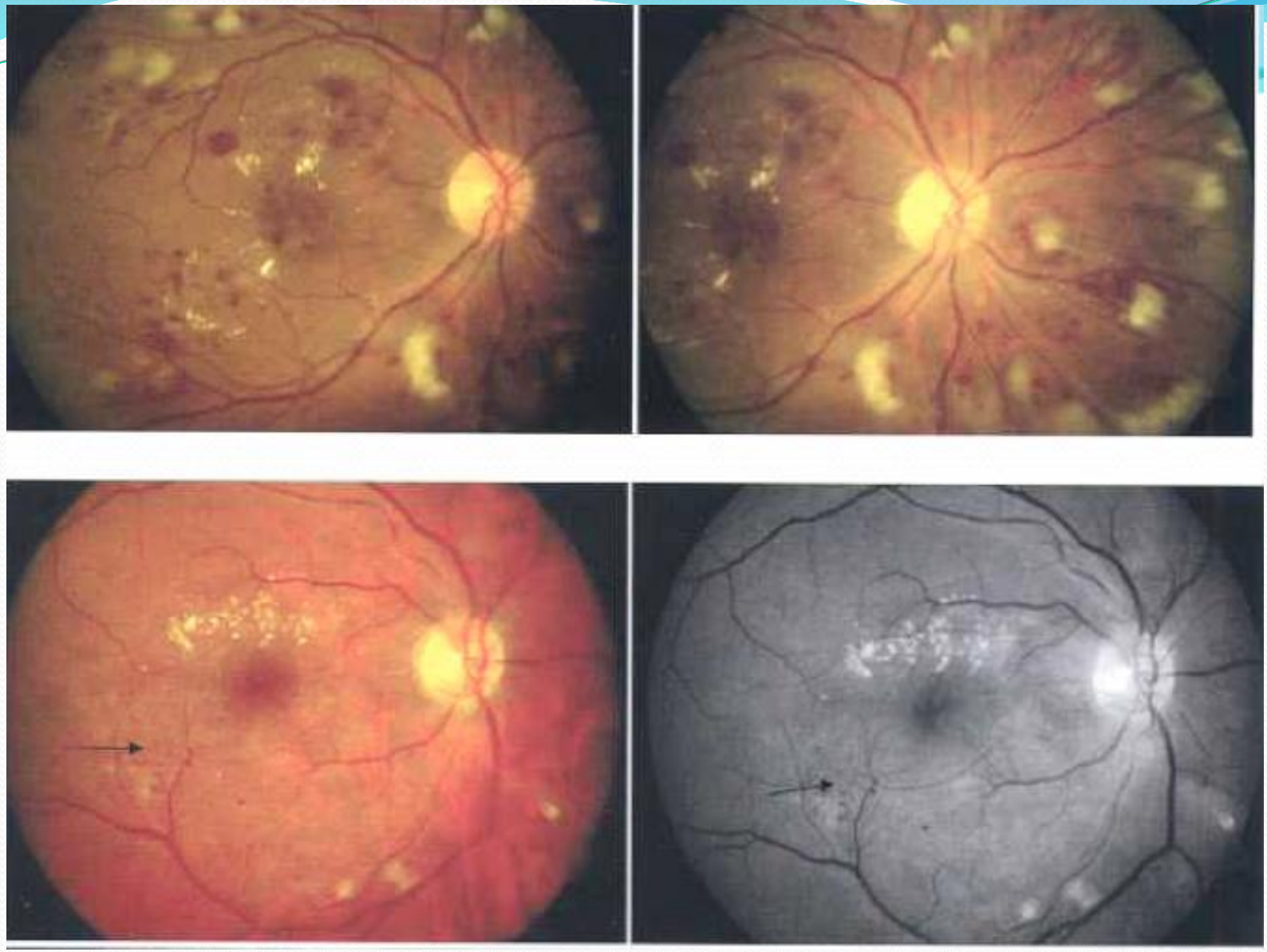












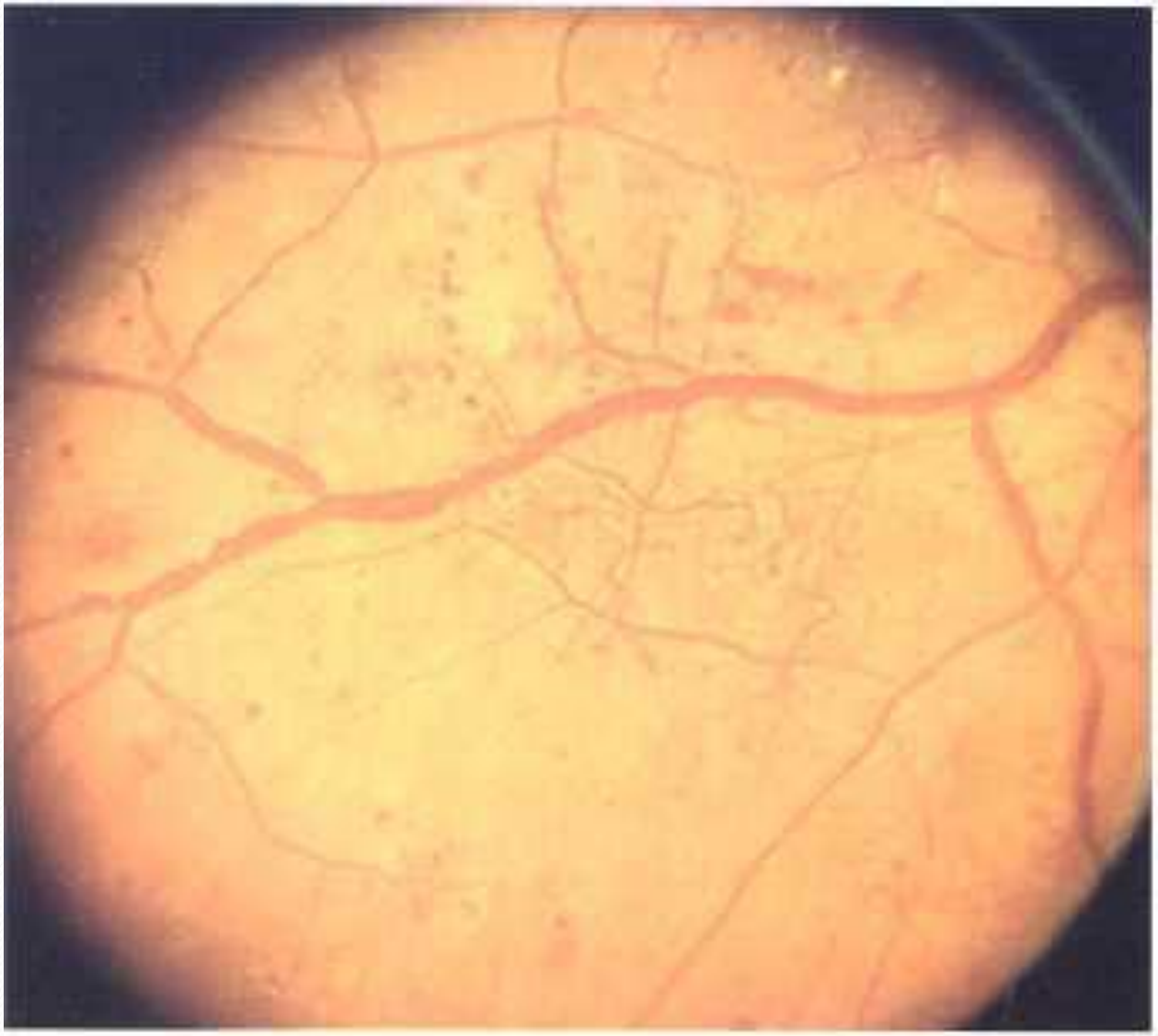
ETDRS Classification

- **Mild NPDR**: Only microaneurysms .
- **Moderate NPDR**: Hemorrhages and or microaneurysms more
- than standard 2A in all the quadrants.
- **Severe NPDR**: 4:2:1 rule
- Hemorrhages/ microaneurysms more than 2A in all the four
- Quadrants, Definite venous beading in more than 2 quadrants
- IRMAs more than standard photograph 8A in one quadrant
- **Very Severe NPDR**:
- 2 or more of the features of severe NPDR

Modified Airlie House classification of DR

Figure 1

Standard photograph. A: 2A. Notice the intraretinal hemorrhages. If 4 quadrants have intraretinal hemorrhages of at least this magnitude then by definition severe non-proliferative retinopathy is present; B: 6A. Notice venous beading (VB). If 2 quadrants or more have VB of at least this magnitude then by definition severe non-proliferative retinopathy is present; C: 8A. Notice the intraretinal microvascular abnormalities (IRMA). If one or more quadrants has IRMA of at least this magnitude then by definition severe non-proliferative retinopathy is present.



Diabetic Macular Edema

Mechanisms for Diabetic Macular Edema

- **1. Hyperglycemia causes breakdown of the blood-retina barrier. The cellular structure of retinal capillaries consists of endothelial cells and pericytes with one to one ratio of these two cells.** Uncontrolled diabetes causes loss of pericytes resulting in saccular outpouching of the capillary wall clinically seen as **microaneurysm**.

- **2. Dilated retinal arterioles have less resistance that increases the blood flow and hydrostatic pressure in the capillaries and venules,** thus causing the fluid to move out of the vascular compartment according to Starling's law.

- 3. In diabetes, there is **increased retinal leukostasis,** that affects retinal endothelial function, retinal perfusion, and vascular permeability.

DME is the most common cause of moderate visual loss in patients with diabetes.

DME can develop any time during the progression of diabetic retinopathy; however, its incidence increases with advancing retinopathy.

It is reported in 3 percent eyes with mild NPDR, 38 percent with moderate to severe NPDR, and 71 percent with PDR.

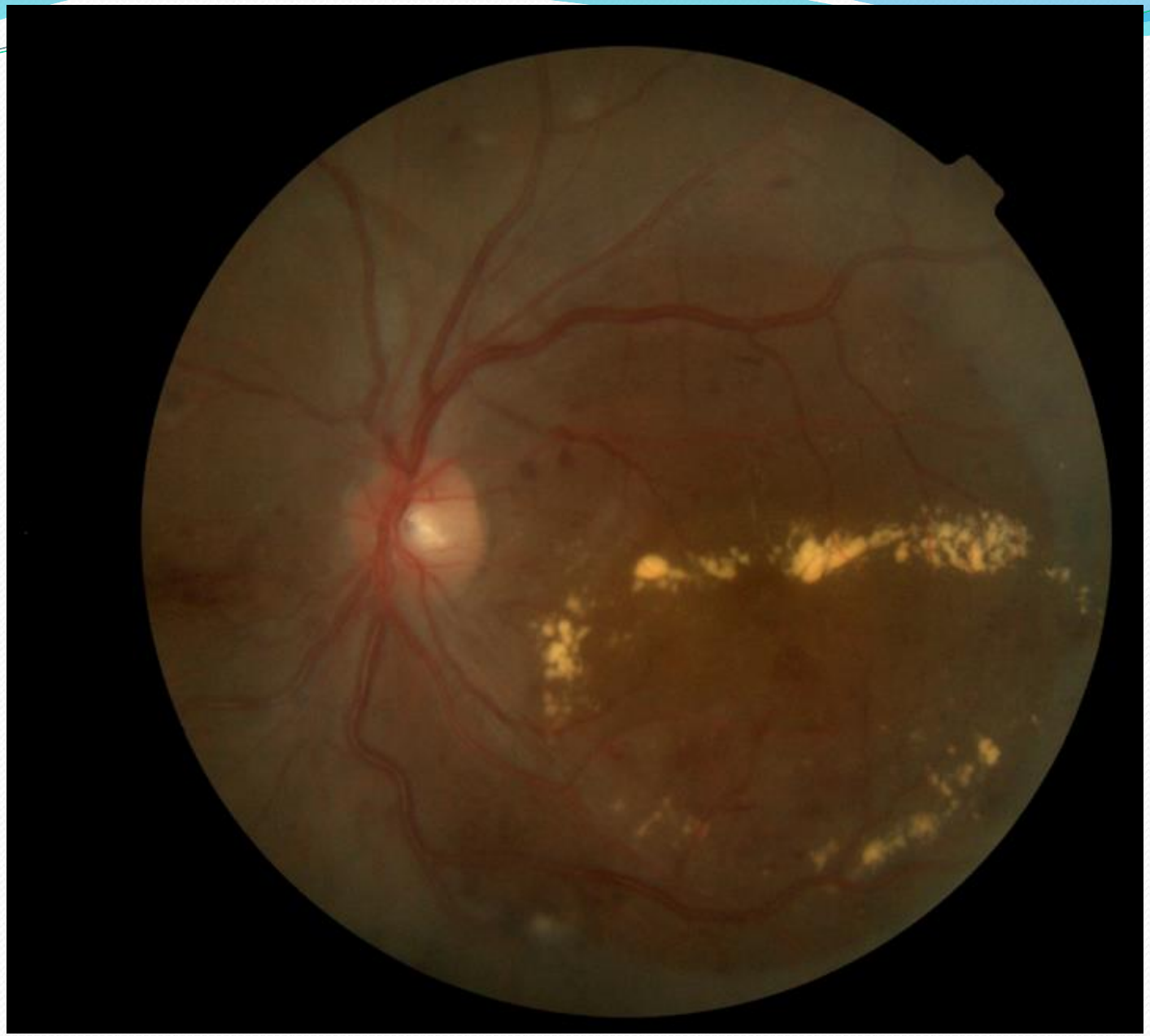
Diabetic macular edema has multifactorial etiologies and its incidence increases with :

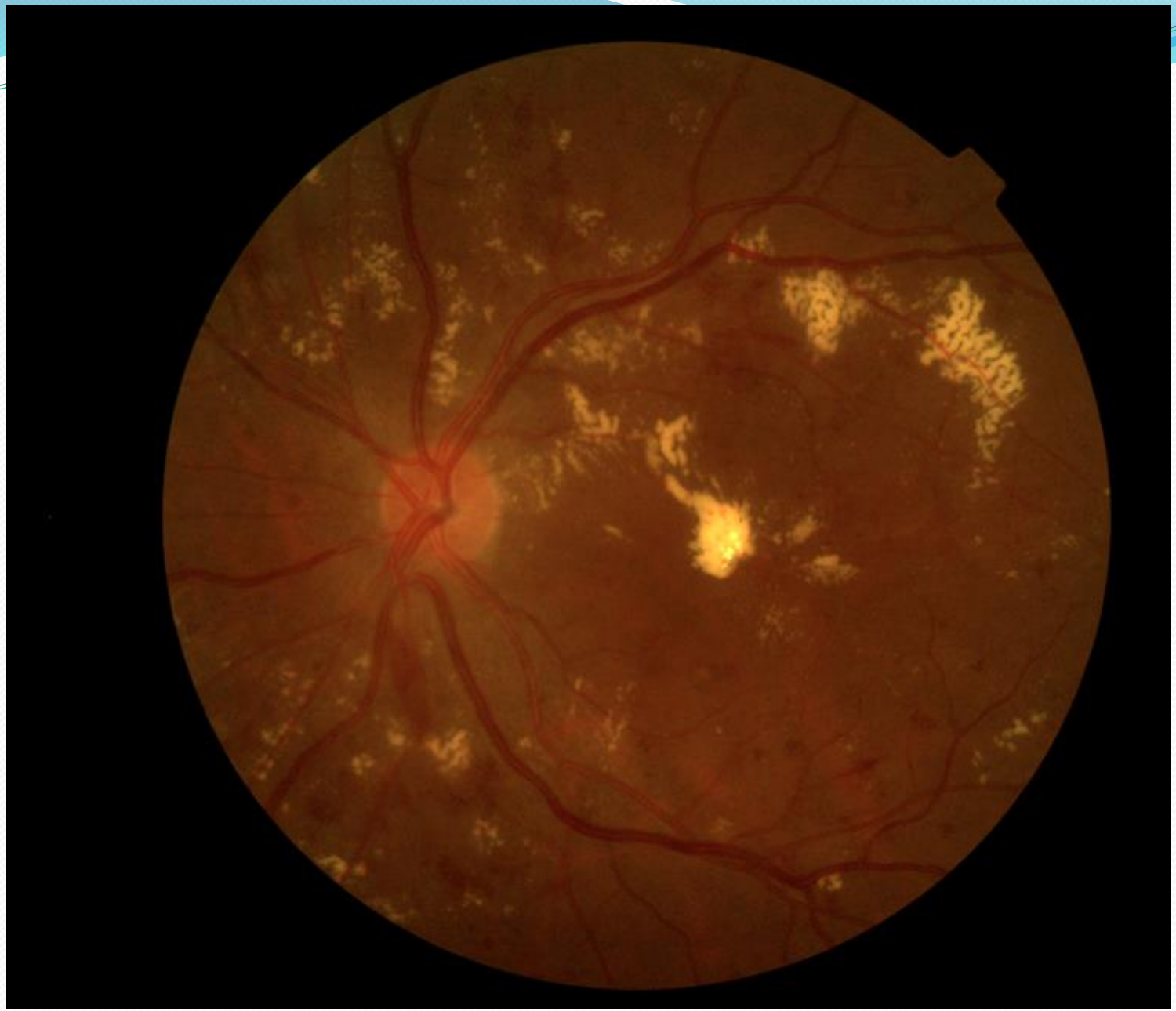
the type of diabetes, duration of the disease, age of patient, use of insulin, uncontrolled diabetes and associated risk factors including hypertension, hyperlipidemia, anemia and nephropathy.

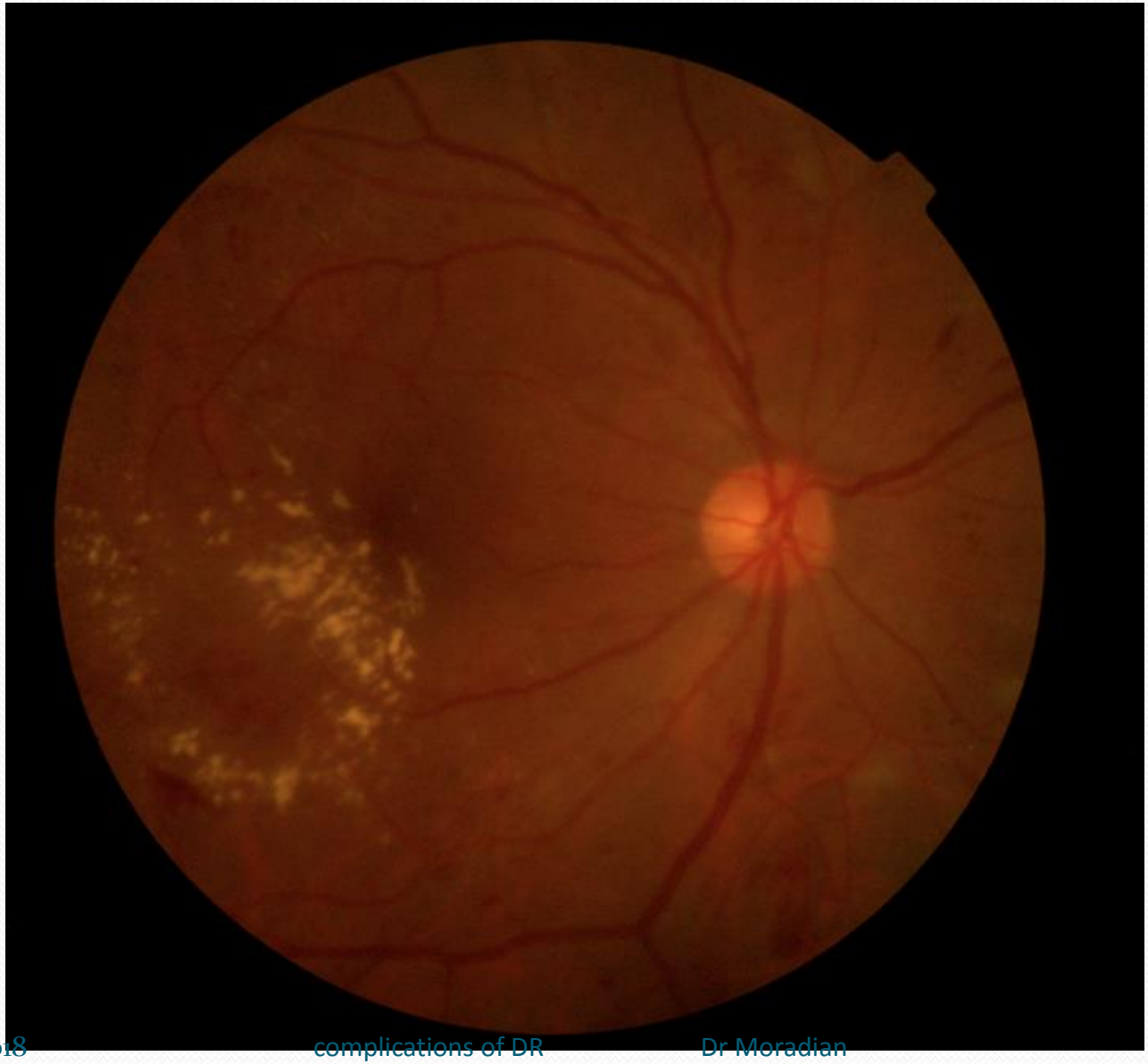
CLASSIFICATION:

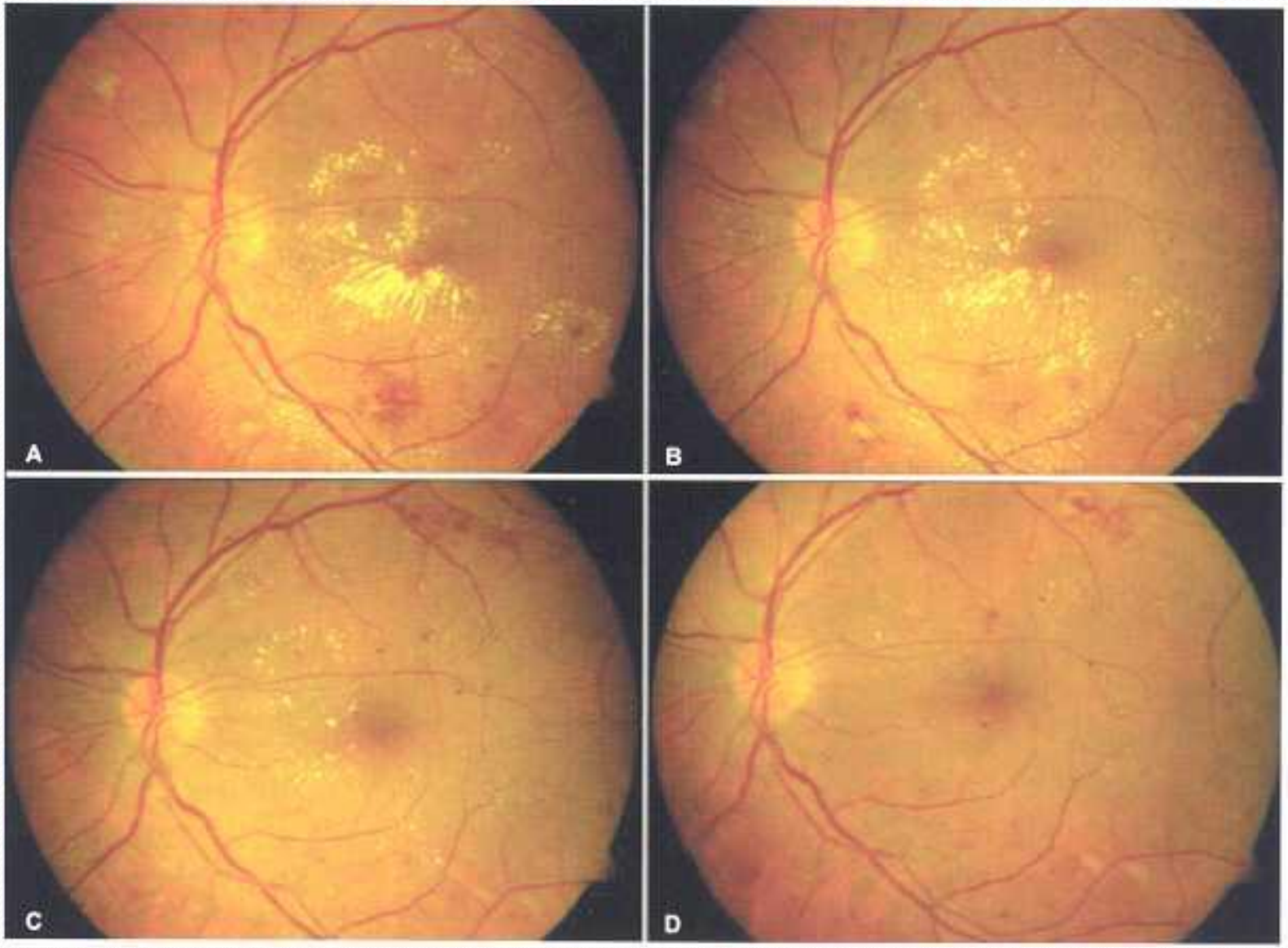
- It is divided into two subtypes i.e. **focal or diffuse**
- **macular edema.**
- **Diffuse edema** is usually not associated with hard

exudates ,cystoid spaces develop more commonly ,has a tendency to be bilaterally symmetrical, may disappear spontaneously at the same time in both eyes even without laser treatment only to reappear later.







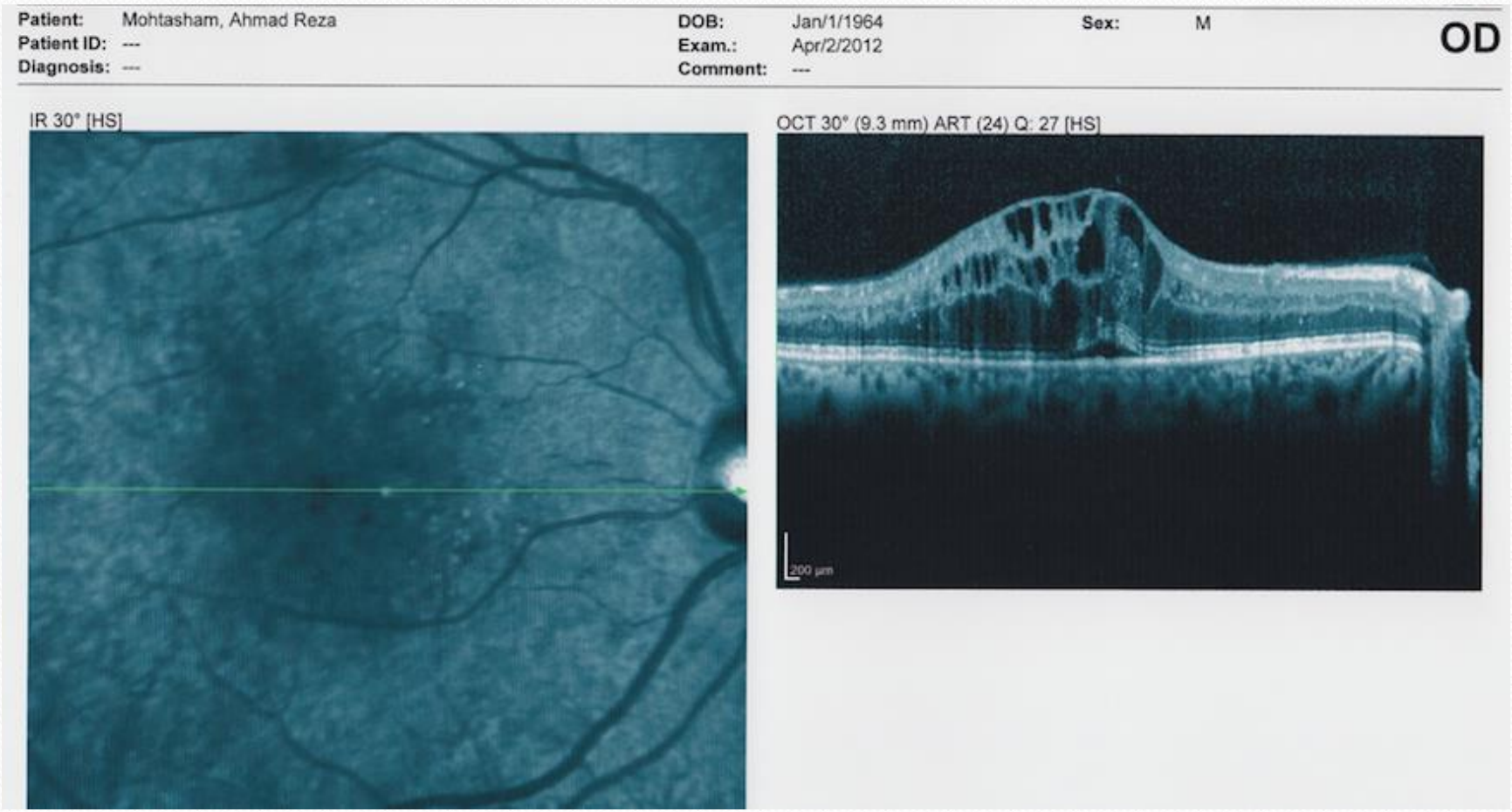

A
B
C
D

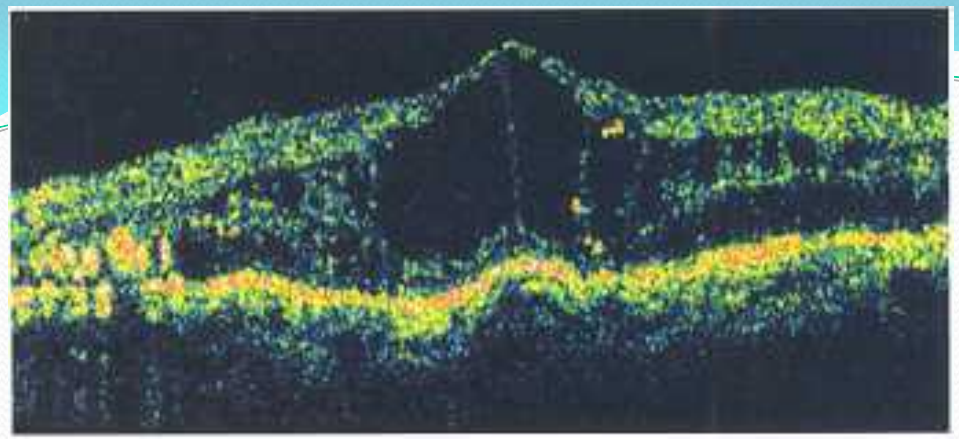
OCT in DME

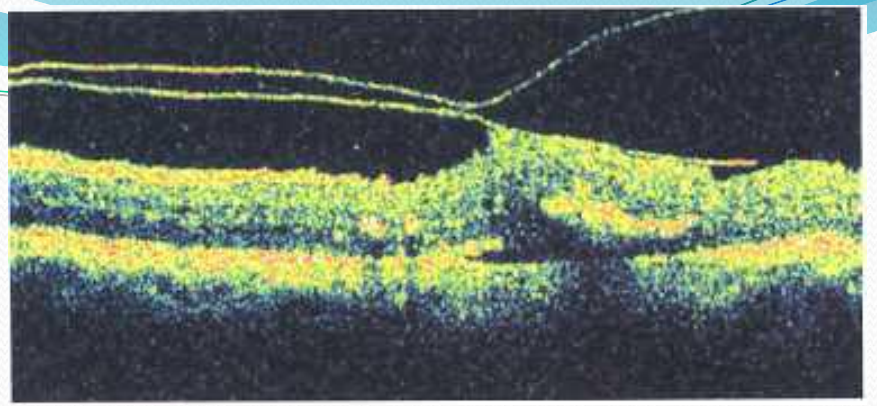
Diabetic macular edema has five distinct patterns on the OCT:

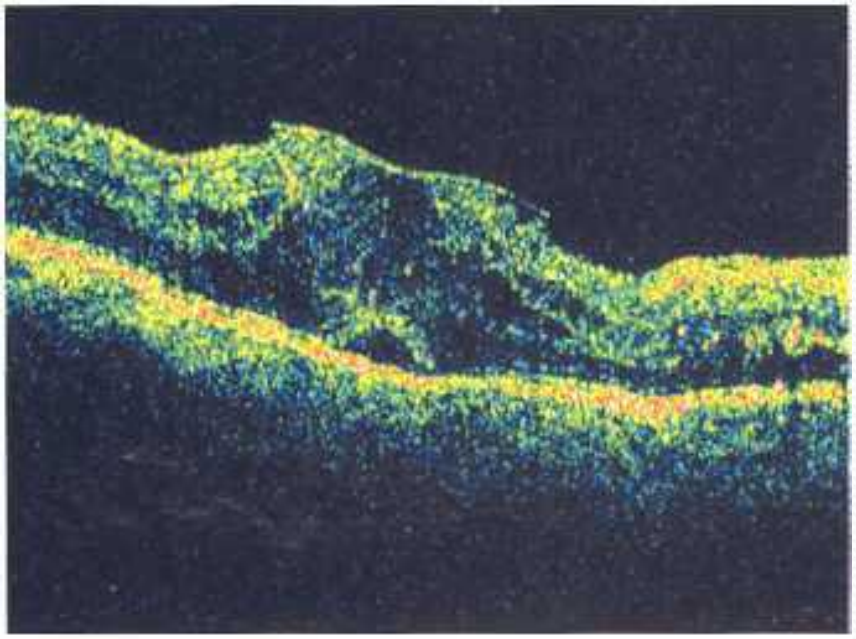
1. Sponge like retina
2. Cystoid macular edema
3. Serous retinal detachment
4. Tractional macular edema
5. Taut PHF

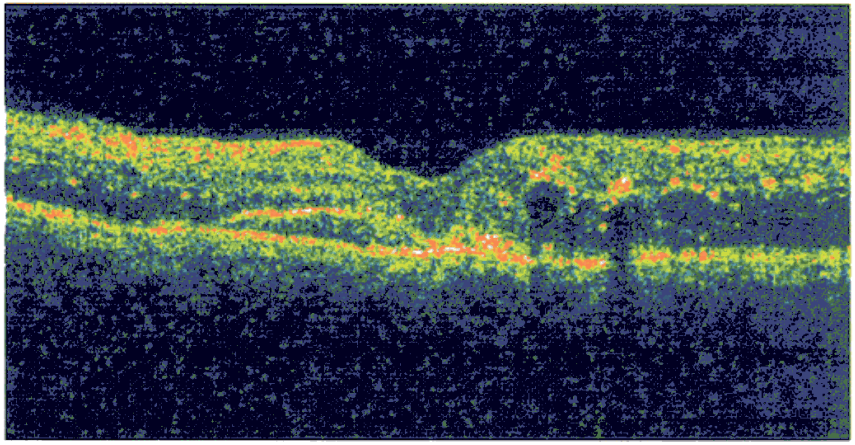

Diagnosis: ---
Comment: ---
IR 30° [HS]
OCT 30° (9.3 mm) ART (17) Q: 25 [HS]
200 µm
200 µm


Patient: Mohtasham, Ahmad Reza
Patient ID: ---
Diagnosis: ---
DOB: Jan/1/1964
Exam.: Apr/2/2012
Comment: ---
Sex: M
OD
IR 30° [HS]
OCT 30° (9.3 mm) ART (24) Q: 27 [HS]
200 µm

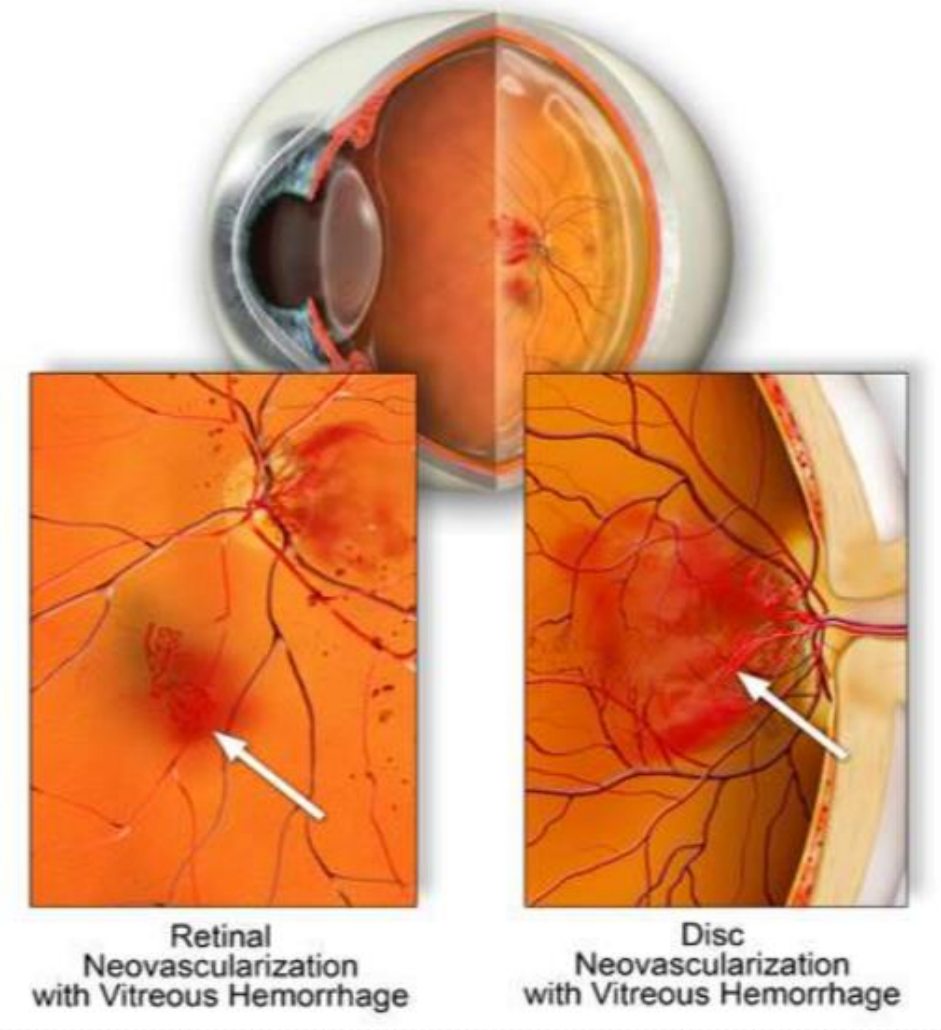




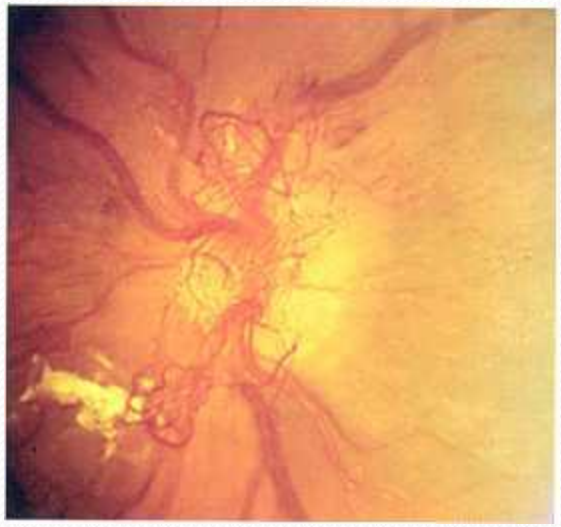


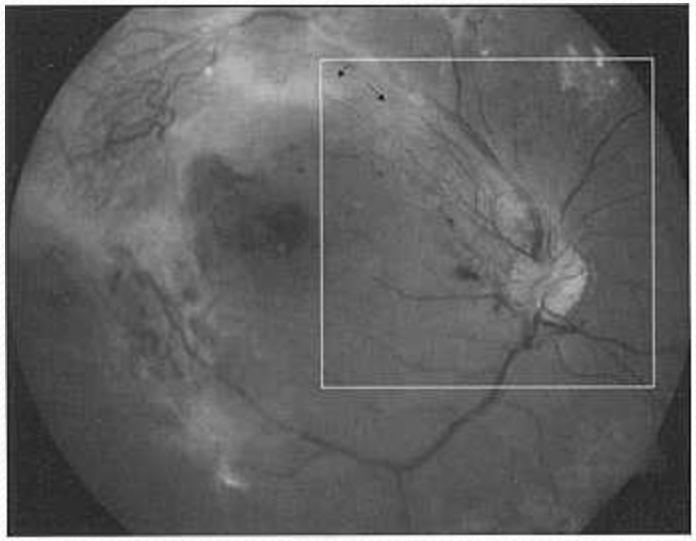


Proliferative Diabetic Retinopathy



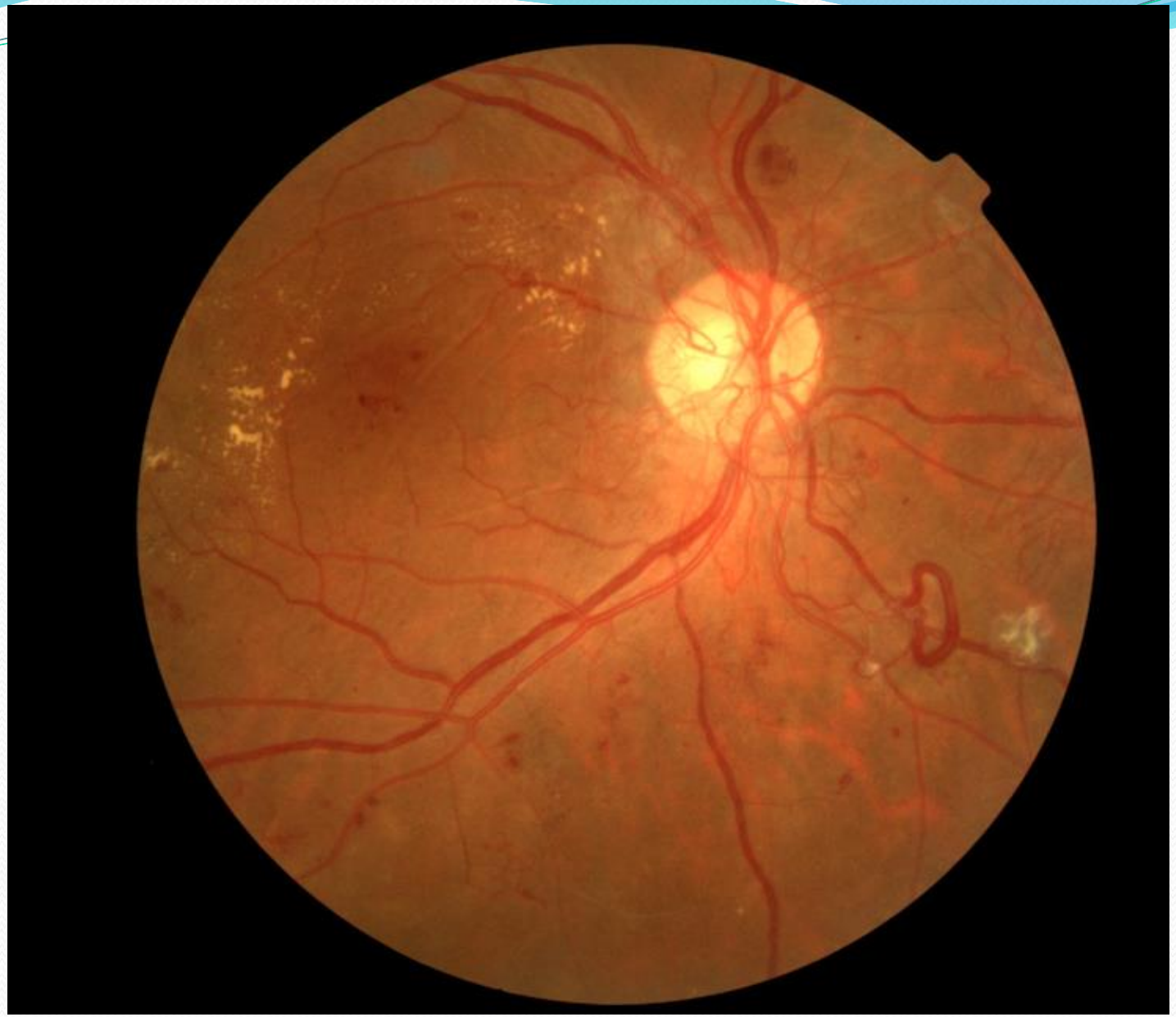
Proliferative Diabetic Retinopathy

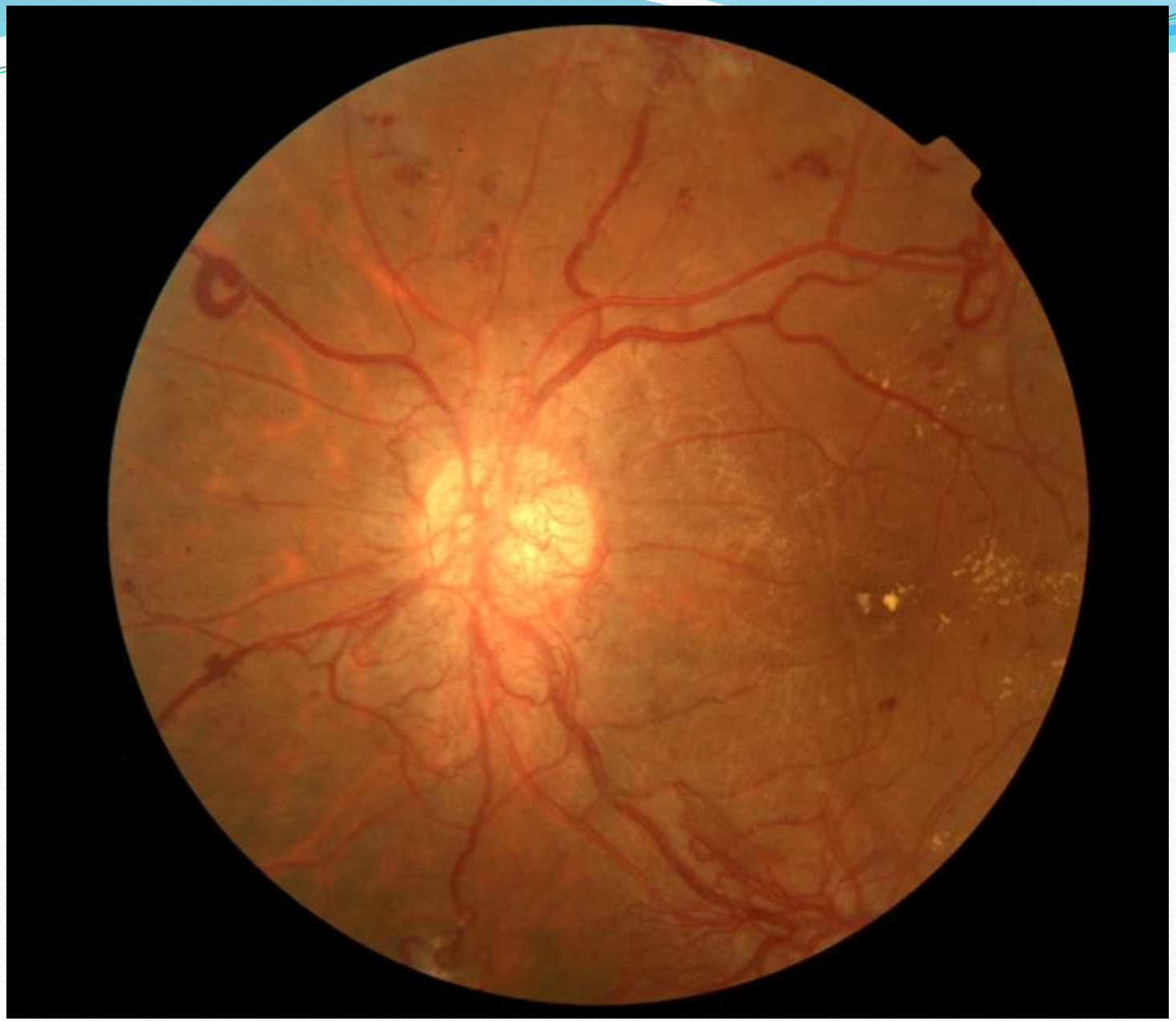


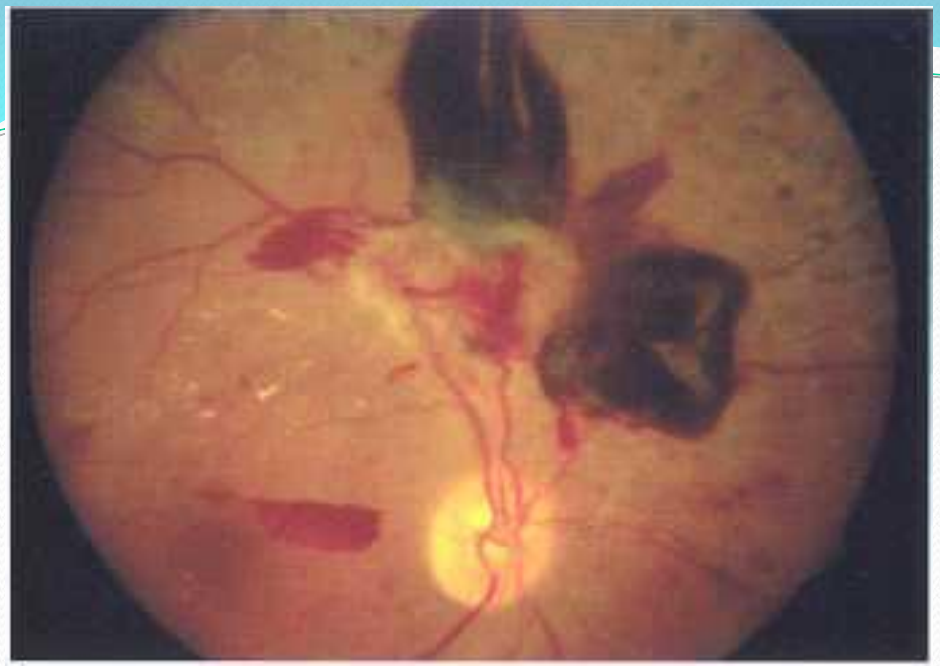


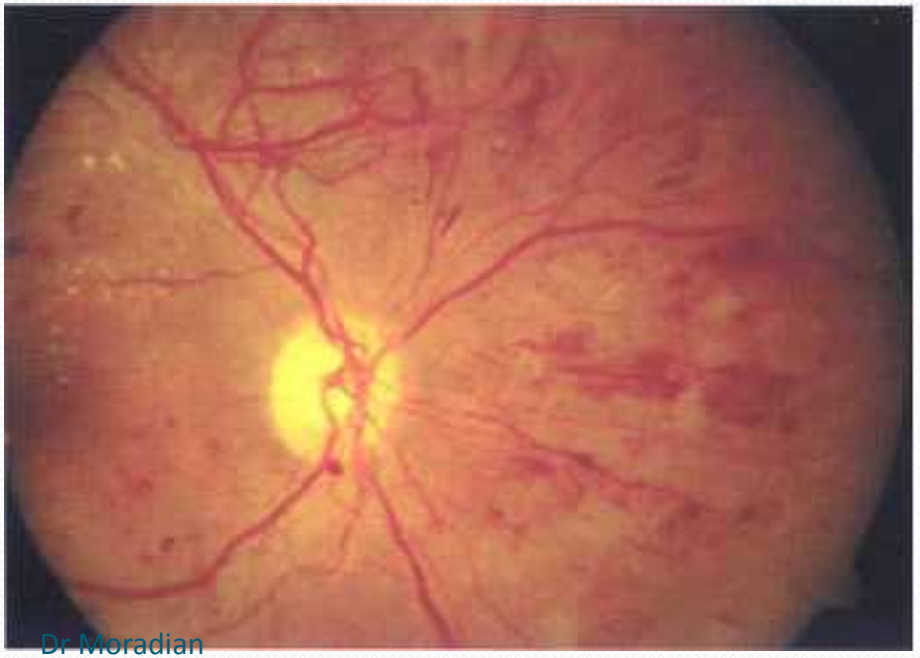
PDR is characterized by the proliferation of new vessels on the optic disc (NVD) or elsewhere (NVE).

NVs usually arise from the retinal veins. **NVD results when more than 1/4th of the retina is ischemic**.

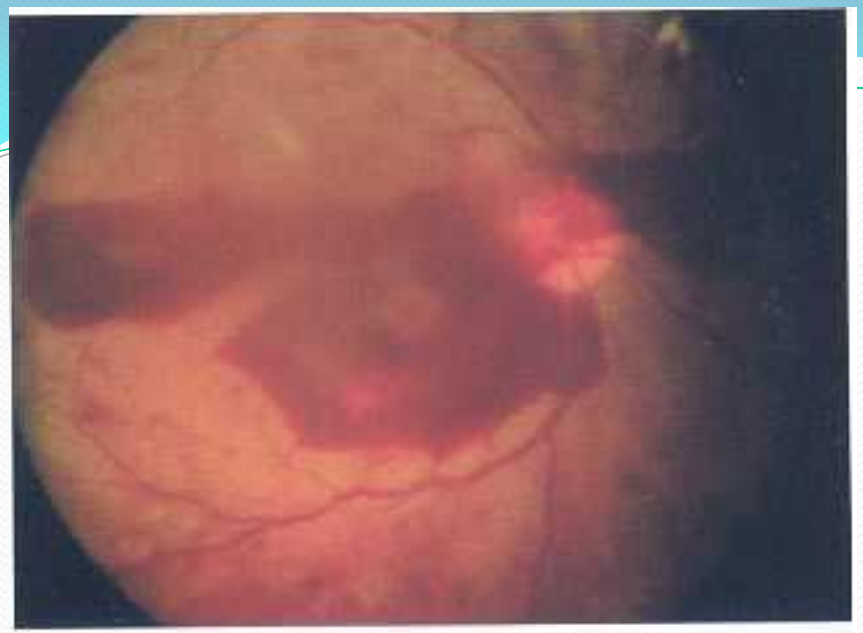


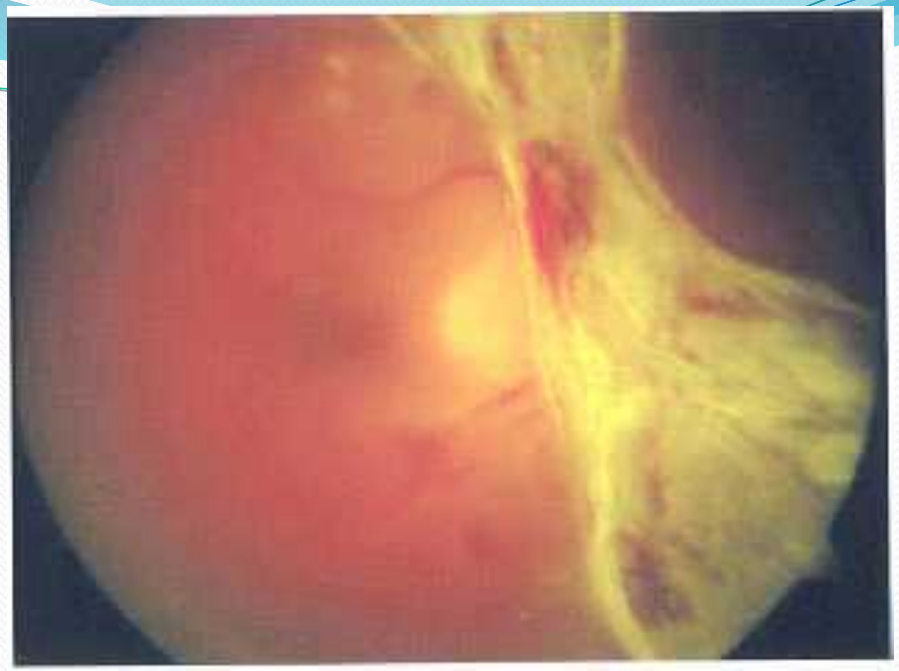


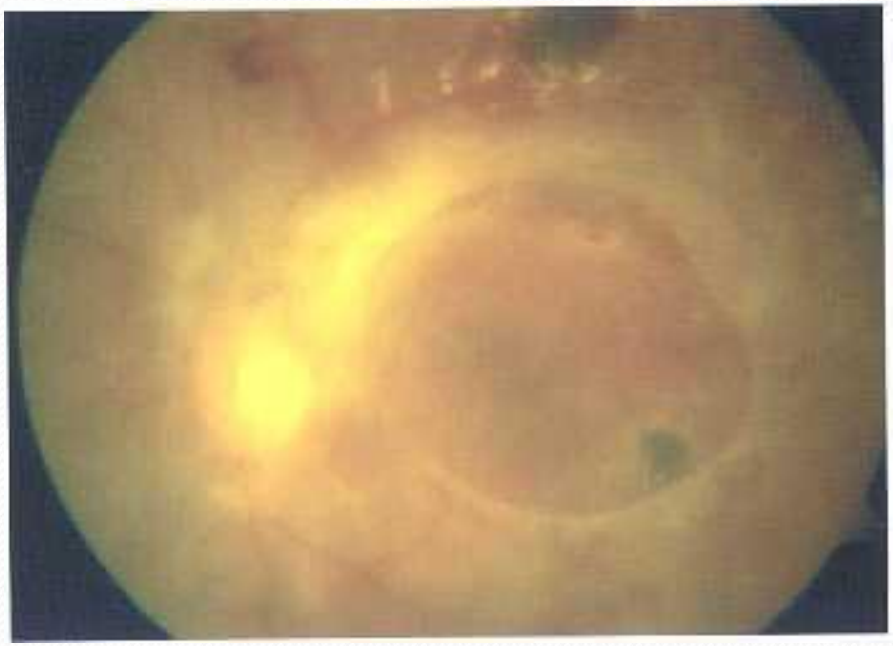


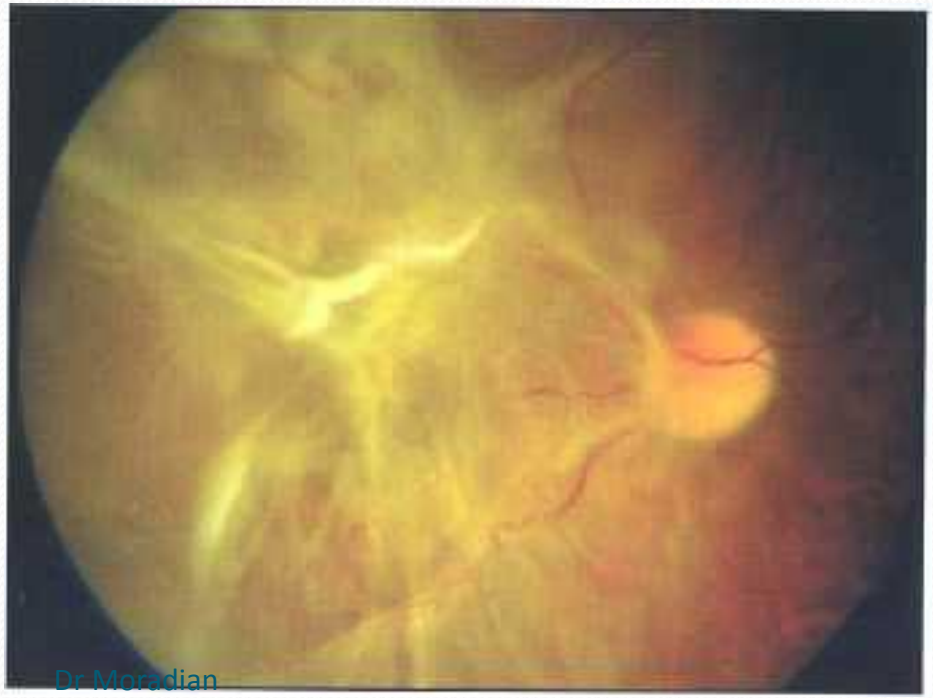


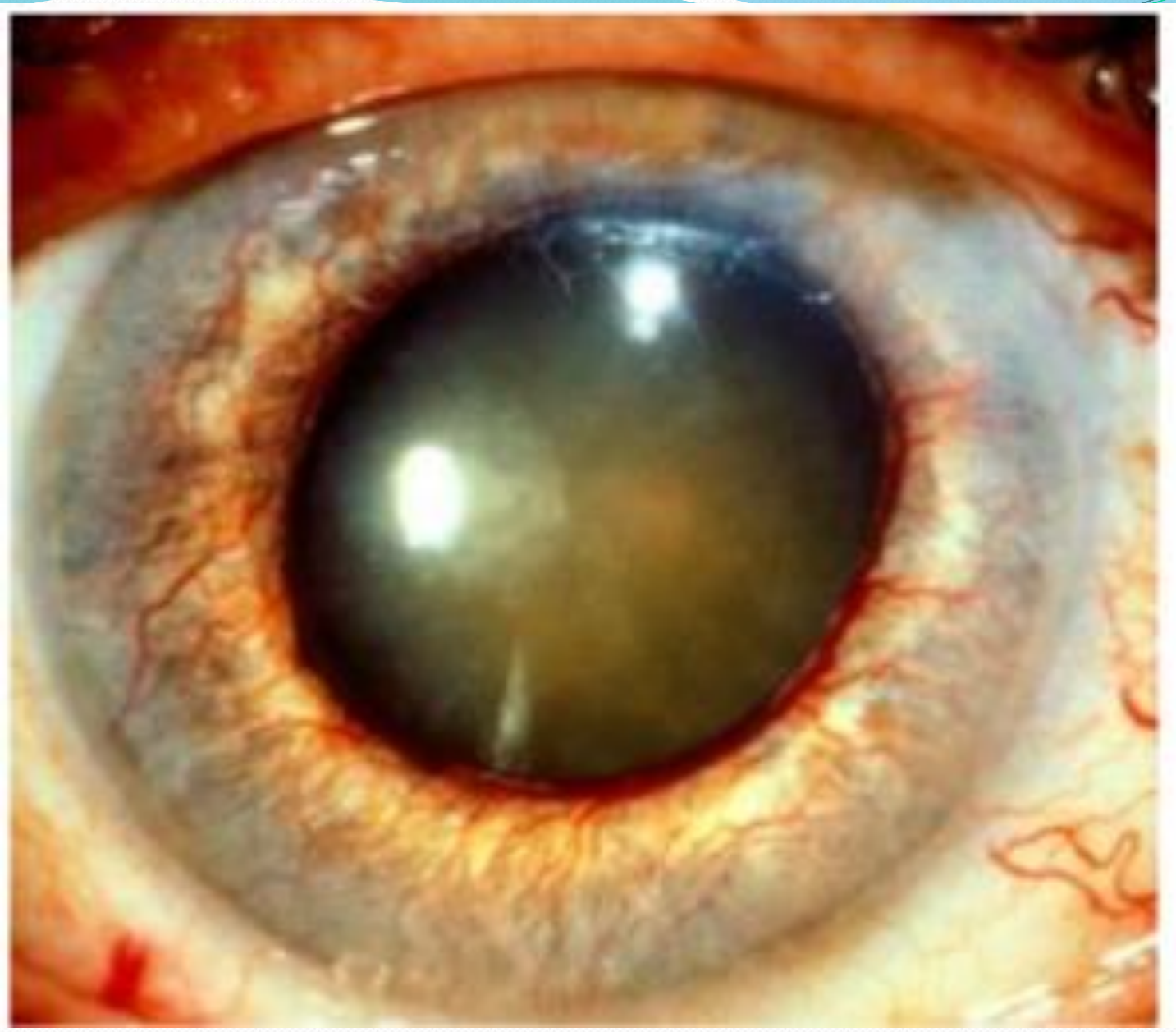
The fibrous tissue is very commonly found along the vascular arcades, and contraction of this fibrous tissue around the arcades results in the development of tabletop traction.

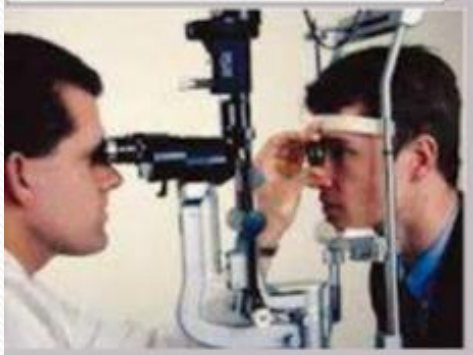








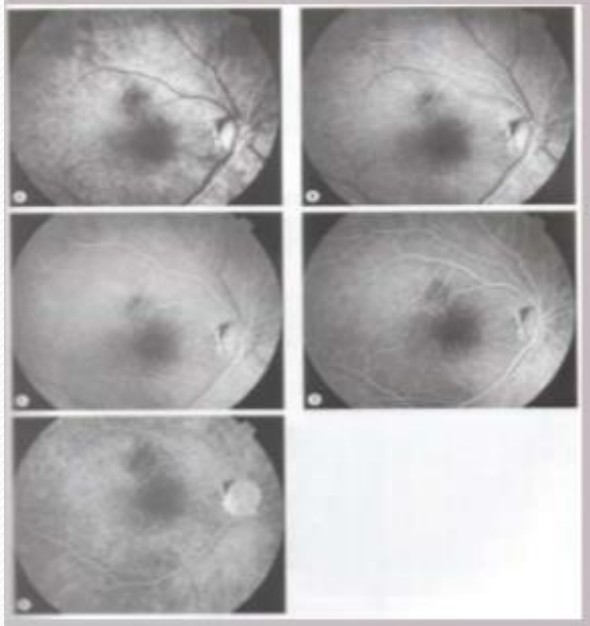




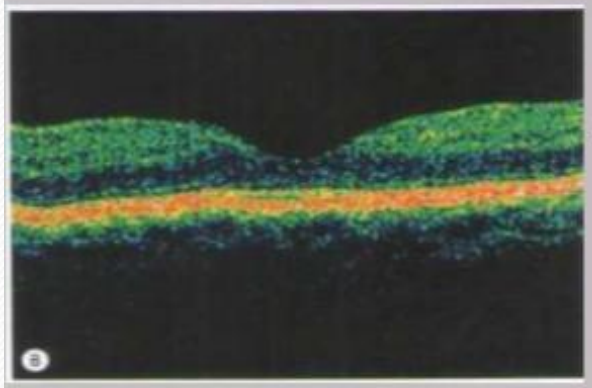
Workup : Examination

- Visual acuity
- Measurement of IOP
- Gonioscopy when indicated (for neovascularization of the iris or increased IOP)
- Slit-lamp biomicroscopy
- Dilated funduscopy including stereoscopic examination of the posterior pole
- Examination of the peripheral retina and vitreous, best performed with indirect ophthalmoscopy or with slit-lamp biomicroscopy, combined with a contact lens

Work up : Ophthalmic Investigations



- Fundus Photography
- Fluorescein Angiography
  - to guide treatment of CSME
  - to identify Ischemic maculopathy
  - IRMA vs NV
  - evaluation in hazy media
  - not a screening modality
  - not a routine investigation



- Optical Coherence Tomography
  - Retinal thickening
  - assessment & Monitoring of edema
  - vitreo macular traction
- USG – B scan

Treatment

Once sight-threatening DME or HRPDR has been detected, the treatment options recommended are **systemic control, laser photocoagulation, pharmacological agents** such as steroids, Protein Kinase C inhibitors, Anti VEGF agents including Macugen, Avastin, Lucentis and Aflibercept **and vitrectomy** .

DCCT and UKPDS have conclusively proven that good glycemic control can prevent or retard the progression of diabetic microangiopathic complications.

However, prevention of macroangiopathic complications could not be achieved.

- Therefore, the concept of **comprehensive diabetic control** has emerged including:
- Body mass index (BMI) < 25 kg/m^2, waistline 90 cm
- in men and 80 cm in women, HbA1c < 7 percent, BP
- <130/80 mm Hg and <120/75 mm Hg with diabetic
- renal disease, LDL-cholesterol < 100 mg/dl, urinary
- albumin<30 mg/24 hours.

Recommended target values (ADA 2005. Standards of Medical care in diabetes. Diabetes Care 2006;

	Target values
HbA_{1C}	<7.0%
FBS	90–130 mg/dl (5.0–7.2 mmol/l)
PPBS	<180 mg/dl (<10.0 mmol/l)
Blood Pressure Systolic/Diastolic	<130/80 mmHg
Triglycerides	<150 mg/dl (<1.7 mmol/l)
Low-density Lipoproteins	<100 mg/dl (<2.6 mmol/l)
High-density Lipoproteins	>40 mg/dl (>1.1 mmol/l)
Albuminuria (μg/mg creatinine)	
Normal Microalbuminuria	<30

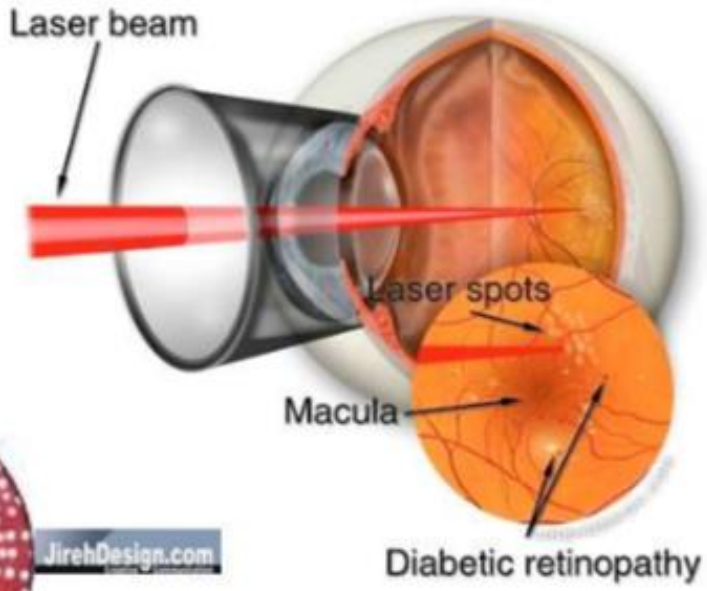
Laser therapy for DR

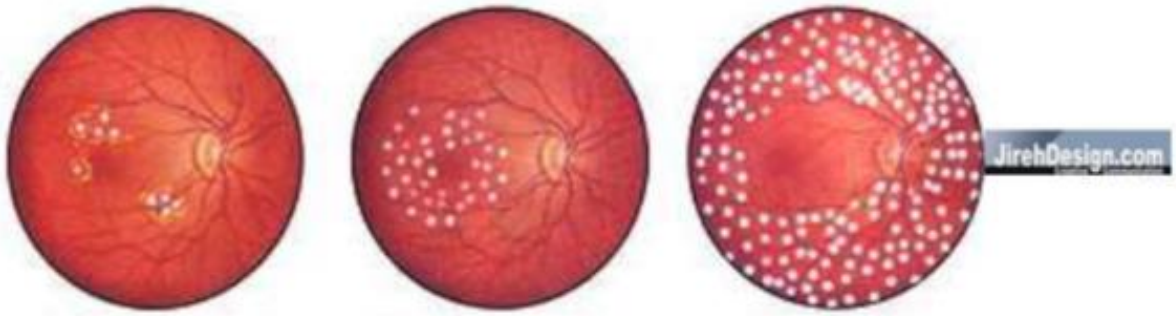
In two situations laser therapy initiated for the treatment of DR :1-CSME, 2- HRPDR

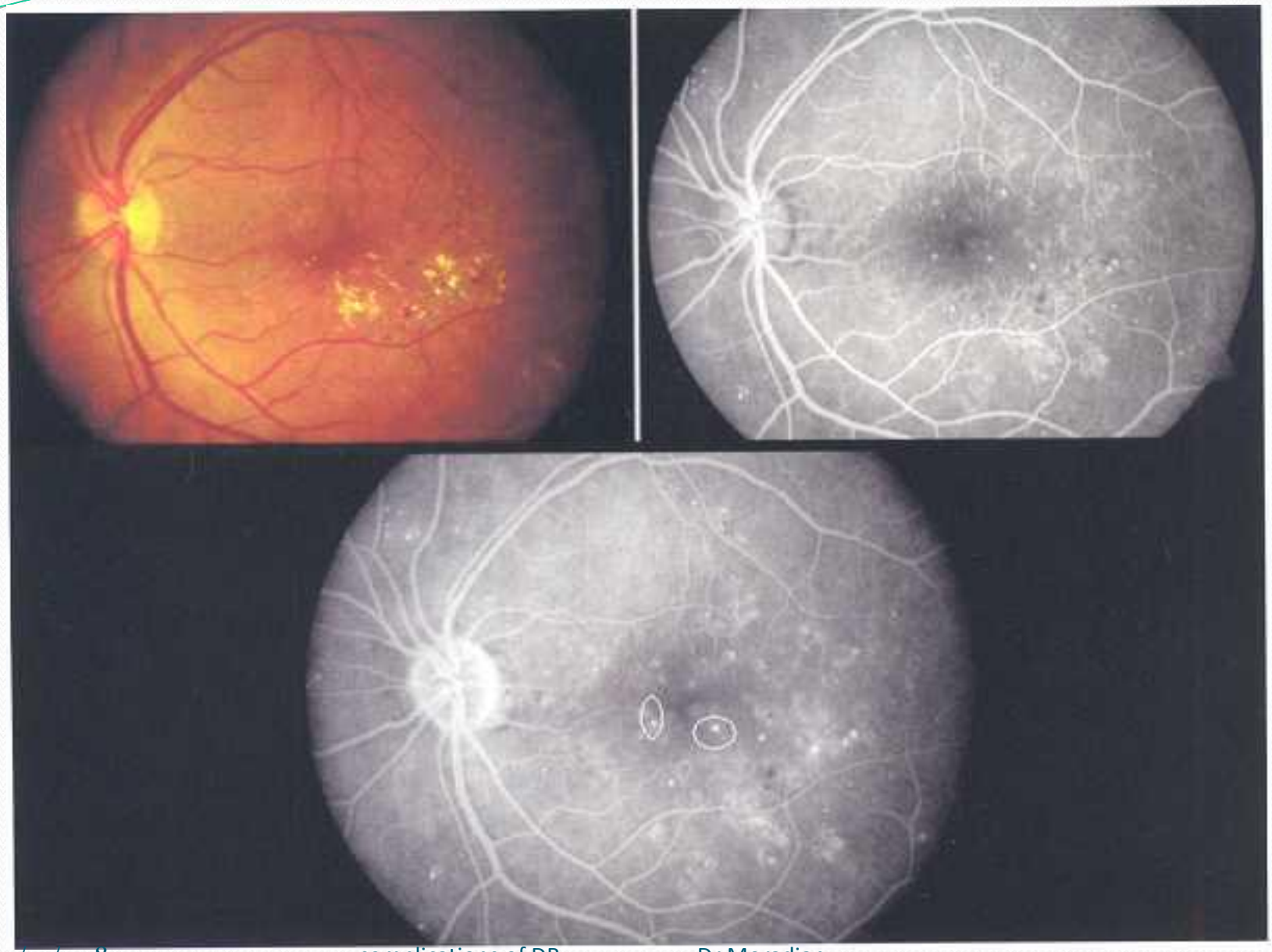
1- In CSME, MPC is used in 2 manner, focal and grid MPC

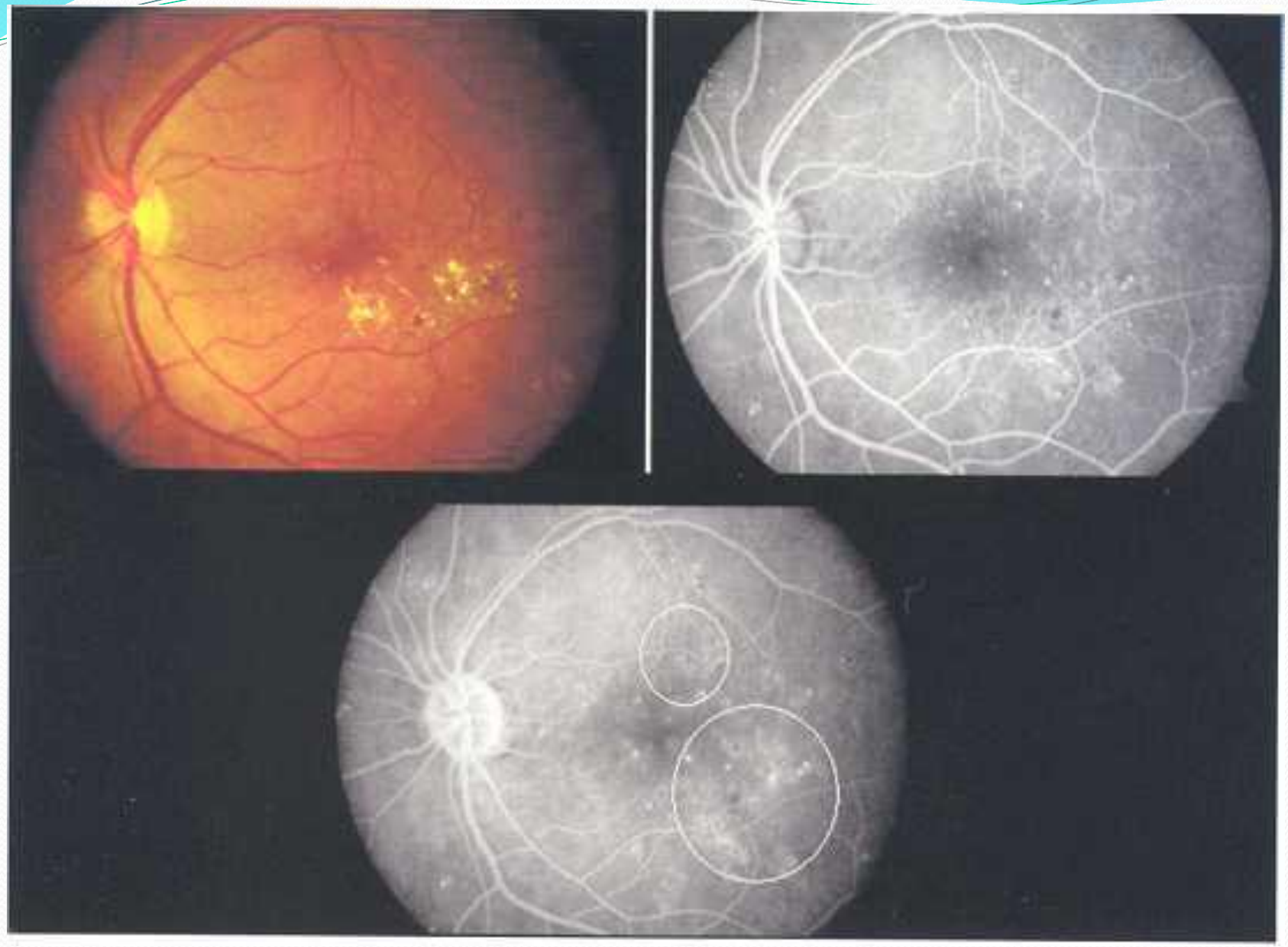
2- In HRPDR PRP is used.

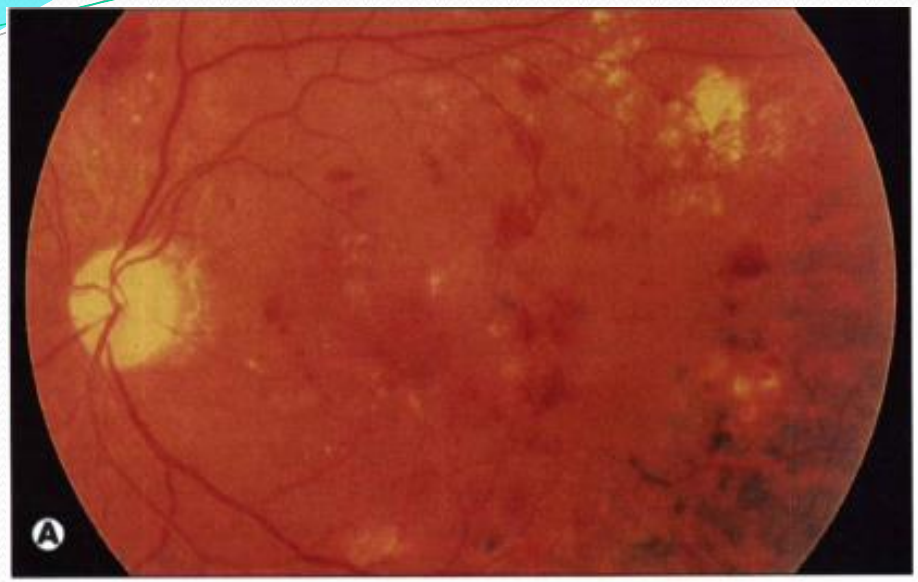
* Focal or Grid
  * CSME in both NPDR and PDR
* Panretinal (PRP)
  * PDR







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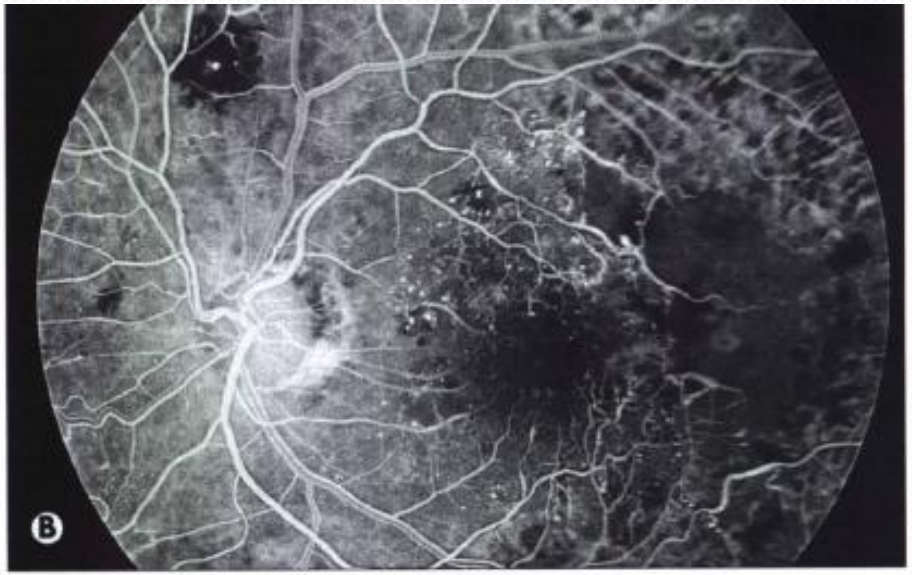
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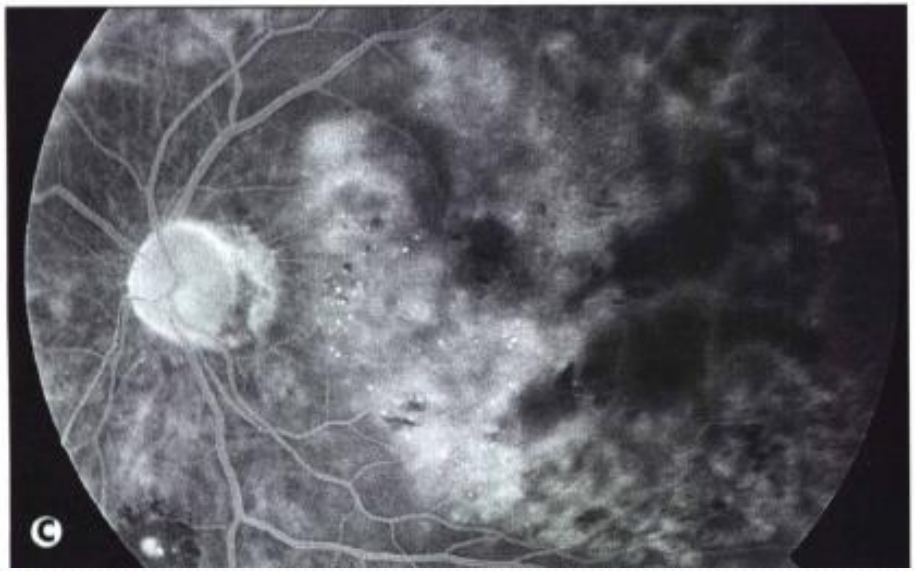
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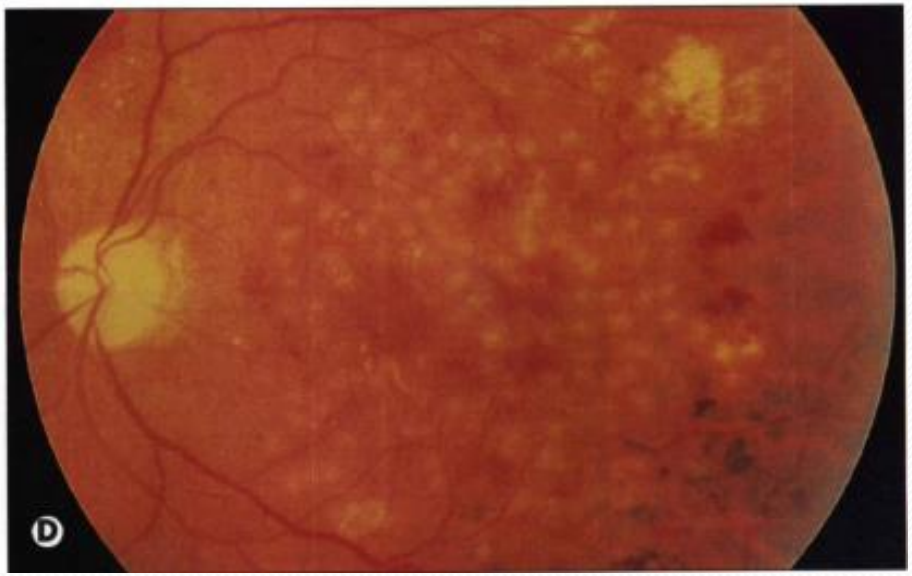
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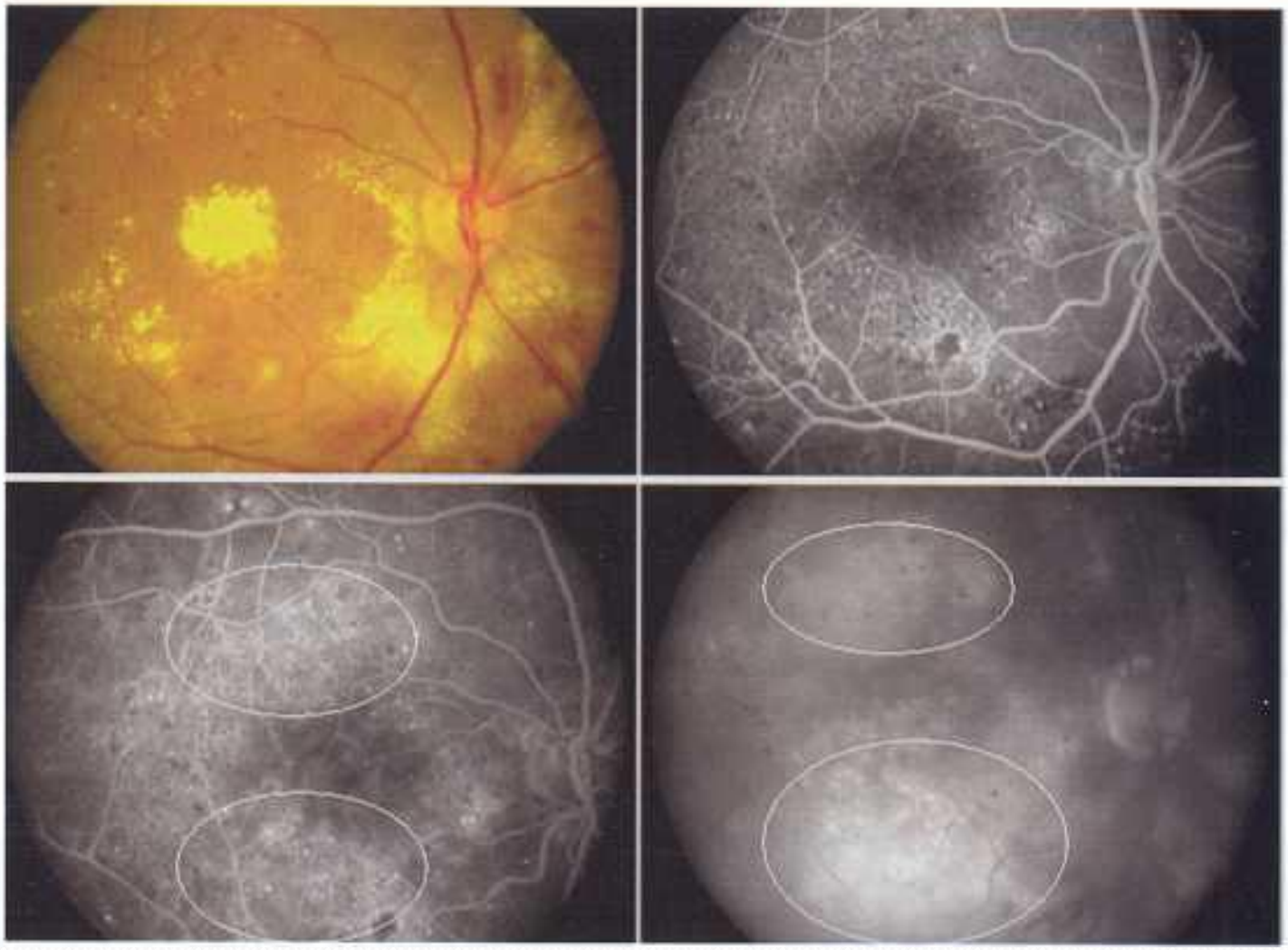
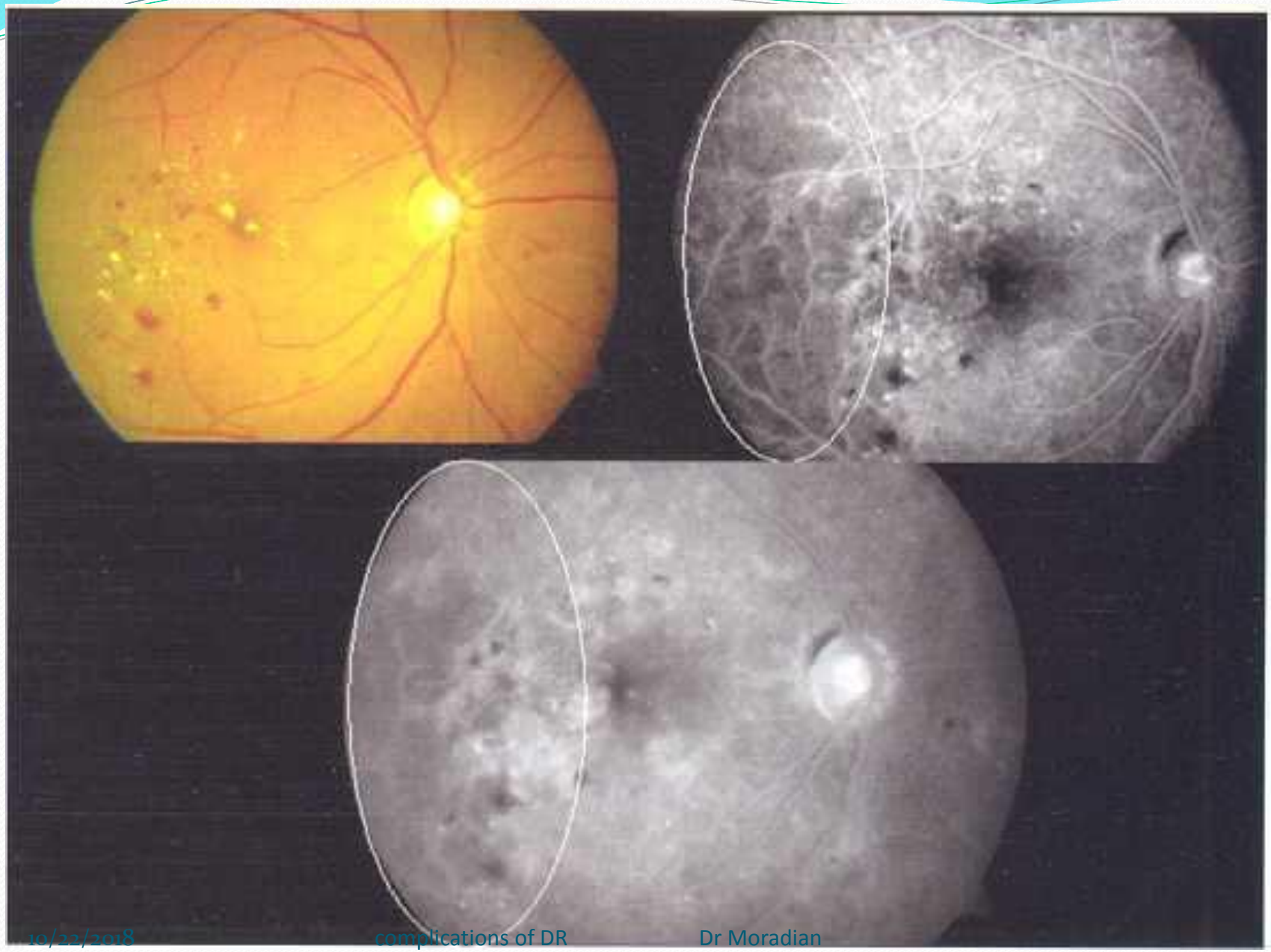
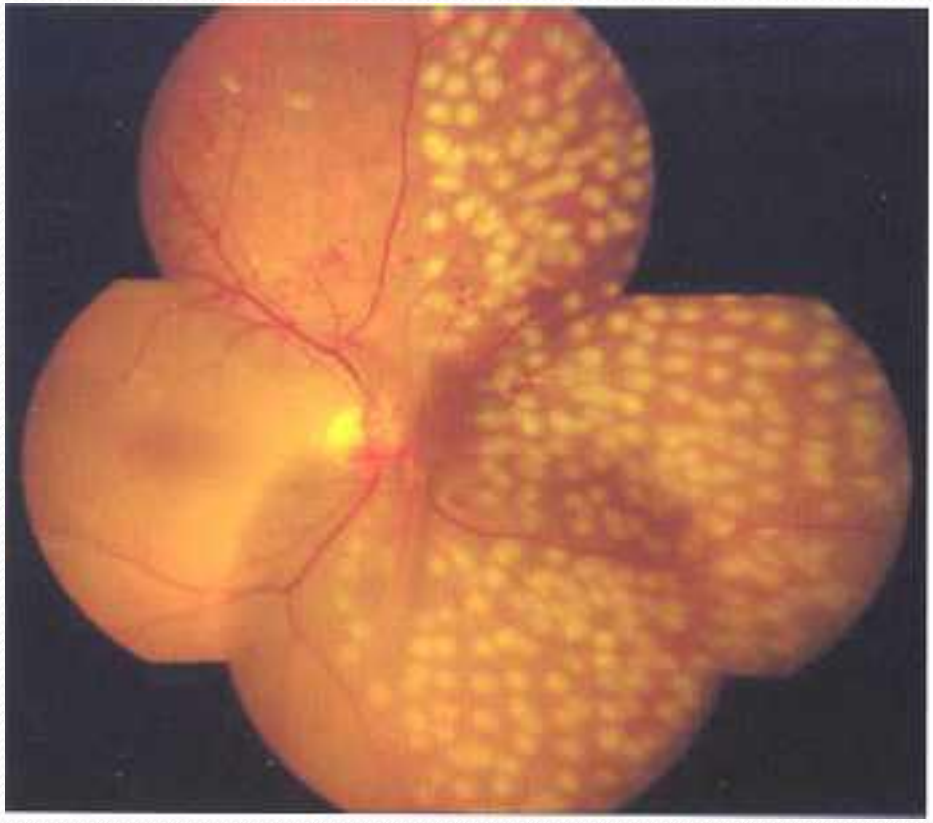
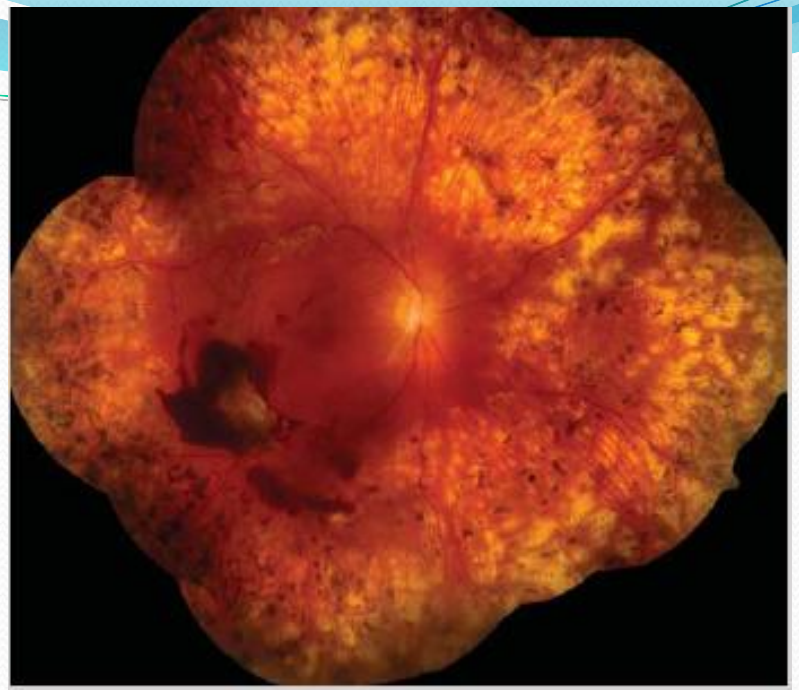
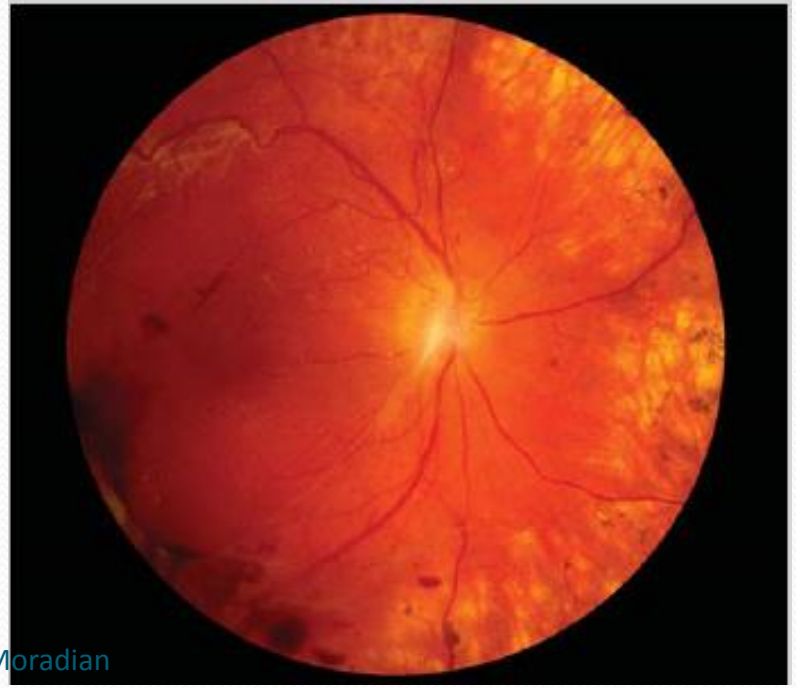
Diabetic Retinopathy











PHARMACOTHERAPY

1- Aldose Reductase Inhibitors(sorbinil, ponalrestat, and tolrestat)

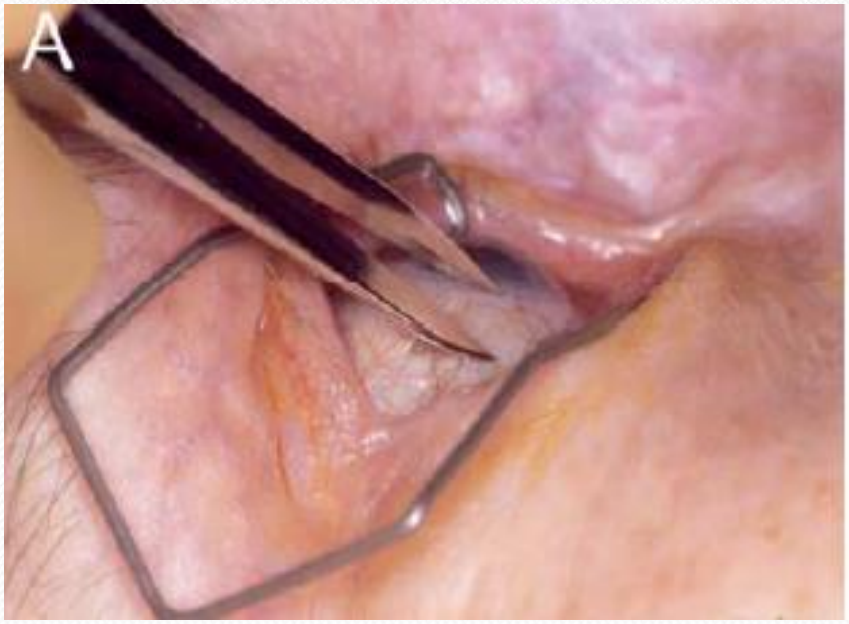
2-AGE Inhibitors (aminoguanidine)

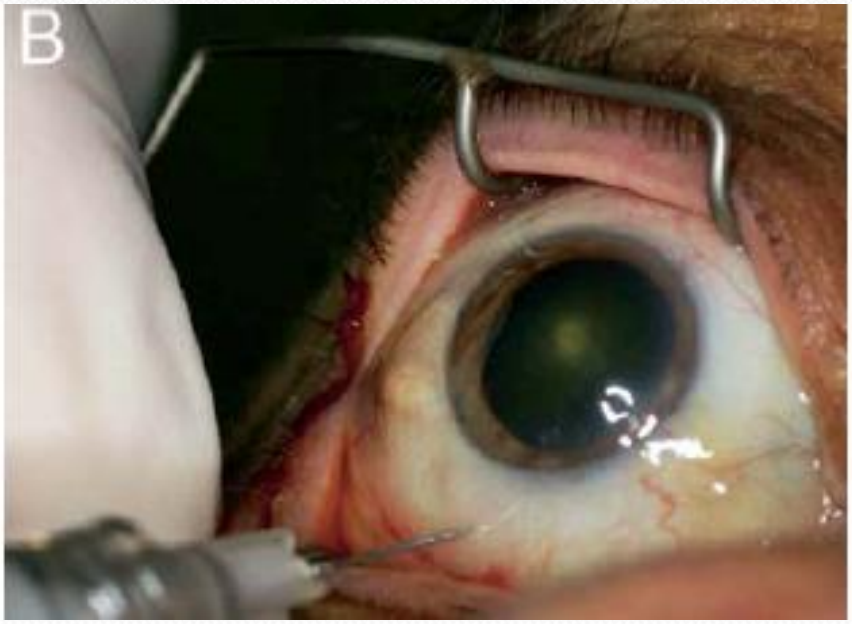
3-PKC-B Inhibitors (Ruboxistaurin)

4- Antioxidant Compounds

5-Anti-angiogenic Agents

Drugs that inhibit the bioactivity of VEGF represent a new paradigm in the treatment of retinovascular disease and macular edema.





Pegaptanib **(Macugen; Eyetech Pharmaceuticals, Inc., New York, NY), an anti-VEGF aptamer, and was the first anti-VEGF drug to be approved for the treatment of neovascular AMD.**

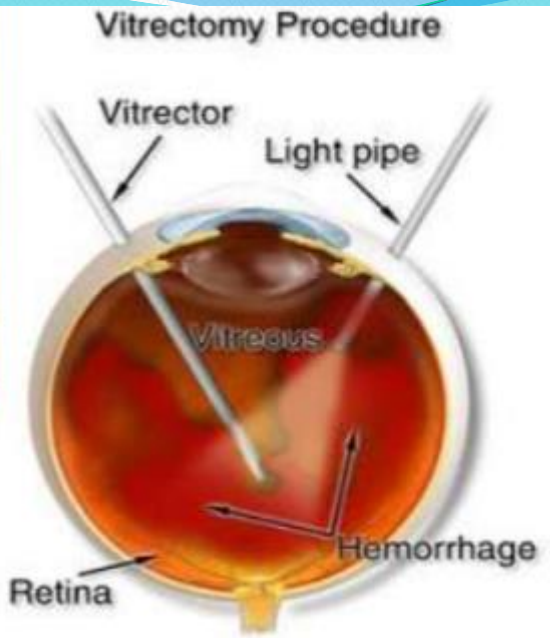
Ranibizumab **(Lucentis, Genentech Inc.) is a smaller 48-kD Fab fragment derived from the same murine antibody as bevacizumab.**

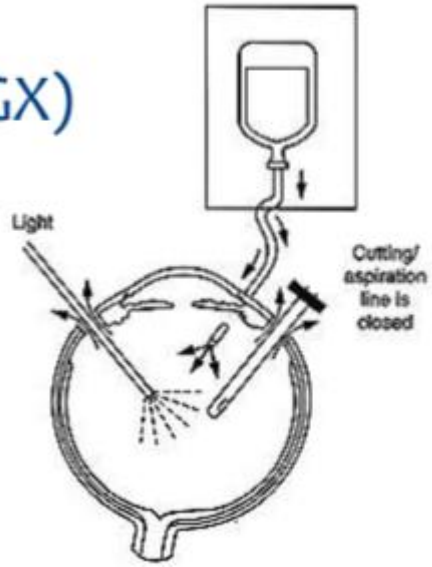
Bevacizumab **(Avastin; Genentech, Inc., South San Francisco, CA) is a full-length humanized murine monoclonal antibody against the VEGF molecule. It is approved by the FDA for the treatment of metastatic colorectal cancer and binds all isoforms of VEGF (VEGF110, VEGF121, VEGF145, VEGF165, VEGF183, VEGF189, and VEGF206).**

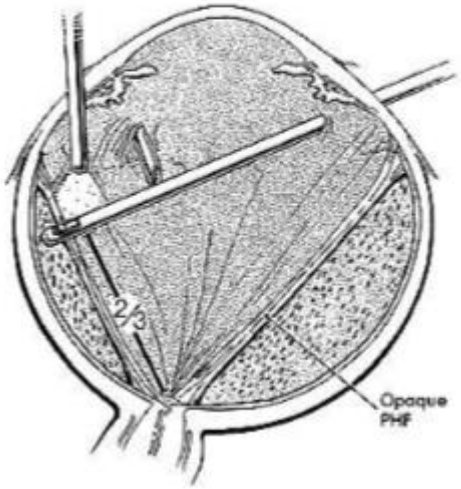
Aflibercept **(Eylea)** is a recombinant fusion protein invented by Regeneron pharmaceuticals, approved in the US and Europe for the treatment of wet AMD under the trade name **Eylea**, and for metastatic colorectal CA as **Zaltrap.**

Vitreoretinal Surgery

* Pars plana vitrectomy (PPV)
* Membrane peeling (MP)
* Endolaser (EL)
* Fluid gas exchange (FGX)
  * SF_6
  * C_3F_8







Management Recommendations for Patients with Diabetes

Severity of Retinopathy	Presence of CSME*	Follow-up (Months)	Panretinal Photocoagulation (Scatter) Laser	Fluorescein Angiography	Focal and/or Laser†
Normal or minimal NPDR	No	12	No	No	No
Mild to moderate NPDR	No	6-12	No	No	No
	Yes	2-4	No	Usually	Usually*^
Severe NPDR	No	2-4	Sometimes‡	Rarely	No
	Yes	2-4	Sometimes‡	Usually	Usually**
Non-high-risk PDR	No	2-4	Sometimes‡	Rarely	No
	Yes	2-4	Sometimes‡	Usually	Usually^
High-risk PDR	No	2-4	Usually	Rarely	No
	Yes	2-4	Usually	Usually	Usually**
Inactive/involuted PDR	No	6-12	No	No	Usually
	Yes	2-4	No	Usually	Usually

INTRAVITREAL BEVACIZUMAB (AVASTIN) INJECTION ALONE OR COMBINED WITH TRIAMCINOLONE VERSUS MACULAR PHOTOCOAGULATION AS PRIMARY TREATMENT OF DIABETIC MACULAR EDEMA

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BIJAN BIJANZADEH, MD,*† MEHDI YASERI, PHD,*
HAMID AHMADIEH, MD,*† MOHAMMAD H. DEHGHAN, MD,*†
MOHSEN AZARMINA, MD,*† SIAMAK MORADIAN, MD,*†
HOMA TABATABAEI, MD,*† GHOLAM A. PEYMAN, MD‡

Purpose: To report the efficacy of a single intravitreal bevacizumab injection alone or in combination with intravitreal triamcinolone acetonide versus macular laser photocoagulation (MPC) as primary treatment of diabetic macular edema (DME).

Methods: In this randomized, three-arm clinical trial, 103 eyes of 97 patients with clinically significant DME and no previous treatment were enrolled. The eyes were randomly assigned to one of three study arms: the intravitreal bevacizumab (IVB) group, patients who received 1.25 mg of intravitreal bevacizumab (37 eyes); the IVB/IVT group, patients who received 1.25 mg of intravitreal bevacizumab and 2 mg of intravitreal triamcinolone (33 eyes); and the MPC group, patients who underwent focal or modified grid laser (33 eyes). Primary outcome measure was change in visual acuity.

Results: Visual acuity changes ± SD at 12 weeks were −0.22 ± 0.23, −0.13 ± 0.31, and + 0.06 ± 0.31 logarithm of the minimal angle of resolution in the IVB, IVB/IVT, and MPC groups, respectively. The marginal regression model based on generalized estimating equation analysis demonstrated that the visual acuity changes in the groups were statistically significant at both 6 weeks ($P < 0.0001$) and 12 weeks ($P = 0.024$). The significant treatment effect was demonstrated at both 6 weeks and 12 weeks in the IVB group and only at 6 weeks in the IVB/IVT group. Significant central macular thickness (CMT) reduction was observed in eyes in the IVB and IVB/IVT groups only up to 6 weeks; however, CMT changes were not significant in the groups.

Conclusion: Up to 12 weeks, intravitreal bevacizumab treatment of patients with DME yielded better visual outcome than laser photocoagulation, although it was not associated with a significant decrease in CMT. No further beneficial effect of intravitreal triamcinolone could be demonstrated. Further clinical trials with longer follow-up are required to evaluate the long-term visual outcomes and complication profiles after primary treatment with such medications.

RETINA 27:1167–1195, 2007

Randomized Trial of Intravitreal Bevacizumab Alone or Combined with Triamcinolone versus Macular Photocoagulation in Diabetic Macular Edema

Report 2

Masoud Soheilian, MD,[1,2] Alireza Ramezani, MD,[1,2] Arash Obudi, MD,[1,2] Bijan Bijanzadeh, MD,[1,2] Masoud Salehipour, MD,[1,2] Mehdi Yaseri, PhD,[3] Hamid Ahmadieh, MD,[1,2] Mohammad H. Dehghan, MD,[1,2] Mohsen Azarmina, MD,[1,2] Siamak Moradian, MD,[1,2] Gholam A. Peyman, MD[4]

Purpose: To compare the results of intravitreal bevacizumab (IVB) injection alone or in combination with intravitreal triamcinolone acetonide (IVT) versus macular laser photocoagulation (MPC) as a primary treatment of diabetic macular edema (DME).

Design: Randomized 3-arm clinical trial.

Participants: A total of 150 eyes of 129 patients with clinically significant DME and no previous treatment.

Methods: The eyes were randomly assigned to 1 of the 3 study arms: the IVB group, patients who received 1.25 mg IVB (50 eyes); the IVB/IVT group, patients who received 1.25 mg of IVB and 2 mg of IVT (50 eyes); and the MPC group, patients who underwent focal or modified grid laser (50 eyes). Retreatment was performed at 12-week intervals whenever indicated.

Main Outcome Measures: Change in best-corrected visual acuity (VA) at week 24.

Results: VA changes among the groups were statistically significant at 6 ($P<0.001$) and 24 ($P = 0.012$) weeks. The significant treatment effect was demonstrated in the IVB group at all follow-up visits and in the IVB/IVT group at 6 and 12 weeks. VA changes ± standard deviation at 36 weeks were -0.28 ± 0.25, -0.04 ± 0.33, and $+0.01\pm0.27$ logarithm of minimum angle of resolution in the IVB, IVB/IVT, and MPC groups, respectively ($P = 0.053$). Significant central macular thickness (CMT) reduction was observed in all groups only up to 6 weeks; however, CMT changes were not significant among the groups in all visits. Overall, retreatment was required for 27 eyes up to 36 weeks (14 in the IVB group, 10 in the IVB/IVT group, and 3 in the MPC group). In the IVB group, in which a greater VA improvement was observed, only 1 injection was required in 72% of the cases. VA improvement >2 Snellen lines at 36 weeks was detected in 37%, 25%, and 14.8% of patients in the IVB, IVB/IVT, and MPC groups, respectively.

Conclusions: Intravitreal bevacizumab injection in patients with DME yielded a better visual outcome at 24 weeks compared with macular photocoagulation. A change in CMT beyond the 6-week time point that corresponded to the vision change was not detected. No adjunctive effect of IVT was demonstrated.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2009;xx:xxx*

Graefes Arch Clin Exp Ophthalmol (2008) 246:1699–1705
DOI 10.1007/s00417-008-0914-4

RETINAL DISORDERS

Intravitreal bevacizumab in active progressive proliferative diabetic retinopathy

Siamak Moradian · Hamid Ahmadieh · Mohsen Malihi · Masoud Soheilian · Mohammad Hossein Dehghan · Mohsen Azarmina

Received: 9 April 2008 / Revised: 29 June 2008 / Accepted: 14 July 2008 / Published online: 12 August 2008

Abstract
Background Vitreous concentration of vascular endothelial growth factor (VEGF) rises significantly during proliferative diabetic retinopathy (PDR). Bevacizumab (Avastin) is a humanized monoclonal antibody to VEGF. Intravitreal administration of bevacizumab (IVB) has recently been shown to be effective in some ocular neovascularizations, including PDR. In this study we evaluate the efficacy of IVB in eyes with active, progressive PDR.
Methods In an interventional prospective case series, eyes with active, progressive PDR underwent one to three IVB injections (1.25 mg) at intervals of either 6 or 12 weeks. Complete ophthalmic examinations and color fundus photography were performed at baseline and 1, 6, 12, and 20 weeks after the first injection. Fluorescein angiography (FA) was performed before injection and 20 weeks after. The primary outcome measures were clearing of vitreous hemorrhage (VH) and regression of active fibrovascular tissue (FVT). The secondary outcomes were any change in best-corrected visual acuity (BCVA) and any incidence of adverse events.
Results Thirty eight eyes of 38 patients with a mean age of 54.7±10.1 years were included in the study. VH resolved significantly after 1 week ($P=0.014$), 12 weeks ($P=0.0001$), and 20 weeks ($P=0.002$). The vascular component of FVT regressed, though the FVT area did not change. Mean BCVA improved significantly compared to baseline at all follow-up examinations. Two cases showing moderate fibrous proliferation developed traction retinal detachment (TRD).
Conclusions IVB has significant therapeutic effect on eyes with active, progressive PDR: the treatment causes a significant amount of VH resolution and neovessel regression. At the same time, this procedure may increase the risk of TRD in eyes with fibrous proliferation.

Keywords Active progressive PDR · Fibrovascular tissue · Intravitreal bevacizumab · Vitreous hemorrhage

The authors have no proprietary interest in this study.

The authors have full control of all primary data, and they agree to allow Graefes Archive for Clinical and Experimental Ophthalmology to review their data upon request.

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Introduction

Panretinal photocoagulation (PRP) is the standard treatment for proliferative diabetic retinopathy (PDR). However, laser treatment of this progressive vasoproliferative disorder fails to cause disease regression in 40% of cases [1]. Early vitrectomy to provide media clarity and remove the fibrovascular tissue (FVT) has been suggested for these difficult cases [2, 3]. Despite laser therapy and vitreous surgery, severe visual loss may occur in cases of progressive diabetic retinopathy. Thus, researchers have focused on pharmacologic treatment for such cases [4]. Octreotide, a somatostatin analog with growth hormone inhibitory and antiproliferative effects, has been proposed as a way to inhibit retinal neovascularization [5, 6].

The key role of vascular endothelial growth factor (VEGF) in inducing retinal neovascularization has recently

Graefes Arch Clin Exp Ophthalmol (2008) 246:483–489
DOI 10.1007/s00417-007-0688-0

RETINAL DISORDERS

Intravitreal bevacizumab with or without triamcinolone for refractory diabetic macular edema; a placebo-controlled, randomized clinical trial

Hamid Ahmadieh · Alireza Ramezani · Nasser Shoeibi · Bijan Bijanzadeh · Ali Tabatabaei · Mohsen Azarmina · Masoud Soheilian · Gholamreza Keshavarzi · Mohammad-Reza Mohebbi

Received: 7 April 2007 / Revised: 13 August 2007 / Accepted: 10 September 2007 / Published online: 5 October 2007

Abstract
Purpose To evaluate the effect of three intravitreal injections of bevacizumab (IVB) alone or combined with triamcinolone (IVT) in the first injection for treatment of refractory diabetic macular edema (DME).
Methods In this prospective, placebo-controlled, randomized clinical trial, 115 eyes of 101 patients with refractory DME were included. Subjects were randomly assigned to one of the three study arms: 1) three injections of IVB (1.25 mg/0.05 ml) at 6-week intervals, 2) combined IVB and IVT (1.25 mg/0.05 ml and 2 mg/0.05 ml respectively) followed by two injections of IVB at 6-week intervals, and 3) sham injection (control group). The primary outcome measure was change in central macular thickness (CMT). Secondary outcome measures were change in best-corrected logMAR visual acuity (BCVA) and incidence of potential adverse events.
Results Central macular thickness was reduced significantly in both the IVB and IVB/IVT groups. At week 24, CMT change compared to the baseline was −95.7 μm (95% CI, −172.2 to −19.26) in the IVB group, −92.1 μm (95% CI, −154.4 to −29.7) in the IVB/IVT group, and 34.9 μm (95% CI, 7.9 to 61.9) in the control group. There was a significant difference between the IVB and control groups (P=0.012) and between the IVB/IVT and control groups (P=0.022). Improvement of BCVA was initiated at weeks 6 and 12 in the IVB/IVT and IVB groups respectively. In terms of BCVA change compared to the baseline at 24 weeks, the difference between the IVB and control

The 6-week result of this study was presented as a paper at the Annual Meeting of American Academy of Ophthalmology, November 2006, Las Vegas, NV, USA.

The authors have no proprietary interest in this study. The authors have full control of all primary data, and they agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data upon request.

Clinical Trial registration reference number: NCT00370422 (ClinicalTrials.gov).

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Posterior sub-tenon triamcinolone for refractory diabetic macular edema: A randomized clinical trial

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[2]Department of Ophthalmology, Labbafinejad Medical Center
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PURPOSE. *To evaluate the effect of posterior sub-tenon triamcinolone acetonide (TA) injection on clinical, angiographic, and optical coherence tomographic (OCT) parameters in refractory diabetic macular edema (DME).*

METHODS. *In a double-masked placebo-controlled clinical trial, 64 eyes were randomly assigned to two groups. The treatment group (32 eyes) received 40 mg posterior sub-tenon injection of TA and the placebo group (32 eyes) received subconjunctival injection of a placebo. The injections were repeated after 2 months in both groups. Complete ophthalmologic examination, fluorescein angiography, and OCT were performed before intervention and after 4 months. Quantitative measurement of angiographic variables such as the amount of hard exudates (HE), size of foveal avascular zone (FAZ), and leakage severity was performed by computer, using Photoshop software.*

RESULTS. *Initial best-corrected visual acuity (VA) was 0.93±0.39 logMAR in the placebo group and 0.75±0.38 logMAR in the treatment group. At 4 months, corrected VA was 0.88±0.48 logMAR in the controls versus 0.71±0.42 logMAR in the cases. Mean central macular thickness measured by OCT before and 4 months after injection was 392 and 377 microns in the treatment group and 388 and 357 microns in the placebo group, respectively. No statistically significant difference was detected between the two groups. The difference was also not significant in HE, FAZ, and leakage in the angiograms.*

CONCLUSIONS. *Two injections of posterior sub-tenon TA had no therapeutic effect on refractory DME. (Eur J Ophthalmol 2005; 15: 746-50)*

KEY WORDS. *Diabetes, Macular edema, Sub-tenon injection, Triamcinolone, Optical coherence tomography*

Accepted: July 11, 2005

INTRODUCTION

Macular edema is one of the leading causes of vision loss in patients with diabetes mellitus (1). Approximately 29% of patients having diabetes for more than 20 years will exhibit macular edema, with over 50% experiencing a loss of two or more lines of vision after 2 years of follow-up (2, 3). The Early Treatment Diabetic Retinopathy Study (ETDRS) (4) demonstrated a significant benefit of focal edema. It showed a therapeutic benefit in reducing the risk of moderate visual loss by 50%. However, more than 10% of the eyes will still lose a significant amount of vision after 3 years.

The failure of laser photocoagulation in a substantial subgroup of patients has prompted interest in other treatment methods, including surgical (5, 6) and recently medical therapy with corticosteroid drugs.

It has been shown that intravitreal triamcinolone ace-

EXTENDED REPORT

Effect of tranexamic acid on early postvitrectomy diabetic haemorrhage; a randomised clinical trial

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Aims: To evaluate the effect of tranexamic acid on early postvitrectomy haemorrhage in diabetic patients.
Methods: In a clinical trial, 62 diabetic patients scheduled for vitrectomy were randomly assigned to two groups. The treatment group (32 eyes) received two doses of tranexamic acid (10 mg/kg) shortly before and after the operation intravenously, continued orally for 4 days (20 mg/kg/8 hours). The control group (30 eyes) received no medication. Both media clarity and visual acuity were compared during 4 weeks.
Results: Four weeks after surgery visual acuity was low (≤1 metre counting fingers) in 21.4%, moderate (>1 metre counting fingers but<20/200) in 14.3%, and good (≥20/200) in 64.3% of the treated group. Corresponding figures in the control group were 26.1%, 26.1%, and 47.8%, respectively. These differences were of no statistical significance. The ratio of mild to severe vitreous haemorrhage during the first 4 days and after 4 weeks was 79% to 21% and 82% to 18% in the treatment group and 76.7% to 23.3% and 78.3% to 21.7% in the control group respectively, which showed no statistically significant difference.
Conclusion: Tranexamic acid, with the method of administration in this study, had no effect on reducing early postvitrectomy haemorrhage in diabetic patients.

Early vitreous haemorrhage, within a week after vitrectomy, is a common complication in diabetic patients, with an incidence of 29–75%.[1] It may cause severe visual impairment (especially important in monocular patients), interfere with examination and laser therapy, induce ghost cell glaucoma,[2] increase need for vitrectomy,[3] and stimulate the growth of epiretinal membranes and fibrous tissue.

Antifibrinolytic drugs, like tranexamic acid and EACA (ε-aminocaproic acid), inhibit clot lysis through interference with plasmin action.[3] The haemostatic effect of EACA has been proved in different types of operations such as prostatectomy, dental, cardiac, and orthopaedic operations.[4 5] In addition, the role of these drugs in decreasing rebleeding in hyphaema is clear.[2]

These two medications have been used after vitrectomy for diabetic patients in two separate studies and good results were observed in one of them.[6 7] The present study evaluated the effect of tranexamic acid on early vitreous haemorrhage after vitrectomy in diabetic patients with proliferative retinopathy.

MATERIALS AND METHODS

This randomised clinical trial was conducted on diabetic patients scheduled for vitrectomy for advanced retinopathy including non-clearing vitreous haemorrhage, tractional retinal detachment, and progressive fibrovascular proliferation. All registered patients were fully informed of the side effects of tranexamic acid.

After complete history taking and ophthalmic examination, laboratory tests were performed for each enrolled patient that included blood cell and platelet counts, serum

Table 1 Tranexamic acid dosage adjustment according to serum creatinine level

Creatinine level (mg/dl)	Intravenous (mg/kg)	Oral (mg/kg)
2.83–1.36	5	15 (twice daily)
5.66–2.84	2.5	15 (daily)
>5.66	1.7	5 (daily)

performed just before transferring the patient to the operating room. The second tranexamic acid intravenous injection was performed after surgery with the same dose. From the day after vitrectomy, the medication was continued orally in the form of 250 mg capsules (20 mg/kg every 8 hours) for 4 days during hospitalisation. The drug dosage was adjusted according to serum creatinine level (table 1).

Standard three port vitrectomy was performed for all patients under local or general anaesthesia. Only Ringer's solution was used to avoid the anticoagulative effect of citric acid present in balanced salt solution. Additional procedures like endolaser, membrane dissection, etc, were performed if needed. Intraoperative bleeding was controlled by either raising intraocular pressure or endodiathermy. If use of an internal tamponade such as air, gas, or silicone oil was mandatory, that case would be excluded from the study. Blood pressure was monitored during hospitalisation including operation time. Eye pressure was checked at the end of the surgery with the Schiotz device. The surgeons were masked to the randomisation.