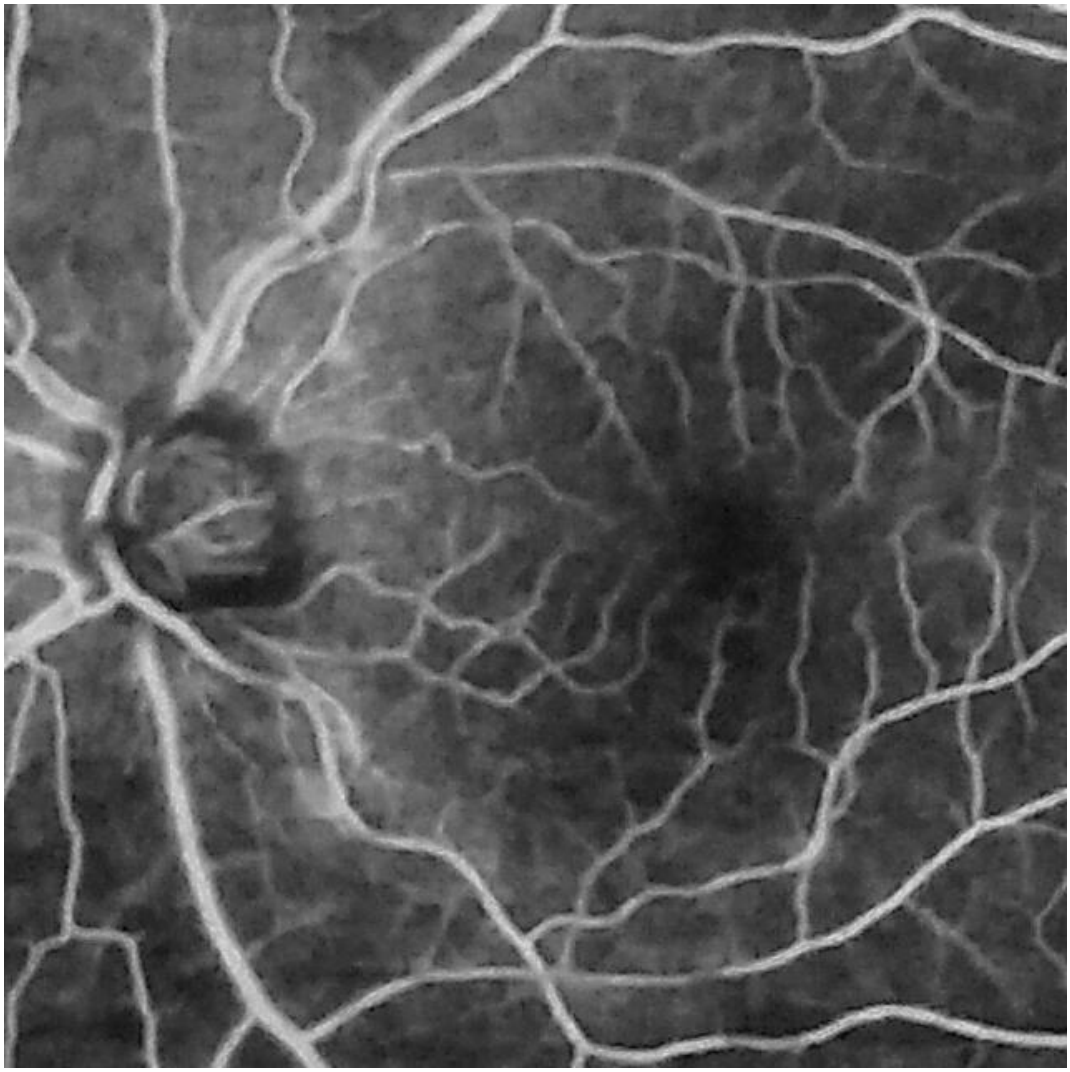

# Guidelines for the Management of Diabetic Retinopathy

***Revised Edition 2025***

**Prof. Dr. M Shakaib Anwar FRCS(Glasg.)**

**MEDICAL RETINA ASSOCIATION OF PAKISTAN**

# Guidelines for the Management of Diabetic Retinopathy

## (Medical Retina Association of Pakistan)

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*Dedicated to*

All the ophthalmologists who follow and preach the ethical practices and work in the best interest of the patients.

# *Acknowledgement*

I am deeply indebted to Ophthalmological Society of Pakistan and Medical Retina Association of Pakistan for entrusting me with this task of preparing the Guidelines for management of Diabetic Retinopathy. I am especially thankful to Prof. Dr. Saleh Memon, Prof. Dr. Nadeem Hafeez, Prof. Dr. Tariq Aziz and Prof Dr. Shahid Jamal Siddiqui for sharing their experience and encouraging me to take up and finish this task. I am also much thankful to Prof. Dr. Asad Aslam Khan and Dr. Haroon Awan to help me bring this project on the platform of National Programme for Prevention & Control of Blindness/ National Committee for Eye Health (NCEH) Pakistan.

*Prof.Dr. M Shakaib Anwar FRCS (Glasg.)*

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# Foreword

I am very pleased to bring in this revised edition of **"Guidelines for the management of Diabetic Retinopathy".** These guidelines have been prepared for qualified ophthalmologists who have some experience of working in retina clinic, thereby omitting unnecessary details. These guidelines give the concept of diagnostic and therapeutic modalities employed in dealing with Diabetic Retinopathy in the current era. Our country is a developing one and so is our health system; but fortunately, modern medical facilities are available in major public and private hospitals. Although strong efforts are being done to develop our primary health care system, especially on the screening side, diabetic retinopathy is mainly managed in tertiary care centers. After taking into consideration RCO, AAO, ICO, NICE guidelines and other literature on the subject, these guidelines have been prepared in accordance with the facilities available in most of our health care centers.

An ophthalmologist plays a key role in reducing the overall morbidity and mortality associated with diabetes by contributing to the effective management of eye problems in patients with diabetes and contributing to the collection, analysis and dissemination of information which is essential for patient management and monitoring its quality and outcomes. Ophthalmologists who may be the first ones to identify type 2 diabetes by ophthalmoscopy have an important responsibility to instruct the patients about the need to have the diabetic control and make the patients aware of the other aggravating factors as raised serum cholesterol levels and hypertension.

I have tried to give an account and utility of the latest diagnostic modalities considering the future trends. The reader of these guidelines are encouraged to keep themselves abreast with the latest developments through the latest material available to read on this subject.

*The Author*

*Prof. Dr. M Shakaib Anwar FRCS(Glasg.)*
*Aug.2025*

# Section 1

## Definition of Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with deranged carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both [1]. It has multiple etiologies.

## Definition of Diabetic Retinopathy

Diabetic retinopathy (DR) is a chronic, progressive and potentially sight-threatening disease of the retinal microvasculature associated with prolonged hyperglycemia and other conditions associated with diabetes mellitus such as hypercholesterolemia and hypertension.

## Epidemiology

Diabetic retinopathy (DR), a major microvascular complication of diabetes, has a significant impact on the world's health systems. It is the 5th commonest cause of acquired visual loss worldwide, and leading one among the working population (46% of all those will be of working age group (40-59 years). The prevalence of DR due to DM type1 and DM type 2 has been reported as 10 - 50% and 25.2% respectively. Globally, the number of people with DR will grow to 191.0 million by 2030. It is expected to have 7.5% cases of PDR and 22.5% of DME. Overall, it is predicted that the total number of people living with diabetes will increase to 552 million by 2030 and those with vision-threatening diabetic retinopathy (VTDR) will rise to 56.3 million by that time [2,3]. Due to sedentary life style, obesity and increased life expectancy, the incidence of type 2 diabetes has risen significantly [4]. It is estimated to be 70% in low-income and middle-income countries (LMIC) [5].

## Classification of DR

Although there are various ways to classify DR, but the main focus remains on the two basic mechanisms leading to compromised vision: **retinopathy** (risk of new vessels) and **maculopathy** (risk of damage to the central fovea).

### A. Retinopathy

It is classified on the basis of presence or absence of abnormal new vessels which affect the visual outcome. The two types are:
a. Non-proliferative (background/pre-proliferative) retinopathy
b. Proliferative retinopathy

**a. Non-proliferative diabetic retinopathy (NPDR) (background/pre-proliferative)**

According to American Academy of Ophthalmology (AAO) classification, NPDR is graded as:
• Mild
• Moderate
• Severe
According to NSC-UK classification, NPDR is graded as:
• Background
• Pre-proliferative
In the Scottish Diabetic Retinopathy Grading system, NPDR is graded as follows:
• Mild background
• Moderate background
• Severe background

**b. Proliferative diabetic retinopathy (PDR)**

It is described according to:

**(i) Location**
- new proliferating vessels on the disc (NVD) or within 1 disc diameter (DD) of the disc margin
- new proliferating vessels elsewhere in the retina (NVE) more than 1DD from the disc.

**(ii) Severity**
- early PDR
- PDR with high risk characteristics
- florid PDR and
- gliotic PDR.
- "Involutionary" PDR is used to describe new vessels which have regressed in response to treatment or (rarely) spontaneously.

## B. Diabetic maculopathy

Affection of macula in diabetes mellitus is separately described as diabetic maculopathy.
It is further classified as:
- Focal edema
- Diffuse edema
- Ischemic
- Mixed

Diabetic Maculopathy may have a tractional element (VMT) due to vitreoretinal pathology or non-tractional (intra-retinal).

# Complications linked to Diabetic Retinopathy

There are certain complications linked to DR which must be kept in mind while managing a case of DR. These may be categorized as under:

**Specific:**

Retinal Detachment
Rubeosis iridis
Cataract
Optic neuropathy

**Non Specific:**

Glaucoma
Retinal vein occlusion
Optic nerve swelling (diabetic papillopathy)

# Risk Factors

Factors that aggravate or enhance DR are called risk factors for DR. These are of two types:

## A. Non modifiable

### *a) Duration and age at onset*

It is a major risk factor although better management of DM can reduce the severity of DR to some extent.

### *b) Puberty*

Children younger than twelve years hardly develop complications of diabetes13. Puberty is a risk factor for developing retinopathy because of the physiological increased resistance to insulin at this age. Surge of growth hormone and inadequate control of glycaemia in adolescence may enhance the progression of DR.
Adolescent diabetics are more prone to vision threatening retinopathy as compared to adult patients. DR may progress rapidly in those with poor glycemic control. At this age, efforts should be directed to screening for early signs of DR and modifiable risk factors3.

### *c) Gender*

Males are more prone to DR because research has shown that females have some inherent resistance to neurodegenerative changes that precede background DR in Type II DM [6].

## B. Modifiable Risk Factors

### *a) Diabetic control*

It is known that good glycemic control has a positive role at any stage in the development of retinopathy; prevention and progression in the early stages of retinopathy and for reducing chances

of severe proliferative retinopathy and visual loss. Intensive control in early diabetes has a positive long lasting effect on DR [7]. Adolescents with loose diabetic control (HbA1C > 10%) for more than 10 years are at risk of developing vision threatening "florid" DR. They should be followed up frequently for fundus examination [8]. In younger children, very strict control can adversely affect development of brain, so a balance has to be struck. The risk of complications is associated independently and additively with hyperglycemia and hypertension with risk reductions of 21% per 1% HbA1c decrement and 11% per 10 mmHg systolic blood pressure decrement [9].

## *b) Blood Pressure*

Good control of blood pressure has a positive role in prevention and management of diabetic retinopathy. A 10 mm of Hg reduction in mean systolic blood pressure reduces microaneurysm count, hard exudates and cotton wool spots over 4-7 years time by 11% as mentioned above [9].
The patients should be encouraged to regularly monitor their blood pressure. Systolic blood pressure should be aimed at ≤130mmHg in those with established retinopathy and/or nephropathy. Anti-hypertension drugs blocking the renin-angiotensin system (RAS) may have beneficial effect, particularly on mild retinopathy, but these are to be discontinued during pregnancy.

## *b) High serum cholesterol*

Raised serum cholesterol levels is an aggravating factor for DR. Statins should be considered in secondary prevention of macrovascular disease as well as in primary prevention [10,11,12].

## *c) Body Mass Index (BMI)*

High BMI has been shown to be a risk factor for developing retinopathy in adolescence [13]**.**

## *d) Vitamin D*

Vitamin D has balancing role in inflammation and angiogenesis. Vitamin D Deficiency may make the patient more prone to DR [14].

## *e) Smoking*

The effect of smoking on retinopathy may be due to its ischemic effects but it is not clear4. Smoking has been shown to be associated with microangiopathy when complications occur early in the course of type 1 diabetes [15] Smoking has not shown to be significantly associated with older-onset diabetes or with progression or progression to proliferative diabetic retinopathy in any of the groups if the known risk factors are well controlled. Patients with DR should be informed that they are at a higher risk of cardiovascular disease and they should quit it for an overall healthy life [16,17].

### *f) Pregnancy*

It has an effect on pre-existing DR. Progression of retinopathy is relatively of low risk in pregnancy. This is established in patients with type 1 diabetes [18].The known duration of diabetes in a pregnant type 2 patient is often short but retinopathy has been reported in 14% in early pregnancy and progressed in a minority. Post-partum worsening of retinopathy is not seen in type 1 diabetes [19]. Patients with DM planning to get pregnant should be made aware of the need for retinal examination before and during pregnancy. Pregnant diabetics should undergo retinal assessment after their first antenatal checkup and then at 28 weeks if the retina was normal. In the presence of DR, retinal assessment should again be performed at 16–20 weeks. Those who have pre-proliferative diabetic retinopathy diagnosed during pregnancy should be followed up for at least 6 months after delivery.

# Clinical Features of Diabetic Retinopathy

Diabetic retinopathy (DR) is essentially, but not exclusively, a microvascular disease. Its clinical features help the ophthalmologist to predict the visual prognosis of a patient. The classification of DR is mainly based on two features:

a. Presence or absence of new vessels (proliferative or non-proliferative)

b. Presence or absence of sub-foveal macular edema

The newer imaging techniques are now working on the roles of retinal pigment epithelium and choroidal circulation as well.

## A. Non Proliferative DR

### i. Isolated Capillary Occlusion

Early funduscopic findings in diabetic retinopathy are due of isolated capillary occlusion resulting in dilatation of adjacent non-occluded capillaries and formation of saccular or fusiform swellings called microaneurysms. The capillary circulation, as such, can only be detected through high penetration OCT or fluorescein angiography [20].

### *a) Microaneurysms (Ma)*

Microaneurysms appear as isolated red spheres or dots. These may leak producing dot hemorrhages, edema and exudates. These may thrombose spontaneously to disappear or remain visible as white dots.

### *b) Dot Hemorrhages (DH)*

These are small, discrete hemorrhages which are difficult to differentiate clinically from microaneurysms so these can be documented as dot hemorrhage/ microaneurysm (H/Ma). Fluorescein angiography and OCT-A can differentiate between the two.

## ii. Diffuse Capillary Occlusion

Persistent and progressive capillary occlusion results in significant ischemia and infarction. These in turn lead to development of blot hemorrhages, intraretinal microvascular anomalies and venous changes (Fig.1). Extensive capillary occlusion results in neovascularization.

### *a) Blot hemorrhages (BH)*

These represent deep retinal infarcts in the outer plexiform layer (Fig.2). On fluorescein angiography, these do not mask the overlying capillary bed unlike dot and flame hemorrhages which are in more superficial layers of retina. Peripheral, large blotch hemorrhage indicate extensive ischemia; such patients often develop neovascular glaucoma.

### *b) Cotton wool spots (CWS)*

These develop as a result of build-up of axoplasmic flow at the edge of the infarct; most oftenly seen on the nasal side of the optic disc. These are not specific to DR and unless extensive, do not definitely predict new vessel formation [20].

### *c) Intra-retinal Microvascular Anomalies (IRMA)*

During the progression of DR when capillary network between arteriole and venule is significantly closed, the capillary remnants are dilated. These are easily detected on fundus fluorescein angiogram FFA. These may also represent a variant of collateral vessels formation in the vicinity of capillary closure. These resemble telangiectatic vessels in young but can be differentiated on FFA as telangiectatic vessels leak along their length and also lead to retinal edema and exudation.

### *d) Venous Beading*

This may represent foci of venous endothelial cell proliferation that have failed to develop into new vessels. Fluorescein angiography shows vessel wall staining.

### *e) Venous Reduplication*

This is infrequent and usually occurs along venous beading.

### *f) Venous Loops*

These are thought to develop due to small vessel occlusion and opening of alternative circulation. This too is an infrequent finding.

### *g) Retinal pallor*

This is non-specific feature and is related to choroidal microcirculation. Detected best on FFA, OCT angiography (OCTA) and red-free fundus photographs.

### *h) White lines*

These represent vessel wall staining or thrombosed arterioles, usually seen with retinal pallor and in areas of extensive capillary closure.

## iii. Macular Changes in Non-Proliferative DR

### *Macular Edema*

Diabetic macular edema (DME) can be focal or diffuse depending upon discrete source of leakage like a microaneurysm or widespread capillary leakage respectively. It can be subfoveal or away, making it more or less significant respectively (Fig.3) or very severe (Fig.4).

## iv. Macrovascular disease

Diabetic retinopathy is not exclusively a microvascular disease. In the horizontal nerve fiber layer, mainly the arterioles and not the capillaries are occluded leading to flame shaped hemorrhages and cotton wool spots.

## vi. Optic Disc Changes

Optic disc swelling, diabetic papillopathy, is seen occasionally in diabetics. It has no direct relationship with the gravity of DR. Visual functions on the whole are intact, although visual acuity may be disturbed [20].

# B. Proliferative DR (PDR)

## i. NVD and NVE

Vascular proliferation occurs at the junction of perfused and non-perfused retina in response to the extensive capillary closure and resulting ischemia (Fig.5,6). This is Proliferative diabetic retinopathy (PDR). New vessels, which usually grow from post-capillary venules, can appear on the disc (NVD) or elsewhere on retina (NVE). NVD appear on or within one disc diameter (DD) from the disc. These are difficult to differentiate from fine normal vessels on the disc. The later

taper off from the disc and do not return to disc, while NVs always loop back, may form a network and are wider at top of the loop. These leak on FA. NVD can form as a result of generalized retinal ischemia or even widespread macular ischemia.
New vessels elsewhere (NVE) occur along the border between healthy retina and areas of capillary occlusion. These resemble IRMAs which occur within areas of capillary occlusion. IRMAs never form loops. An unusual blood vessel forming loops is supposed to be a new vessel until proven otherwise.
Formation of new vessels on the iris (NVI) indicates more widespread retinal ischemia and it may lead to neovascular glaucoma by formation of new vessels in the anterior chamber angle (NVA).
New vessel formation on the anterior hyaloid surface usually occurs after vitrectomy if insufficient ablation of the peripheral retina is done [20].
The scale of capillary closure, assessed clinically or through OCT-A or FFA is predictor of amount and speed of new vessels formation. A large isolated ischemic area may lead to earlier vascular proliferation as compared to generalized low grade ischemia. Similarly spread out small clusters of capillary closure may not cause early proliferation of new vessels.

## ii. New Vessels at the Vitreoretinal Interface.

Symptoms arising from growth of new vessels at the VR interface occur as a result of complications of the dynamic interaction between blood vessels and posterior hyaloid face and not by mere presence of new vessels. This interaction leads to an inflammatory response and scar formation which is transparent initially but pulls the new vessels from the retinal surface. Further contraction ultimately leads to subhyaloid (pre-retinal) or intra-gel hemorrhage and tractional retinal detachment in turn. Posterior hyaloid face is strongly adherent to the pars plana, the optic disc and the major retinal arcades.
When the vitreous detaches, subhyaloid blood, which is held between post hyaloid face and retinal surface, enters the vitreous cavity converting it into the vitreous hemorrhage.
Repeated vitreous hemorrhage incites more gliosis, traction bands formation leading to retinal folds or traction retinal detachment which progresses slowly unless a hole is formed and a combined traction/rhegmatogenous detachment occurs. The proliferating blood vessels occasionally autoinfarct but mostly the patients need photocoagulation or anti VEGF injections. Signs of regression or inactivity are disappearance of retinal hemorrhages, resolution of IRMA and normalization of retinal venous changes.
As the new vessels regress, gliosis (scarring) may increase at the VR interface leading to posterior vitreous detachment (PVD). This may occur after pan-retinal photocoagulation or after injection of an anti-VEGF agent, mostly as a late complication.

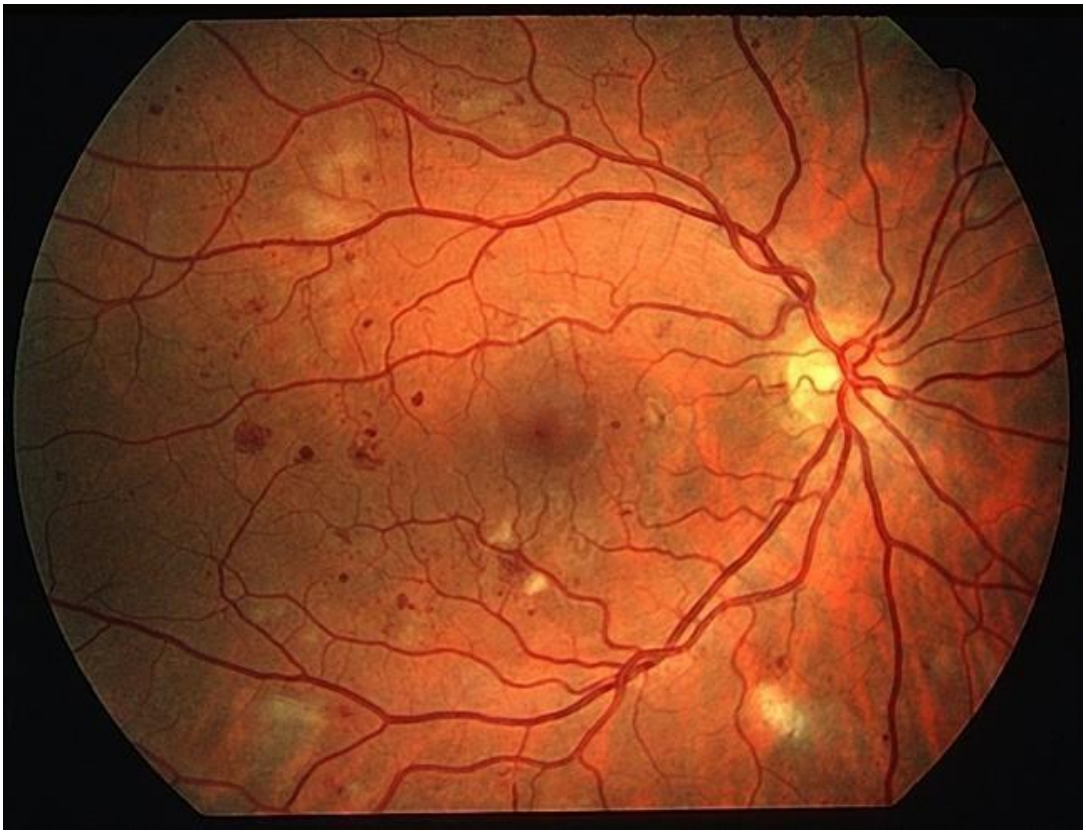


Fig.1 Microaneurysms, haemorrhages, cotton wool spots, IRMA

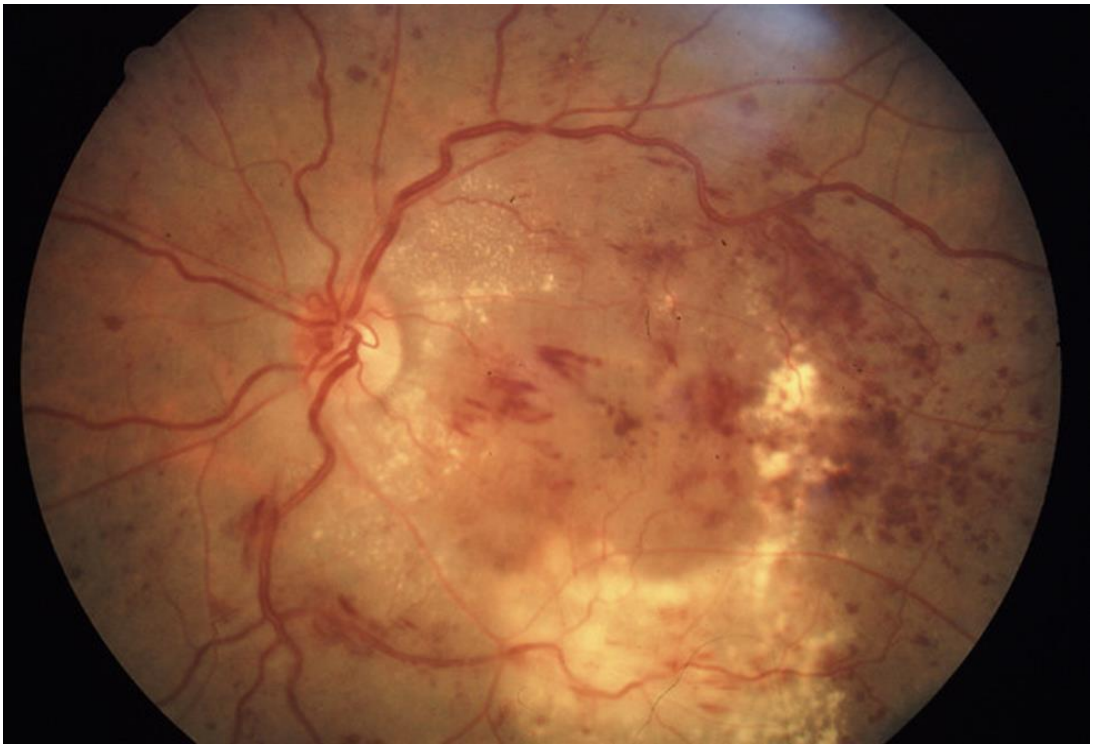


Fig.2.Advanced NPDR with maculopathy

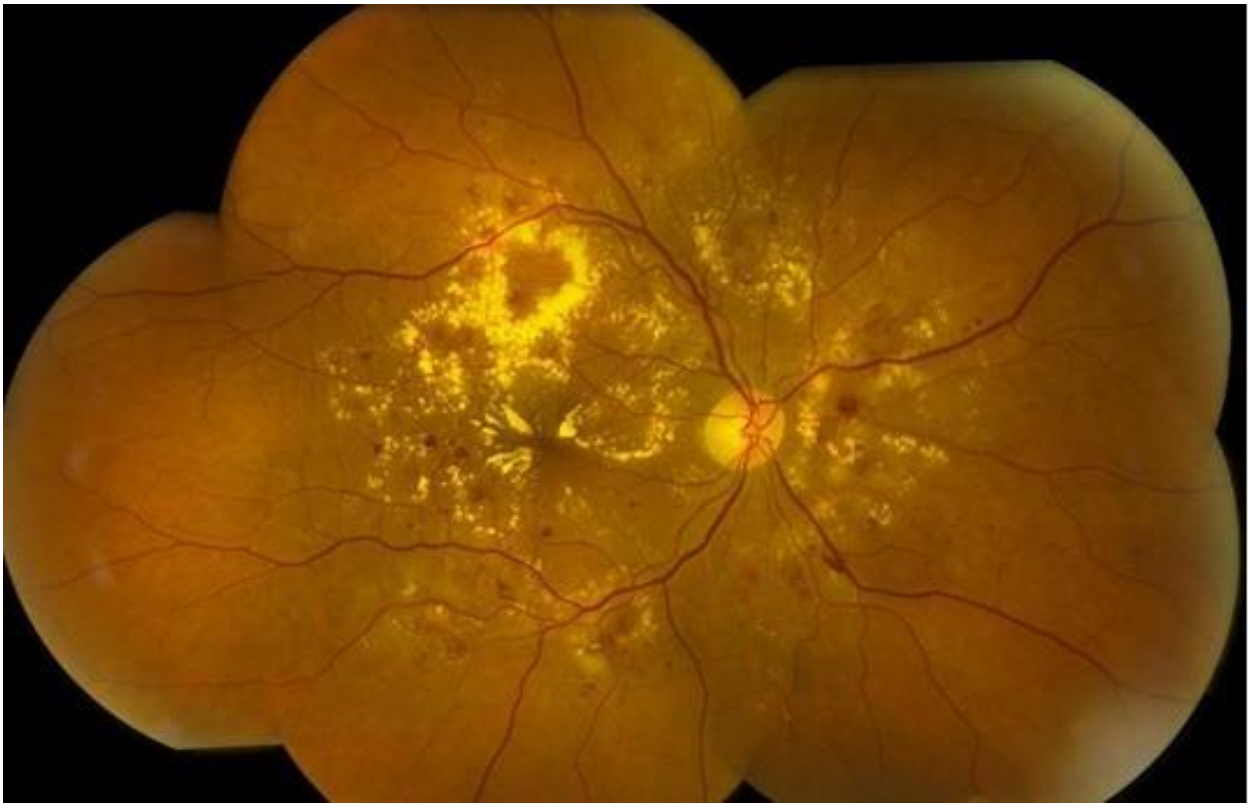


Fig.3. NPDR with maculopathy

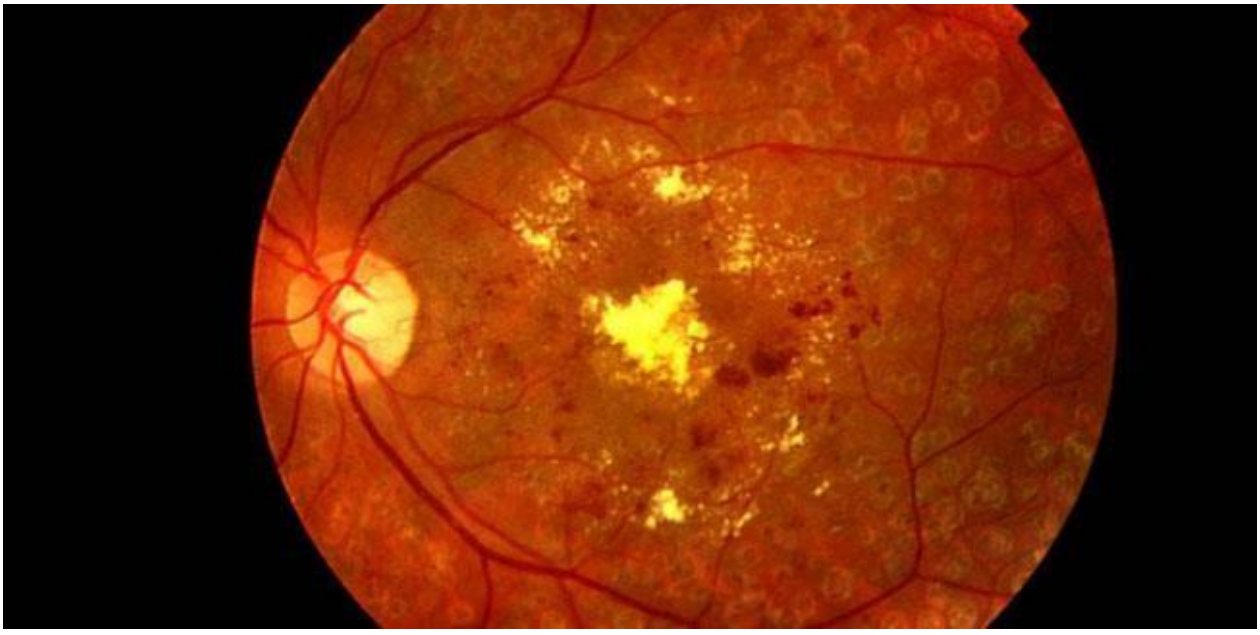


Fig.4. Severe maculopathy. Blot hemorrhages are seen

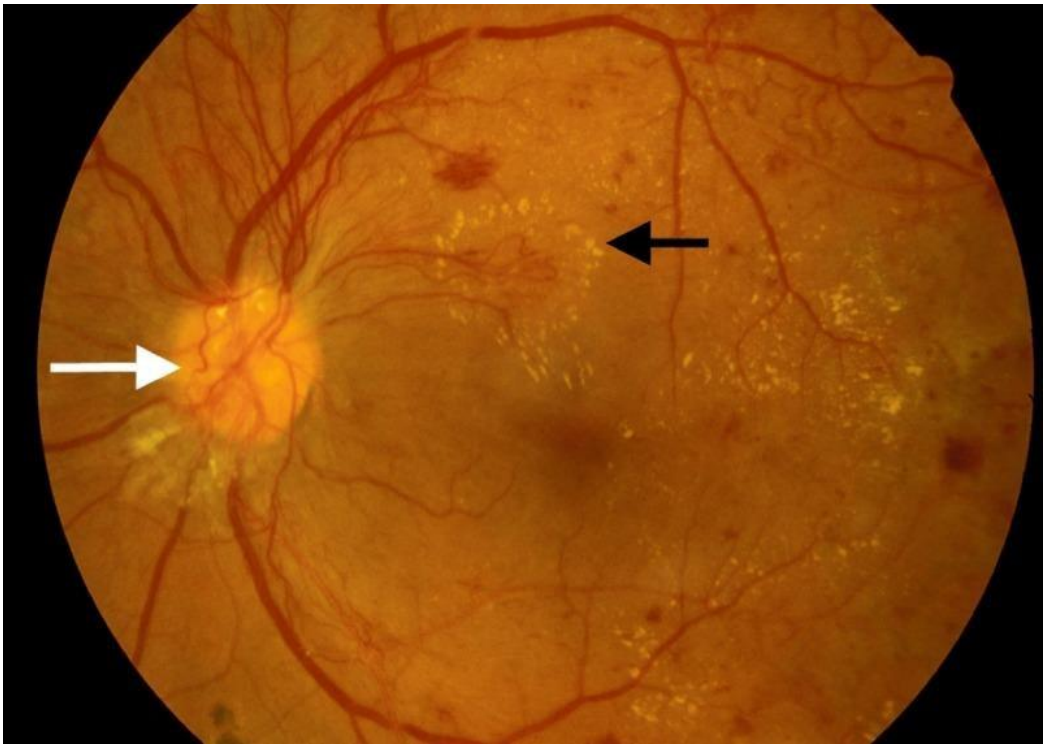


Fig.5. PDR.  NVD & NVE. Blot hemorrhages are seen.

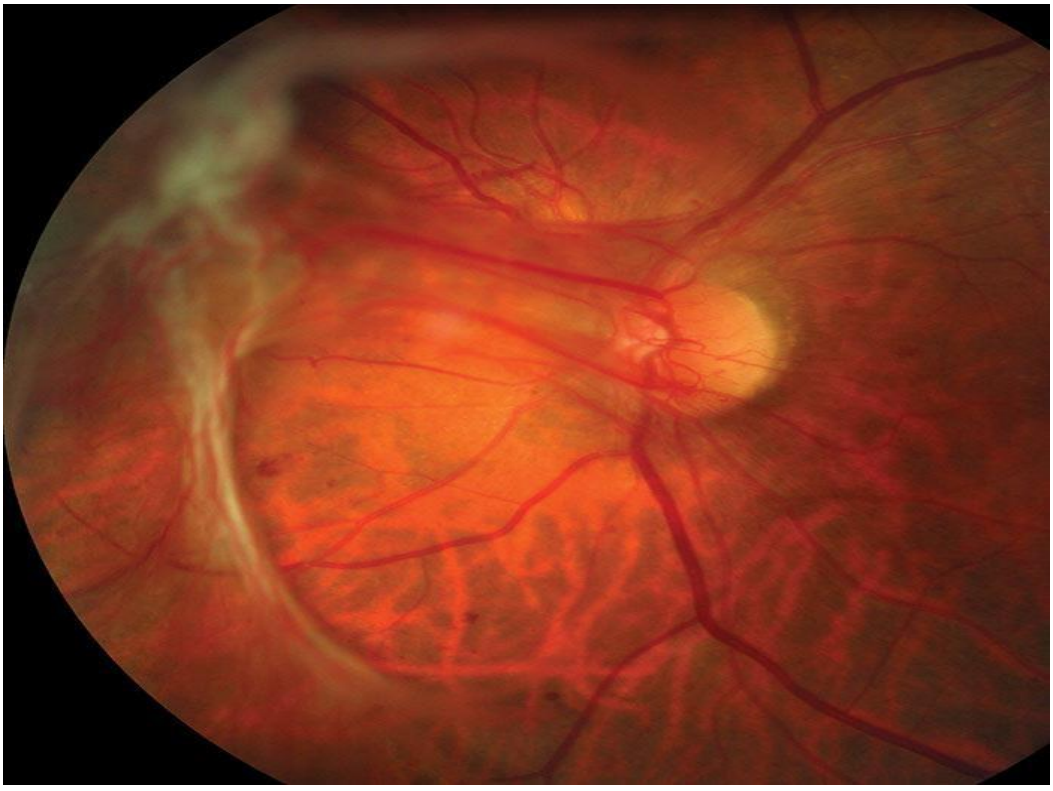


Fig.6. Advanced complicated PDR

# Section 2

## Screening for Diabetic Retinopathy

The *definition of screening* that was adapted by the WHO11 in 1968 was 'the presumptive identification of unrecognized disease or defect by the application of tests [20], examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. It is important to recognize that screening acts as a sieve and, as with all screening programs, not every case of sight threatening retinopathy will be detected with the screening test used. (Refer to **section 7** for quick labeling guide of levels of DR at primary health /optician level). The role of the ophthalmologist is pivotal in screening program and management of patients and is responsible [20].

to lead the delivery of the screening program in collaboration the treating diabetologists.
to get help of local management concerned with health system.
to maintain quality assurance.
to ensure the grooming and training of the staff
to ensure the patients easy access to screening program and treatment.
to organize the collection and maintenance of data for record and research purpose.
to maintain an efficient system of follow-up.

### A. Screening of Cases with Type I DM (IDDM)

It is rare to find significant DR within 5 years of diagnosis of IDDM. In children, although minimal DR may be seen but significant and PDR does not occur in pre-pubertal children irrespective of the duration of the disease.

It is known that serum VEGF concentrations are increased in pre-pubertal and pubertal children with diabetes, as in adults, leading to increased chances of microvascular complications [21]. So the children with IDDM need to be screened only when they reach puberty [22] and is recommended that diabetic children and adolescents should be under the care of a multidisciplinary team experienced in managing the different aspects of DM. This includes check on blood pressure and BMI and advice regarding diet, smoking and pregnancy. Children and adolescents with T1DM should undergo dilated fundus photography annually from age 12 years, while children and adolescents with T2DM should undergo dilated fundus photography annually from the time of diagnosis .Those being diagnosed having IDDM at the time of puberty and young adults should be screened within 5 years of the diagnosis of diabetes mellitus.
Prevalence of DR at adolescence has been estimated as:

| | |
|---|---|
| 10-13 years | 1% |
| 14-15 years | 5.8% |
| 16-18 years | 17.7% |

There are various recommendations in the literature regarding the age at which screening for DR should commence. Adopted from ICO guidelines, these have been briefly narrated as under:

a. American Academy of Ophthalmology [23]: Annual screening to start 5 years after onset of diabetes.

b. American Diabetic Association [24]: Screening to commence 3-5 years after diagnosis, and once the patient is 10 years old.

c. American Academy of Pediatrics [20]: Initial examination at 3-5 years after diagnosis if over age 9, and annually thereafter.

d. American Association for Pediatric Ophthalmology and Strabismus [25]: For Type II DM in children there are no separate guidelines.

## B. Screening of Cases with Type II DM (NIDDM)

While considering Type II or NIDDM, a high proportion of patients have significant DR at the time of diagnosis. Therefore all the patients with NIDDM need to be screened for DR at the time of diagnosis or within three months of diagnosis to avoid unnecessary visual loss [26].

## C. Screening of Pregnant women

a. The first screening for DR in pregnant women with pre-existing DM to be done at first antenatal appointment and to be repeated if any DR detected at 16-20 weeks, otherwise next retinal examination is done at 28 weeks.

b. Women with pre-proliferative DR during pregnancy to be followed up for at least six months after child birth.

c. Only Tropicamide 1% to be used for mydriasis.

d. DR is not a contraindication to vaginal birth

## D. Screening of patients with learning disabilities

The Royal College of Ophthalmologists has made the following recommendations for people with learning disability (PWLD).

a. General Practitioners should be encouraged not to exclude PWLD from diabetic eye screening. The screening procedure should be tuned to the convenience of such people.

b. The patients should preferably be dilated at home to reduce the waiting time at clinic [27].

c. Proper consent to be sought for all the procedures during management but this should not be a barrier to screening or treatment.

d. It should be tried to convey the management plan to the patient in an easily understandable way.

# Record Keeping & Documentation of stages of DR through imaging

### i. Colour Fundus Photography (CFP)

This technique is vital for documentation of diabetic retinopathy and is most efficient for retinal screening (Fig.7). This is best for white lesions like cotton wool spots and exudates. Other lesions are better documented through red free (RF) images [20].

### ii. Fluorescein angiography (FA)

The role of FA is waning as better OCT techniques are developing but it is still very useful to detect subtle new vessel formation particularly in macular region to guide laser application.
Evidence of leakage from new vessels on FA at disc or elsewhere can be 'minimal' in early stages and decision for pan-retinal laser is decided on the basis of extent of capillary drop out area.
Leakage in macular area can be 'focal', diffuse' (intermediate) or 'mixed' with additional element of ischemia.
Macular ischemia, seen as a discrete zone of capillary drop out area, may be 'central' involving foveal avascular zone (FAZ) appearing as enlarged FAZ or 'peripheral' (temporal arcade watershed zone or extra-foveal area). Visual prognosis is poor and laser is ineffective when 'perifoveal' vessels of FAZ are affected.
Incidentally, FA remains the most appropriate modality to distinguish a non-leaking from a leaking microaneurysm (MA), identify clearly the presence of IRMA, and mark areas of capillary nonperfusion and widening of the foveal avascular zone (FAZ) in the macular retina . This helps in locating the areas to be eventually treated by laser [28].
Peripheral retinal ischaemia may not always be detectable clinically in the absence of other markers. FA, especially **ultra wide field (UWF)** retinal FA (Fig.8,9,10) plays a vital role in detecting ischaemic changes in this situation. It also points potential areas of retreatment for persistent new vessel formation and enables to identify the patients who need close supervision.
UWF color imaging and UWF fluorescein angiography (FA) can reveal more pathology than conventional field imaging; i.e. peripheral microaneurysms, neovascularization, vascular nonperfusion, and vascular leakage. This can detect early signs that might otherwise be missed pointing to greater disease severity [29,30,31].

Fig.7. Ultra Wide Field (UWF) colour image of NPDR with peripheral changes.

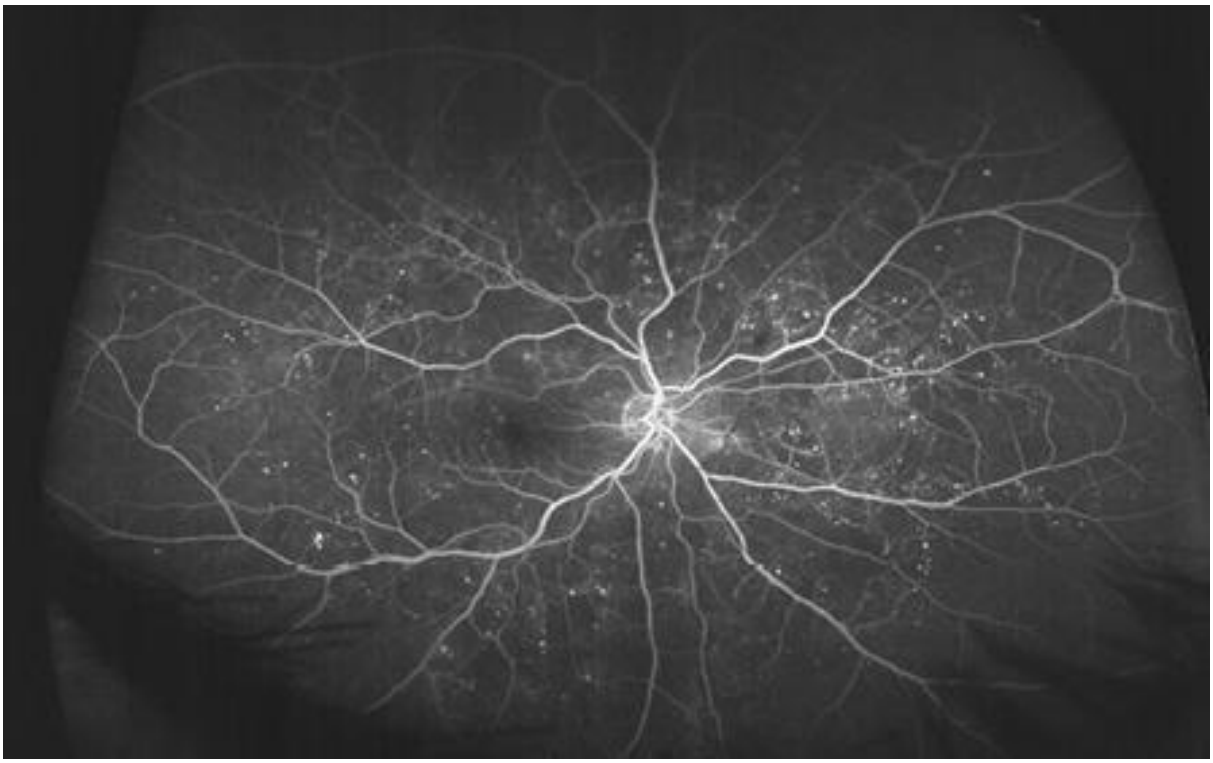


Fig. 8. UWF FA Showing peripheral vascular changes in early DR

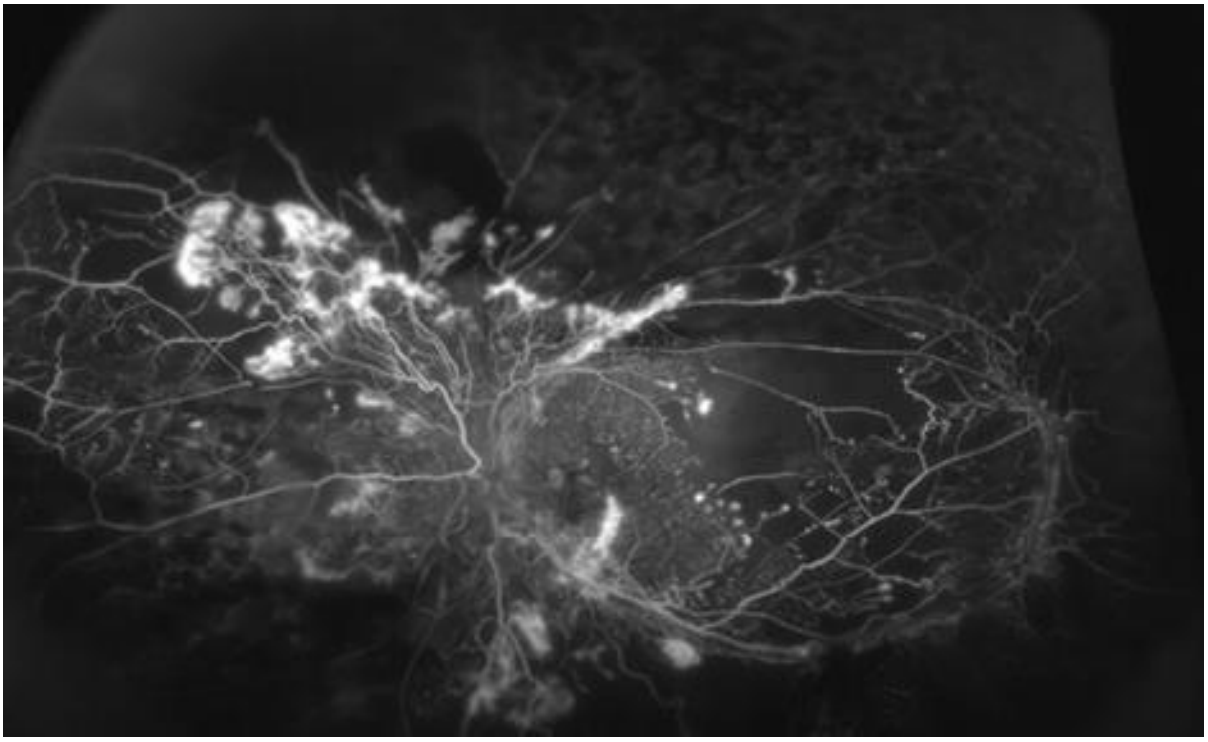


Fig. 9. UWF FA Showing PDR with extensive peripheral non perfusion

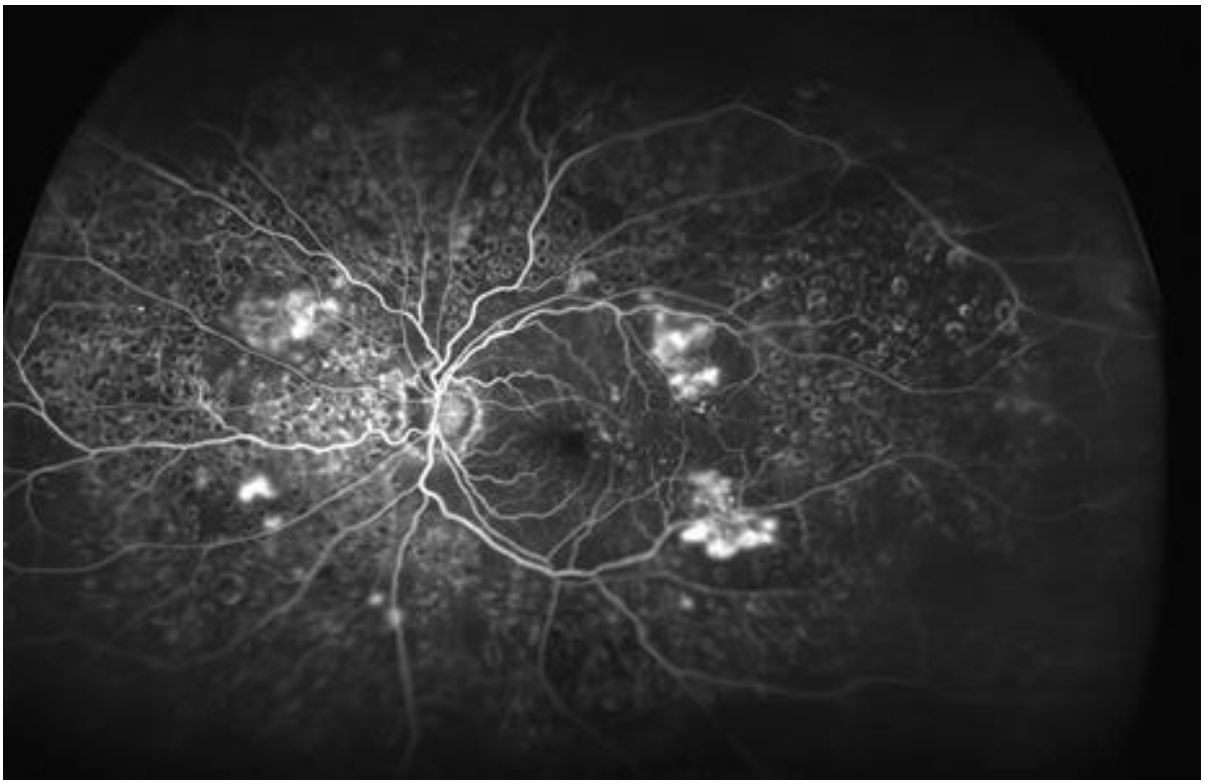
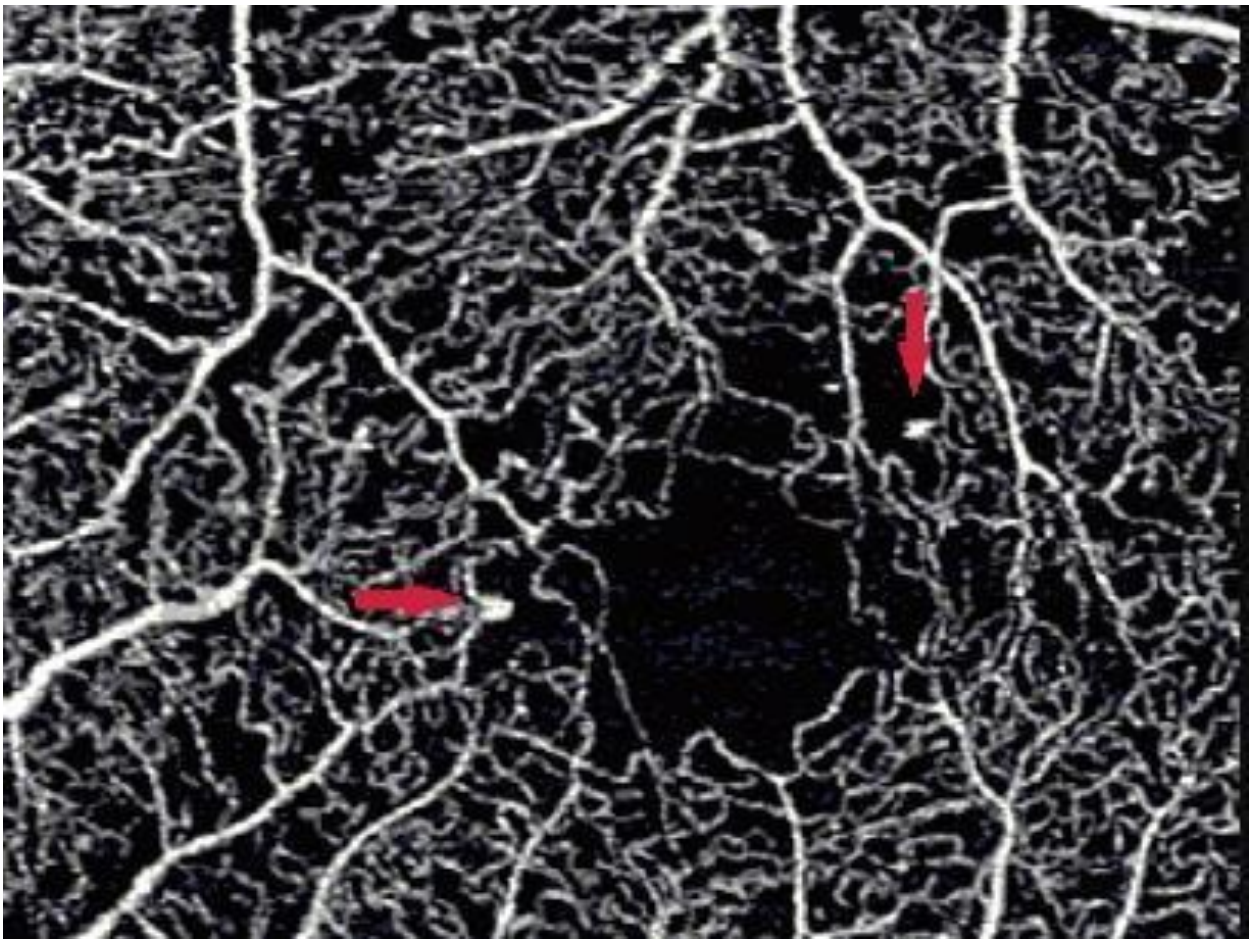


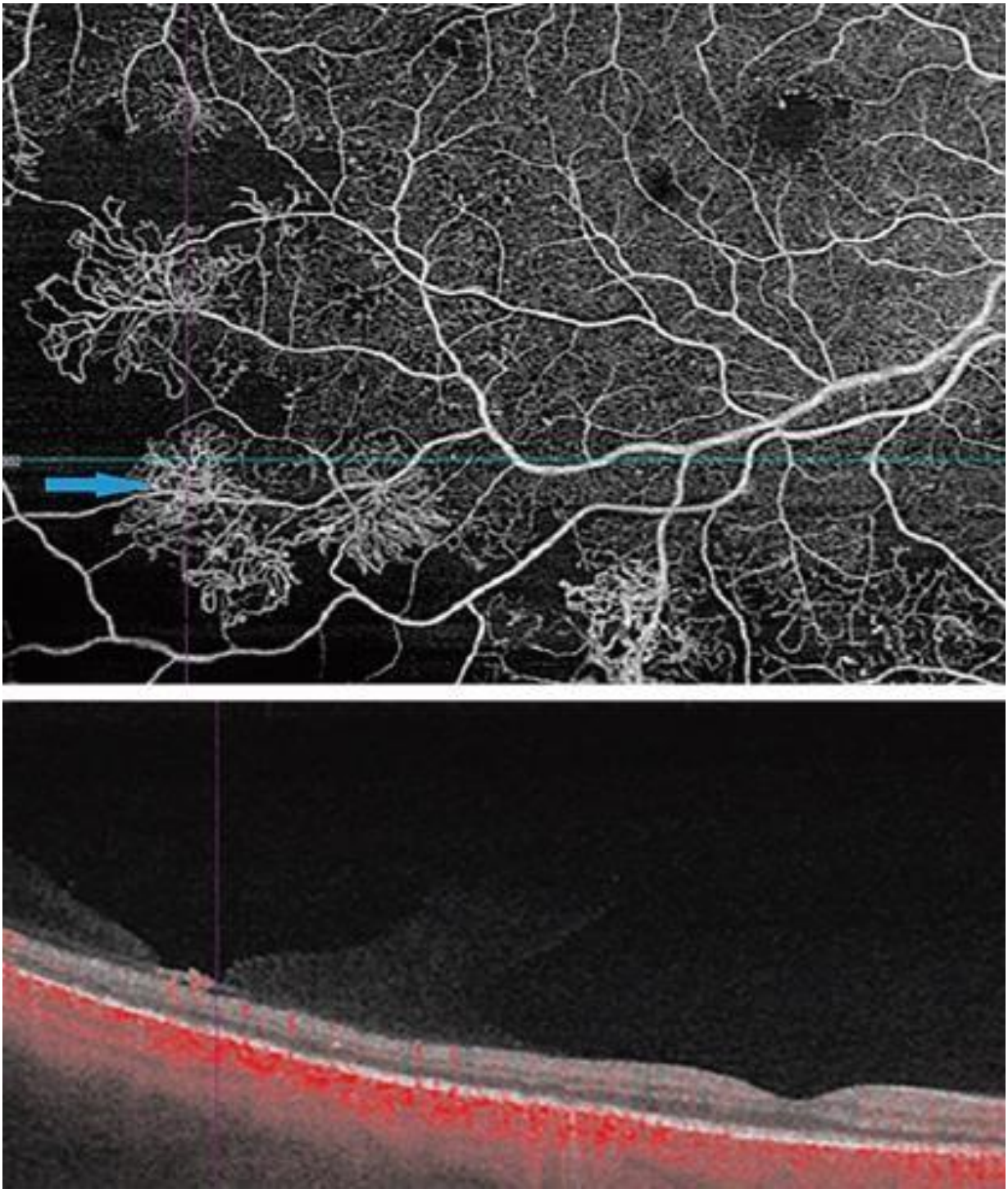
Fig.10. Colour UWF FA showing previous PRP with new neovascularization

**Optical Coherence Tomography (OCT)**

Currently, OCT, being fast and non-invasive, is the most frequently used diagnostic imaging tool in ophthalmology. The recent, third-generation OCT technology, uses a swept-source (SS) light source that allows more penetration, looking into choroidal vessels, and very fast imaging provides three dimensional raster images of high microstructural resolution (optical histology) [20]. OCTA is based on a motion contrast technique, assuming that in a static eye, the only moving aspect is vascular flow. Successive OCT B-scans are taken at the same location and differences between these scans are analyzed and used to generate the OCTA image [32]. Second-generation OCT, SD-OCT is slower than SS-OCT. All OCT generations are able to assess central retinal thickness (CRT) values, subretinal fluid (SRF), intraretinal cystoid fluid (IRC), disruption or thickness changes of retinal layers i.e. disorganization of the retinal inner layers [DRIL]; and the status of the vitreomacular interface . It can also visualize the destructive response of the retina with laser application.



OCTA. Microaneurysms appear hyperreflective vascular lesions surrounded by area of non-perfusion



OCTA (Upper). PDR. Blue arrow. Structural B Scan (Lower) points to blood flow above ILM [33].

OCT is exceptionally vital in the identification of macular edema and is particularly suited to determine whether retinal fluid is center involving or not, however, it cannot identify the source of leakage, nor the degree of capillary drop out present. Standard spectral-domain OCT (SD-OCT) cannot identify foveal ischemia and widening of the FAZ which are important prognostic

indicators of outcome. However, OCT-A has the potential to focus on different retinal layers in depths and highlight alterations at the level of the deep capillary plexus as a primary event in DR. It thus helps to select those patients who are best suited for intravitreal injection therapy (center involving) or those for laser (extrafoveal). FA might still be needed in some cases to guide treatment, for example in cases of juxta foveal leakage and retinal thickening. A micro-aneurysm is often undetectable in the flow-based OCT-A. To date, FA allows a more comprehensive assessment of the extent of the structural damage to the macular microcirculation before initiation of treatment and therefore better monitoring of results of treatment. On the contrary OCT-A depicts perfusion instead of structural vascular features. There is an ongoing work on the improvement of OCT-A technology in terms of hardware like swept source, longer wavelength, and software like improved algorithms for slow flow detection and elimination of projection artifacts. Contrarily, it has also been reported that areas of DME acts like a flow voids and these on OCTA appear frequently larger than the cystoid spaces themselves (Fig.11) giving an inaccurate impression as seen in figure below [34].

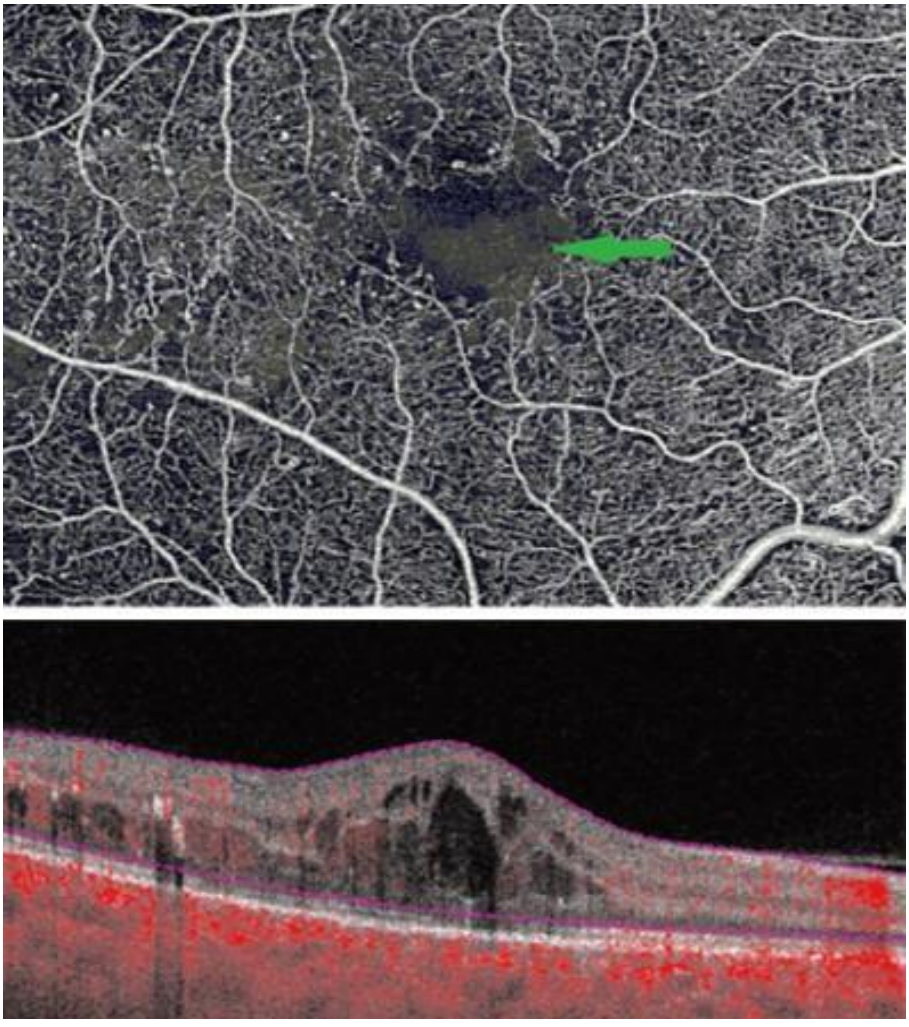


Fig.11. En face OCTA (upper) Diabetic macular edema. OCTA B- Scan (lower) Structural image shows severe edema

OCT is very effective in detection of hemorrhage, exudate and photoreceptor atrophy which can be supplemented by colour photography. OCT effectively assesses vitreoretinal interface at macula in differentiating Vitreoretinal attachment from vitreoretinal traction, such as vitreomacular traction (VMT).

Retinal thickening can occur due to VMT, excess glial tissue in the nerve fiber layer, intra-retinal edema /cysts and sub-retinal fluid. Thickening of the nerve fiber layer occurs early but does not affect vision. Intra-retinal edema /cysts in the absence of retinal thickening occur more frequently than previously thought. OCT depicts the consequence of prolonged edema on the retinal structure in the form of large cysts with thin intervening pillars, ruptured cysts and pseudo holes. However OCT changes do not always commensurate with the effect of edema on visual function.

Although, FA has already established enlargement of the foveal avascular zone (FAZ) in patients with DR as well as further enlargement with progression of DR. OCTA has further confirmed these findings [35]. Quantitative FAZ metrics on OCTA have been devised to demonstrate these trends, like FAZ area, acircularity index, axis ratio, area, and perimeter [36] (Fig.12). Both acircularity index and axis ratio are found to be significantly greater in eyes with DR [37].

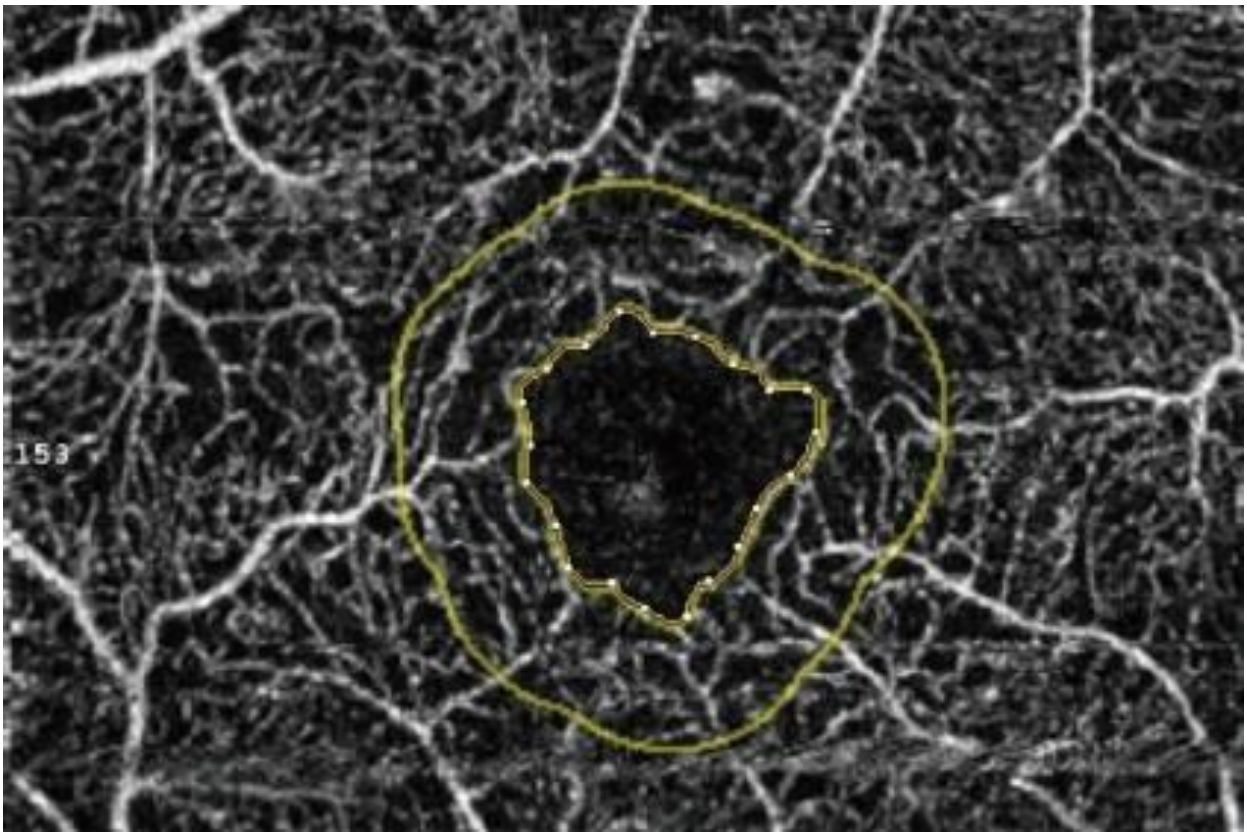


Fig.12. Calculation of FAZ and FAZ perimeter.

Advances in OCT like Doppler-OCT and OCT-A allow the visualization of vascular structures and can differentiate between perfusion and non-perfusion. Nevertheless, these advances are still lacking the ability of visualizing vascular leakage.

The gold standard in diagnosing DME still remains FA. It can detect different hallmarks of DR like MAs,

PDR, ischemic areas and especially DME due to vascular leakage. OCT can be used for screening, classification, monitoring, and treatment evaluation of DME. It has the ability to provide information on CRT as well as distinct morphological features of the edema. Additionally, it can show persistent morphological changes after DME treatment

It is recommended that for proper diagnosis and monitoring of DME, FA should be done along with OCT and continued fundus biomicroscopy. OCT in combination with visual acuity measurements can be used to monitor recurrence. The disorganization or disruption of the inner retinal layers, disruption of the inner and outer photoreceptor segments and/or ELM, and a thin subfoveal choroid at baseline may predict bad visual acuity after therapy. It is recommended to monitor disease activity through monthly OCT in order to detect any morphological change at the earliest.

**Fundus Autofluorescence (FAF)**

FAF is a noninvasive modality. Short-wavelength FAF derives its signal mainly from lipofuscin in the retinal pigment epithelial (RPE) while near-infrared (NIR) FAF derives its signal from melanin, found both in RPE and choroid. Melanin is mostly present in the apical parts of the RPE cells and is thought to be protective of the RPE [38].

Mostly short-wavelength FAF is employed and increased autofluorescence is seen in patients with DME [39,40,41,42]. Other patterns of FAF are seen, such as a single or multiple cysts of increased autofluorescence [39], single-spot increased FAF and multi-spot increased FAF [43] (Fig.13).

FAF represents the metabolic activity of the retinal pigment epithelium. Through FAF the visual potential of patients may be predicted indirectly by assessing the status of the retinal pigment epithelium and the health of the adjacent photoreceptors. Previous laser photocoagulation treatment marks which are not clinically evident can be easily detected with FAF, helping in guiding any re treatment.

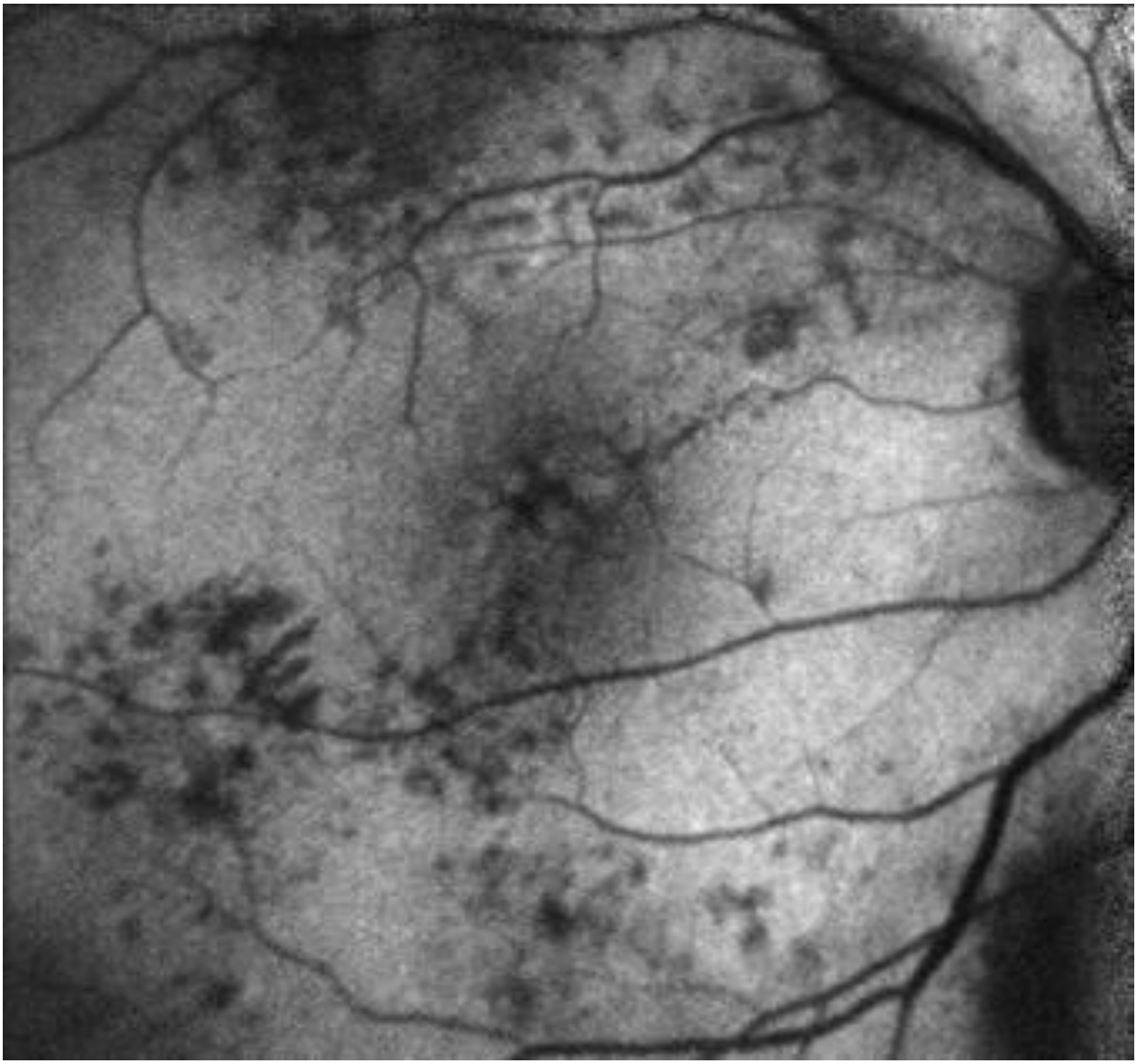


Fig.13. FAF. Areas of hyper and hyper-reflectivity in macular edema. Multiple areas of hyper-reflectivity at fovea corresponds to intra-retinal cysts.

# Section 3

# Treatment Modalities

## Retinal Lasers

Despite the current wide use of anti-VEGF agents, laser photocoagulation still enjoys its substantial role in the treatment of DR. Laser energy is delivered to the retina through a dilated pupil using wide field lenses like Volk, Mainster or Rodenstock and slit lamp bio-microscope. Photocagulation is also done using an indirect ophthalmoscope where needed. These lenses give an inverted but good view of the macula, pre and post- equatorial retina.
Generally, laser treatment is done in a single or multiple sessions and both eyes can be treated in the same session. While treating macular area one should be careful if there are exudates lying close to fovea; as these can increase when edema is treated and may spill over to fovea leading to permanent effect on central vision. Pan retinal photocoagulation is done to ablate the non-perfused or ischemic retina. Re-treatment can be performed within one to three months if the response is inadequate. Laser can also be applied during vitrectomy through indirect ophthalmoscope or endolaser.

There are certain **side effects** of the laser treatment as well, such as:

### *a) Pain*

It may be due to the direct heat effect on the branches of posterior ciliary nerves. It is usually experienced with prolonged treatment in one sitting or lasing the previously treated area during re treatment. Topical anesthesia is usually sufficient but periocular or even general anesthesia may be needed in certain cases when complete laser is to be done in a single sitting. Simple analgesics may be prescribed at the end of laser session.

### *b) Vitreous Hemorrhage*

Laser therapy results in contraction regression of the new vessels which were pulled forward from the retinal surface and were adherent to the posterior vitreous face. These vessels may bleed during the dynamics of regression leading to subhyaloid or vitreous hemorrhage. The patient should be informed of this occasional happening prior to treatment.

### *c) Visual Functions*

After complete PRP the visual field is reduced by about 40-50% which can affect the driving ability of the patient. This effect can be reduced by limiting the burn size to around 200 microns.

Some loss in contrast sensitivity and ERG is also expected [44]. Fovea may also be damaged inadvertently leading to gross visual handicap. Photophobia is also reported.

### *d) Choroidal Neovascularization (Secondary)*

If laser energy is too high, especially in macular area, retinal pigment epithelium and Bruch's membrane may be disrupted leading to chorioretinal neovascularization resulting in loss of central vision. Laser power must be reduced while moving from peripheral towards central retina while doing PRP. Similarly one should be conscious about the lens tilt as well.

### *e) Macular edema*

Pan-retinal photocoagulation may also lead to development or worsening of macular edema which is usually transient. Patient must be warned of this expected happening after PRP. If there is pre-existing macular edema, it should be treated prior to or along PRP [45-48].

### *f) Other side Effects:*

Pallor of the optic disc after PRP can be seen sometimes with disturbed pupillary reaction.

There may be, retinal detachment, pre and sub retinal fibrosis or increased vitreoretinal traction.

Choroidal effusion, shallow anterior chamber or angle closure and raised intraocular pressure may also occur. Iris discolouration and atrophic patches can be seen.

Corneal burns have also been reported.

## Intravitreal VEGF Inhibitors

It has been established that VEGF levels are raised in vitreoretina in patients with DR. Vascular permeability is increased by VEGF by increasing the phosphorylation of tight junction proteins so plays as an important mediator in the breakdown of BRB [49] leading to retinal thickening and macular edema

### Pegaptanib

Pegaptanib (Macugen) was the first anti VEGF agent used and found useful in the treatment of DME. It is specific to 165 isoform of VEGF A. It has been used in the doses of **0.3mg, 1mg and 3mg** intravitreal. After initial trials, no further studies were pursued on this drug, so its use is no more in vogue.

## Ranibizumab

Pharmacologically, Ranibizumab is a recombinant humanized Fab fragment of a monoclonal antibody. It has been prepared for intravitreal injection. It binds and inactivates all isoforms of VEGF-A. The approved dose in Europe is **0.5 mg** per injection and **0.3 mg** in the US. Treatment is initiated early with monthly intravitreal injections. If signs of improvement i.e. improvement in visual acuity, decrease in central retinal thickness (CRT) or other morphological markers of the disease are seen, monthly injections are continued until visual acuity and/or OCT indicate stability or the disease is inactive. Thereafter, patients are monitored at monthly interval for one year with visual acuity testing and OCT imaging. Thereafter the interval is tailored according to the patient response. If there is a stage when no further benefit is seen, the treatment must be stopped and monitoring interval is decided for each patient individually.
Several studies have proved its superior efficacy over laser treatment. Even when laser is used in combination, no additional benefits have been found on DME. It is found to be systemically also very safe on monthly administration without an increase in cardiovascular events. Studies are available on all three types of regimens; fixed monthly injections [50], **PRN (pro re nata) regimen** [51] and 'treat and extend' regimen. Monthly injections are feasible in the start of therapy for initial 3-6 months. After this the number of injections need to be dropped [52,53,54,55]. The therapy may also be started with a PRN regimen with comparable improvement in BCVA [56]. Follow up visits and monitoring can be adjusted to the disease response. Usually monthly or bimonthly monitoring is recommended. An alternative approach is the **"treat and extend regimen."** This is suggestive of a flexible treatment regimen with extended intervals, bimonthly or so. This may be more viable and less burdensome strategy for most of the patients.
Generally, Ranibizumab is recommended for patients with a baseline BCVA letter score of **69** letters or above and CRT greater than **400µm** (preferably) on OCT. The use of ranibizumab in patients with poorer baseline visual acuity, the results are achieved at a slower rate as compared to Aflibercept.
Early laser treatment, where needed, combined with Ranibizumab shows better results as compared to deferred laser treatment.

## Bevacizumab

Bevacizumab is a full-length, humanized, monoclonal antibody that attaches to all VEGF isoforms and inactivates them. This was basically developed to metastatic colon cancer by inhibiting the vessel growth in the tumor tissue [57]. Its intravitreal dose is **1.25 mg in 0.05 ml**. Intravitreal half-life of bevacizumab in human vitreous ranges from 3 to 6.7 days [58]. Systemic plasma levels are significantly reduced at 4 weeks after a single bevacizumab injection [59, 60]. The treatment regimens can be the same as those of Ranicizumab.
Comparing the efficacy and safety of bevacizumab, aflibercept, and ranibizumab in treatment of DME, the results depend upon baseline BCVA letter score. While aflibercept and ranibizumab are the drugs of choice for BCVA letter score of less than **69**, all are equivalent in improving vision in eyes with a baseline BCVA letter score of **69** or more. Systemic adverse effects are minimal and Bevacizumab is much lower in cost as the injection vial can be shared among several patients.

## Aflibercept (VEGF-Trap-Eye)

Aflibercept is a recombinant (soluble VEGF receptor fusion protein) decoy receptor type of inhibitor of VEGF and placental growth factor that binds to all isoforms of VEGF-A as well as placental growth factor and inactivates them. It has been shown to be better than laser as regards visual and anatomical outcome. It is the drug of choice in DME patients with baseline visual acuity letter score of **69** or worse and shows better results than Ranibizumab and Bevasizumab. Its results are comparable to other two agents in patients with BCVA letter score **69** or better. The intravitreal dose per injection is **2.0mg**.The choice is open to the ophthalmologist's judgement; whether to adopt a course of loading injections at 4-weekly intervals followed by bimonthly injections or a PRN regimen with monthly monitoring.
Aflibercept offers a chance of visual improvement and fewer injections to the patients (from second year onward) with DME involving foveal center. It has a higher binding affinity compared to that of ranibizumab and bevacizumab and a longer duration of action [61, 62]. This makes it suitable for treatment of DME, being a chronic problem.

## High-dose Aflibercept (HD)

FDA has approved a higher aflibercept dose of 8mg for the treatment of wet AMD, DME and DR, allowing for extended intervals between treatments of up to 16 weeks. The recommended regimen is monthly injections for the first three months followed by treatments every eight to 16 weeks in wet AMD and DME and every eight to 12 weeks for DR.

This happened due to the positive results of two clinical trials, Pulsar and Photon, which demonstrated non-inferiority and clinically equivalent vision gains at 48 weeks with eight-, 12- and 16-week dosing regimens after the three initial monthly doses in nAMD and DME[63,64].

Adverse reactions, seen in 3% or fewer of patients, include cataract, conjunctival hemorrhage, increased intraocular pressure, ocular discomfort, eye pain or irritation, blurry vision, floaters, vitreous detachment, corneal epithelium defect and retinal hemorrhage

## Step Therapy

With all these new treatment options, the current reality is that treatment decisions depend not only on doctor preferences, but logistical considerations and patients' affordability. In many cases some sort of "step therapy" might be required where more affordable options like Bevacizumab to be tried first, and then changed in a stepwise approach if response is suboptimal. While there are many concers regarding step therapy, the results of DRCR Network Protocol AC have been reassuring that, on average, patients will not be harmed by step therapy[65].

## Faricimab

FDA approved it in January 2022 for the treatment of nAMD and DME.

It is a bispecific humanised monoclonal antibody (IgG1). It has two different antigen-binding domains (Fab) on the antibody [66,69] . After binding, it inhibits both vascular endothelial growth factors, factor A (VEGF-A) and angiopoietin-2 (Ang-2). Angiopoietin has two isoforms, Ang-1 and Ang-2, that bind to tyrosine kinase (Tie-2) endothelial receptors to regulate vasculogenesis.[66] Ang-1 is an agonist of Tie-2 and has vessel-stabilizing effects,[67] while Ang-2 is an antagonist which leads to endothelial destabilisation, pathological angiogenesis and loss of pericytes resulting in vascular leakage and

inflammatory response. In presence of Ang-2, blood vessels become more sensitive to VGFA-A. Ang-2 and VEGF-A potentiate each other to cause vascular permeability and neovascularisation. By inhibiting the two agents, faricimab decreases vascular permeability, inflammatory response and neovascularization thereby stabilizing the retinal vascular structure.

Usually, for diabetic macular edema (DME), faricimab is injected every 4 weeks for the first 4 doses. After that, a personalized treatment interval similar to treat and extend (T&E) may be adopted. The interval may be adjusted according to the response of CMT as measured by OCT.[70] The two types of regimens that are mentioned in literature are :

1. 6 mg (0.05 mL of 120 mg/mL solution) given by intravitreal injection 4 weekly (approximately every 28 days ± 7 days) for at least 4 doses. If after at least 4 doses, resolution of edema based on the central macular thickness (CMT) as measured by OCT and visual acuity evaluations is achieved, the interval of dosing may be extended by 4-8weeks through week 52.

2. 6 mg (0.05 mL of 120 mg/mL solution) can be administered every 4 weeks for the first 6 doses, followed by intervals of every 8 weeks (2 months) over the next 28 weeks. Patients must be assessed regularly.'

Common side effects include conjunctival hemorrhage, eye pain, vitreous floaters and increased intraocular pressure. Serious potential adverse effects include endophthalmitis , retinal detachment, vitreous hemorrhage, retinal vasculitis, and retinal vascular occlusion. Less common side effects include blurred vision, change in vision, redness of the eye, sensitivity to light and thromboembolic events like stroke. Rare but serious adverse effects like severe intraocular inflammation and even blindness have also been reported.

## Brolucizumab

Approved by FDA in 2019 for the treatrment of DME and nAMD

6 mg (0.05 mL of 120 mg/mL solution) by intravitreal injection q6Weeks (~39-45 days) for first 5 doses, followed by 6 mg q8-12Weeks

The main advantage of brolucizumab is that with about half of the patients in both the nAMD and DME trials were able to maintain stability at q12 week dosing schedule.[71,72]

The main disadvantage of this drug is that it carries about 4% risk of intraocular inflammation including severe vasculitis.[73]

## Steroids

Recently, inflammation has been found to play a role in development of DME. Pathologically, leukocytes accumulate on the surface of retinal capillaries leading to the upregulation of intracellular adhesion molecule (ICAM)-1, attracting monocytes and neutrophils to the vascular endothelium. This leads to further leukostasis, vascular permeability, and BRB breakdown [74]. Steroids do have a place in treating DME but largely as a second option. These can be considered as first choice treatment in patients who are at a very high risk of major cardiovascular accidents and anti VEGFs are being avoided in them or the cases that are refractory to anti-VEGF (after 3–6 injections generally). Compounds available for intravitreal use include, triamcinolone acetonide, dexamethasone posterior segment delivery system (**0.7mg**), and fluocinolone.
The downside is development of cataract in phakic eyes and raised intraocular pressure.

Pseudophakic patients are preferred for the use of steroids, otherwise patients are informed of this risk. IOP has to be monitored regularly.

### *a) Triamcinolone Acetonide*

Triamcinolone acetonide, **1-4mg** intravitreal, has been recommended for the treatment of DME in patients who have been inadequately responding to other treatments.

### *b) Dexamethasone*

Dexamethasone (**0.7mg**) in the form of intravitreal implant releases the corticosteroid into the vitreous over a period of ≤ 6 months [20]. Retreatment is recommended after 6 months and concurrent treatment of both eyes is not recommended. This is especially suitable for pseudophakic eyes not responding to or unsuitable for other treatment.

### *c) Fluocinolone acetonide*

The approved dose for the fluocinolone acetonide is **0.19 mg**. It is injected as a slow release product and provides sustained delivery in the eye for at least one year [75]. So treatment may be repeated after one year while monitoring visual acuity and CRT.

## PKC β inhibitors

Protein Kinase C has also been considered responsible for increased vascular permeability in DME and PKC inhibitors have been found to reduce VEGF induced [76] vascular permeability. An experimental trial has shown 30% reduction in visual loss by use of an isoform, PKC β (ruboxistarin) in DME [77]. This product is not yet available for clinical use.

## Biosimilars

Biosimilars are the "generic versions" of biological compounds, but these are different from traditional drugs and biological compounds. Traditional drugs are smaller molecules that can be replicated through chemical synthesis while biological compounds, or biologics (anti-VEGFs), are large-complex molecules which cannot be precisely replicated due to their large size and complicated manufacturing. A biosimilar, structurally, is not identical to its reference (traditional or biological) drug but is similar in structure, function, safety and efficacy.[78]
Biosimilars are being created to reduce the cost and replace anti-VEGFs. There are currently two FDA-approved biosimilars of Lucentis available for use in the United States: Byooviz (ranibizumab-nuna, Biogen/Samsung Bioepis) and Cimerli (ranibizumab-eqrn, Coherus BioSciences). Byooviz was the first to receive FDA approval in 2021 for the treatment of nAMD, macular edema following RVO and myopic CNV.[79] The following year, in 2022, Cimerli became approved as an interchangeable biosimilar for the treatment of all prior indications of Lucentis (nAMD, DR, DME, myopic CNV and macular edema following RVO).[80]

It is feared that due to manufacturing and licensing cost, biosimilrs may not reduce the overall cost as much as expected.

In general, production of anti-VEGF biosimilars has the potential to decrease the cost of care and increase accessibility of more effective treatment options. However, it is unclear how well these medications will be accepted by physicians. Complicated manufacturing process of these compounds, where apparently benign changes could lead to increased adverse reactions, with particular concern

for immunological responses.[78] Use on a broader scale will uncover if these concerns are true or not. However, it is positive to have these additional and more affordable options with numerous other biosimilars for Lucentis and Eylea in clinical trials.

## Novel Delivery Methods

Exploration of alternative dosing strategies to overcome the concerns due to repeated and costly intravitreal injections for nAMD, DME and DR, some innovative drug delivery methods have been devised. surged. One of these innovations includes permanent implantable devices such as the port delivery system (PDS; Susvimo implant, Genentech).[81,82] This device received FDA approval for nAMD in 2021 and was in clinical trials for DME and DR.

After surgical implantation of the device, patients had the port refilled every six months, which was more tolerable than frequent intravitreal injections. However, in October 2022, Genentech voluntarily recalled Susvimo due to a mechanical failure of the device during the refill procedure, and the company paused all new implantations, including those in ongoing global clinical trials.[83] Currently, there are no updates on the device's status. As for patients who received the PDS during clinical trials or post-FDA approval, as long as the device is intact, they can continue receiving the appropriate interval refills.

Other delivery devices under investigation include bioerodible implants, such as depot formulations of sunitinib malate GB-102 (Graybug Vision) and genetic therapies that introduce genetic material through subretinal or suprachoroidal injection of adeno-associated virus vectors.[84,85] These genes alter the ocular tissue to produce endogenous anti-VEGF with the hope to seize or reduce the need for intravitreal injections. Several are in various stages of clinical trials for AMD, DR and even GA.

## Alternatives to Injections

In addition to all above therapies, there is potential for topical and oral agents in the treatment of these conditions. OTT166 (OcuTerra Therapeutics), an integrin inhibitor, is a proposed engineered molecule that has shown safety and efficiency via topical application for treatment of DR in early-phase trials. Currently, the DREAM (Diabetic Retinopathy Early Active Management) study is in Phase II trials for further investigation.[86]

APX3330 (Ocuphire Pharma) is an oral agent that—despite failing to meet its primary endpoint of reversal of moderately severe to severe DR (ETDRS severity levels 47 and 53) in its Phase II trial, ZETA-1—did demonstrate good systemic and ocular safety. In addition, it was announced recently that ZETA-1 showed a statistically significant reduction in the progression of DR to more advanced stages in those taking APX3330.[87]

Xiflam (InflammX) is also an oral agent that inhibits inflammasomes. It is currently under investigation for treatment of DR and DME.

## Future Possibilities

Currently, there are nearly 90 investigational novel agents in the pipeline for various retinal diseases, primarily targeting wet and dry AMD, DR, DME and inherited retinal disorders.[88]

# Section 4

# Current Recommendations

## General

### *a) Counselling*

Patient education and counselling plays an important role in management of diabetic patients, in physicians' clinics as well as in the eye clinics. Patients with sight threatening retinopathy need additional counselling on its impact on vision as well as different treatment options.
Patients should be explained clearly and carefully about the risks and benefits of any intervention like laser photocoagulation and intravitreal drug delivery of different types. Emphasis must be laid on regular attendance for further intervention and continuous care.
Ophthalmologists are expected to address to the psychological needs of the patient as well.

### *b) Consent*

Since the treatment is prolonged and needs constant monitoring and follow up, the patient must be well briefed and made aware of the whole treatment plan and prognosis. Patient should be educated about treatment modalities including lasers and anti-VEGF agents likely to be used. On the basis of this, a comprehensive informed consent is to be obtained from the patient before the start of the laser treatment.

### *c) Anesthesia*

For PRP, topical anesthesia is usually sufficient. In certain cases peribulbar or even general anesthesia may be required (laser treatment done through indirect ophthalmoscope or endolaser in operating room) [88]. For intravitreal anti-VEGF injection, topical anesthesia is sufficient.

### *d) Laser delivery*

Laser photocoagulation in an outdoor procedure except in certain cases where it is delivered in the operating room. It should be performed only by a trained and experienced ophthalmologist.

### *e) Reducing treatment side effects*

Impaired night vision and visual field defects which occur after PRP can be prevented by avoiding large confluent burns and using short pulse duration laser. Appropriate counselling is required as complete PRP can aggravate vitreoretinal traction and lead to vitreous hemorrhage. A demarcation

line should be placed temporal to macula while applying laser temporally, using wide angle lens, to avoid accidental macular burn.

### *f) When to stop Laser treatment*

Blunting or replacement of the advancing tips of NVs with fibrous tissue indicate regression. Application of laser to peripheral retina is not necessary for successful control of vasoproliferation and in advanced cases new vessels may persist even after adequate treatment. New vessels which do not bleed or progress and have blunted advancing ends are thought to be stable and do not need further laser treatment. OCT or FFA might have to be repeated to look for the ischemic areas. Cases that do not stabilize even after full treatment, may need vitrectomy and endo-laser.

### *g) Administration of Intravitreal Anti-VEGF*

It has to be done under topical anesthesia and strict antiseptic conditions in operating room preferably or a special room dedicated for this purpose. Pre injection instillation of antibiotic drops and/or 0.5% Povidone-iodine solution in the conjunctival sac is recommended. This should be applied to the eyelids and eye lashes as well. A 30G or thinner, and preferably 18mm (5/6 inch ) (ICO guidelines 2017) long needle to be used preferably to deliver the recommended dose into the vitreous. In case bilateral injection at the same time, injection for each eye should be considered as a separate procedure following full standard procedure. The surgeon should wear sterilized gloves and mask. After applying the eye speculum povidone iodine is applied as the last thing at the intended site just before injection. Injection is given between the horizontal and vertical recti at the pars plana, **3.5 to 4.0 mm** posterior to the limbus in the quadrant suitable to patient's condition or surgeon's preference. A simple perpendicular injection approach is preferred in most settings. After injection an eye pad may be given for a short while if needed. A combination of antibiotic and corticosteroid in the form of eye drops may be given for a few days. The patient may see a bubble or a big floater for a few hours or so.

## Recommendations for Management of Different Stages of DR

### *a) Mild to moderate non-proliferative retinopathy NPDR (Background retinopathy)*

As such no treatment is indicated for this stage of DR [89]. Annual monitoring with digital fundus photography would suffice. Two standard photographic fields can be used so that at least 80% of the sight threatening retinopathy can be monitored (the same is seen in 7 field stereo colour photographs of the same fundus) [90]. The risk of progression of DR with uncontrolled DM [91] can be reduced by intensive blood sugar control in type 1 [92] and by intensive blood pressure control along with blood sugar control in type 2 [93].

### *b) Pre-proliferative diabetic retinopathy (Severe non-proliferative diabetic retinopathy)*

Patients with pre-proliferative DR or advanced NPDR, need more frequent monitoring tailored by an expert ophthalmologist who is experienced to detect features of retinal ischemia. Patients should be examined every 4-6 months. Wide angle retinal examination is preferred. Approximately 3.2% patients progress to proliferative stage with in a year [94]. Digital colour fundus photography (CFP), Fluorescein angiogram (FA) and OCT/OCT-A should be employed to monitor fundus changes. Development of choroidal neovascularization after laser, expected in advanced cases, can be ruled out using swept source OCT or Indocyanine green angiography (ICG).
As this advances further to proliferative stage, laser scatter treatment (PRP) should be considered to prevent progression to high risk PDR and avoid severe visual loss (SVL). This risk is 48.5% within one year which might lead to the need of vitrectomy [95]. Early complete PRP reduces the risk of progression to PDR by 50% and of VSL to 2.6% at 5 years [68].
PRP treatment should be considered in the following cases of severe pre- proliferative DR:

- Elderly patients with DM Type2
- Patients not compliant to regular follow up, or difficult to be examined repeatedly because of other reasons.
- Prior to cataract surgery
- Only eye, the other eye already lost because of PDR

### *c) Proliferative diabetic retinopathy (PDR)*

Full scatter PRP treatment is required for new vessels (NVD, NVE). It should be done as soon as possible within two weeks of diagnosing high risk PDR. Full scatter PRP means treating all four quadrants of pre- and post-equatorial retina outside the macular vascular arcades. Initially the treatment is given to the area outside vascular arcade up to just posterior to ora serrata, particularly addressing ischemic areas avoiding direct application to the new vessels (NV). The risk of SVL in patients with high risk characteristics is reduced by 50% at 2 and 5 years by PRP and by up to 70% in moderate risk patients [96]. Anti VEGF treatment with Bevacizumab, Ranibizumab and Aflibercept in combination or without corticosteroid preparation (Triamcinolone) is in vogue now. It has gained its popularity because of high effectivity, easy availability, low investment cost and less time required to administer. The down side aspects, mainly are: it is costly to the patient, has to be repeated as the effect is not permanent and risk of endophthalmitis.

### *d) Advanced PDR*

In advanced cases of PDR where we see traction bands, traction retinal detachment, extensive hemorrhage and anterior segment involvement (NVI); anti-VEGF treatment and laser PRP may appear to have little effect on new vessel progression. In such cases early vitrectomy can preserve the useful sight and intravitreal injection of anti VEGF just prior to vitrectomy reduces intraoperative complications and operative time.

# Technical Guidelines on PRP

## *a) Intensity, Pulse duration and spot size*

With presently available laser (532nm argon-green laser), the spot size of 300-500µm, duration of 10-50ms and spacing of 1-1.5 burn apart and power setting of 50-100mW are recommended. It is aimed to have a barely-visible, grey/white burn reaction on retina while applying laser. The laser burn intensity at 20ms may continue to increase up to 1 minute after application, so lasing time is to be titrated with patience to avoid excessive burn. This titration is done easily outside the vascular arcade and then should be continually moderated throughout the session. With 20ms pulse, the power would need to be reduced to 50mW while treating the pre-equatorial thin retina to avoid unnecessary damage.

Smaller spot sizes like 200µm /300µm can lead to higher laser power/ laser fluence, risking rupture of Bruch's membrane at 20ms exposure time. This small spot may further shrink to less than100-150µm after healing, resulting in need of further laser therapy. On the contrary, larger retinal spots, 500µm or more will need increase in laser power and duration to produce the same effect, which may make the procedure uncomfortable for the patient.

Although, generally, 20ms exposure time and 400µm retinal spot size are preferable for PRP but these should be titrated for individual patients need, tolerance and laser reaction observed on the retina for a given power setting. This is true for both standard as well as pattern scan laser systems.

Different laser contact lenses have different spot magnification depending upon their make (Table 1), so this factor is to be considered while adjusting the spot size and power level [97,98]. For instance, if 200µm spot size is selected, a Mainster 165 PRP lens (Ocular Instruments Inc.), with spot magnification factor of 1.96 will theoretically produce a retinal burn spot of 392µm. Patient's refractive error affects the field of view of lens being used.

Table-1: Different Fundus Lenses and their magnification effects.

| **Name of lens** | **Field of view (in degrees)** | **Image magnification** | **Laser spot magnification** |
|---|---|---|---|
| Mainster focal/grid | 90-121 | 0.96 | X 1.05 |
| Mainster PRP 165 | 165-180 | 0.51 | X 1.96 |
| Area Centralis | 70-84 | 1.06 | X 0.94 |
| TransEquator | 110-132 | 0.70 | X 1.44 |
| Quadraspheric | 120-144 | 0.51 | X 1.97 |
| Superquad 160 | 160-165 | 0.50 | X 2.00 |

### *b) Burn Spacing*

For mild and moderate PDR, burns should be placed 1 burn width apart; but in severe cases of PDR, traction retinal detachment (TRD) and vitreous hemorrhage, it should be reduced to 0.50 burn width apart to have a better therapeutic effect on wide ischemic area.

### *c) Area to be treated*

Laser burns should be applied as far as possible up to the ora serrata as peripheral retina is the main ischemic area. Usually 510–1280mm2 (2600–6500, 500µm conventional laser burns) of retinal surface area is to be ablated.

## Strategy for Primary PRP

### *a) Early Proliferative Retinopathy*

When the new vessels are flat and the NV complexes (NVD/NVE) are less than 1/3$^{rd}$ of disc diameter (DD), primary PRP is done within two weeks of examination and 1200-1800 burns are applied. The patient is reviewed after 4 months. This is also true for non-pregnant female patients.

### *b) Moderate PDR*

When NVD involve more than 1/3$^{rd}$ DD and the forward extending (leaving the retinal surface) new vessels extend beyond disc margin or NVE are seen in all the quadrants with forward extending complexes in any one quadrant, primary PRP is to be completed in two weeks in single

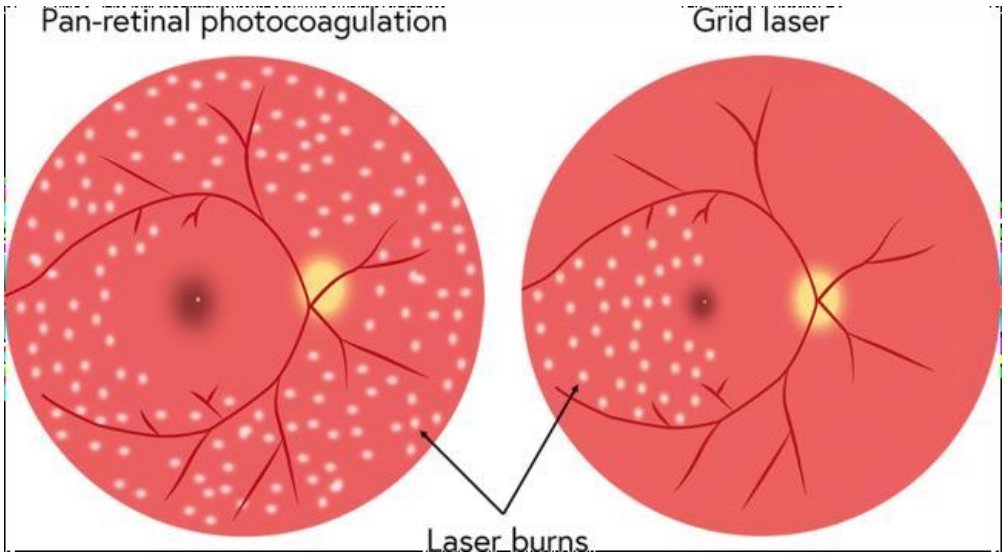



Fig.14

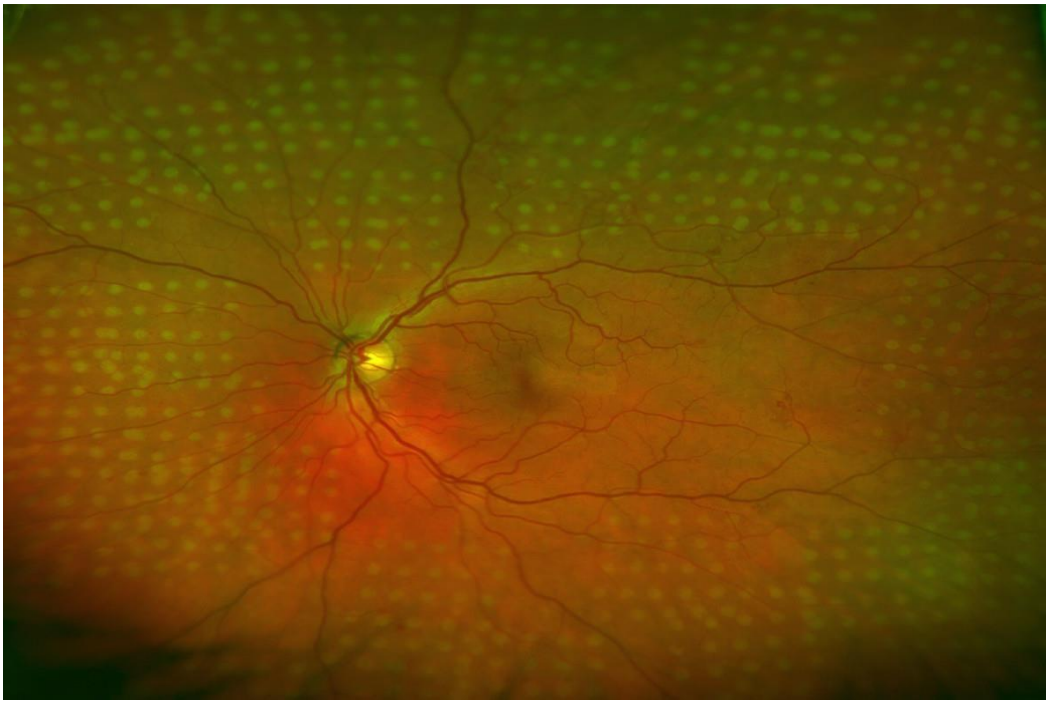


Fig. 15. PRP through pattern scanning laser system.

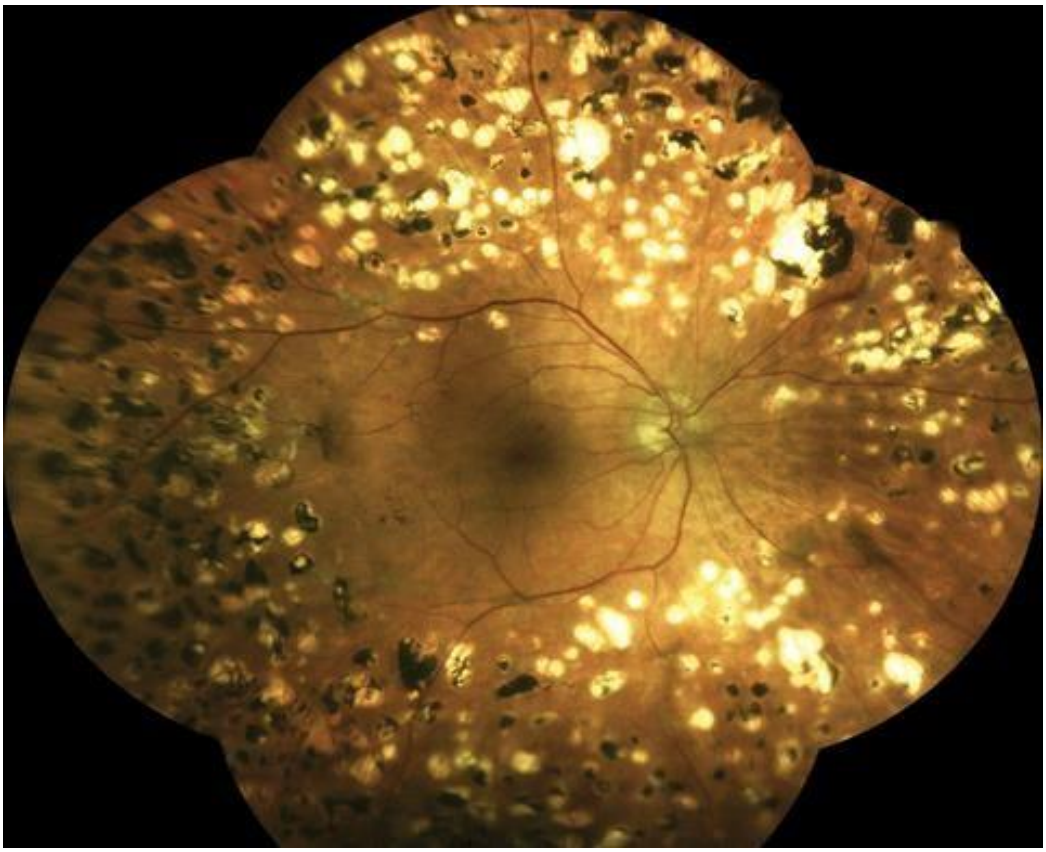


Fig.16. PRP. Laser marks.

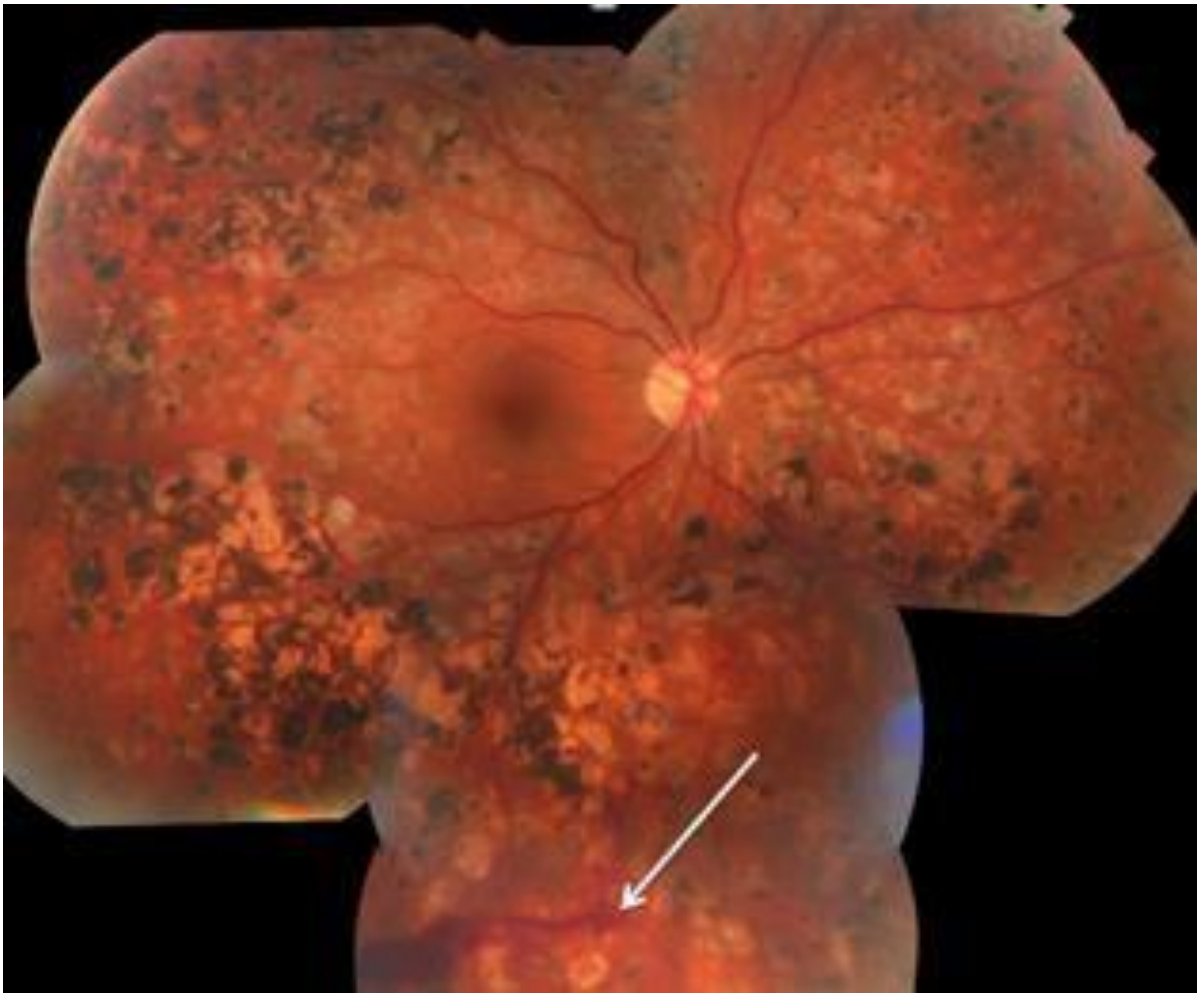


Fig. 17. Recurrence of proliferation after PRP.

or divided sessions applying 2000-2500 burns (Fig.14,15,16). Incase shorter duration laser pulse (20ms) is selected, then number of burns are to be increased and all sessions to be completed in one month's time.
The patient is requested to attend the clinic for review in 3 months but after shorter interval if the diabetic control is poor this also serves to treat the recurrence of proliferation (Fig.17). This is also true for non-pregnant female patients.

## *c) Severe PDR*

Severe PDR is marked by extensive NVE in any quadrant, NVE with tractional retinal detachment, large forward NVD covering whole optic disc and NVD with tractional retinal detachment. These are high risk cases entailing continued hemorrhage and traction following laser therapy. Full PRP coverage of peripheral retina is needed. This means around 3000 burns over 2-3 sessions in 3-4 weeks. If shorter duration (20ms) laser pulse is used more laser burns with treatment duration more than 4 weeks will be needed.
In the presence of retrohyaloid, inferior vitreous or subhyaloid hemorrhage associated with traction bands, laser should be applied to the retinal area with a clear view. The rest should be treated after

the hemorrhage clears. If the vitreous hemorrhage is not clearing and PRP is delayed then vitrectomy and intravitreal anti-VEGF injection is to be considered.

### *d) Pregnant diabetics with PDR*

In pregnant patients PDR can progress rapidly, so a prompt laser is done and patient is reviewed after two weeks after completing PRP. There is no contraindication to normal vaginal delivery if PDR is adequately managed. The ophthalmologist has to be in close touch with other treating physicians of the patient.

### *e) Type 1 Diabetics*

Patients with Type 1 DM of younger age group often have macular ischemia and are more prone to develop macular edema after PRP. The complete treatment should be divided in 3-4 sessions in 4 weeks time.

### *f) Rubeosis Iridis (NVI)*

When it is alone and the media are clear, immediately full retinal photocoagulation is to be done. When it is accompanied by neovascularization in the angle (NVA) without neovascular glaucoma (NVG), prompt PRP is to be done along with consideration for intravitreal injection of anti-VEGF [99]. In the presence of NVG, additional measures as cycloablative laser, cyclocryotherapy, implantation of drainage tubes and trabeculectomy with use of anti-proliferative agents might have to be employed to save vision.

## Management of Diabetic Maculopathy

### *a) Systemic treatment*

Management of diabetic macular edema (DME) starts with control of blood sugar level along with systemic blood pressure and serum cholesterol level. Ophthalmologists must work in close coordination with physicians and diabetologists.

### *b) Laser Therapy*

Before the introduction of anti-VEGF agents, laser photocoagulation had been the mainstay of treatment for DME. It is still in vogue and very effective in expert hands. The following strategy is used:

Microaneurysms lying within 500 to 3000μm of fovea and showing leakage are treated directly with 50μm spot size and pulse duration of 0.05-0.1s. The aim is to have a greyish reaction beneath the microaneurysm and not a total whitening (Fig.18). Areas of retinal thickening are treated with grid pattern laser.

Grid pattern laser is performed from 500 to 3000μm superiorly and inferiorly and to 3500μm temporally from fovea (Fig.19). The spots are kept 2 burn widths apart. No treatment is applied to area within 500μm of the disc margin.

A milder pattern of macular grid laser consists of a total of 200-300, 50μm burns, 2-3 burn width apart including unthickened retina regardless of site of microaneurysms.

Lately developed subthreshold micropulse laser theoretically avoids damaging the inner layers of retina, reducing chances of developing large post treatment scars and paracentral scotomas.

Photocoagulation reduces the risk of severe visual loss, and has a long term effect but currently the use of intravitreal anti-VEGF agents with early or delayed focal laser photocoagulation is the most followed regime in preserving and restoring vision in edema involving the center of macula, where visual acuity is reduced to 20/32 (6/10) or less.

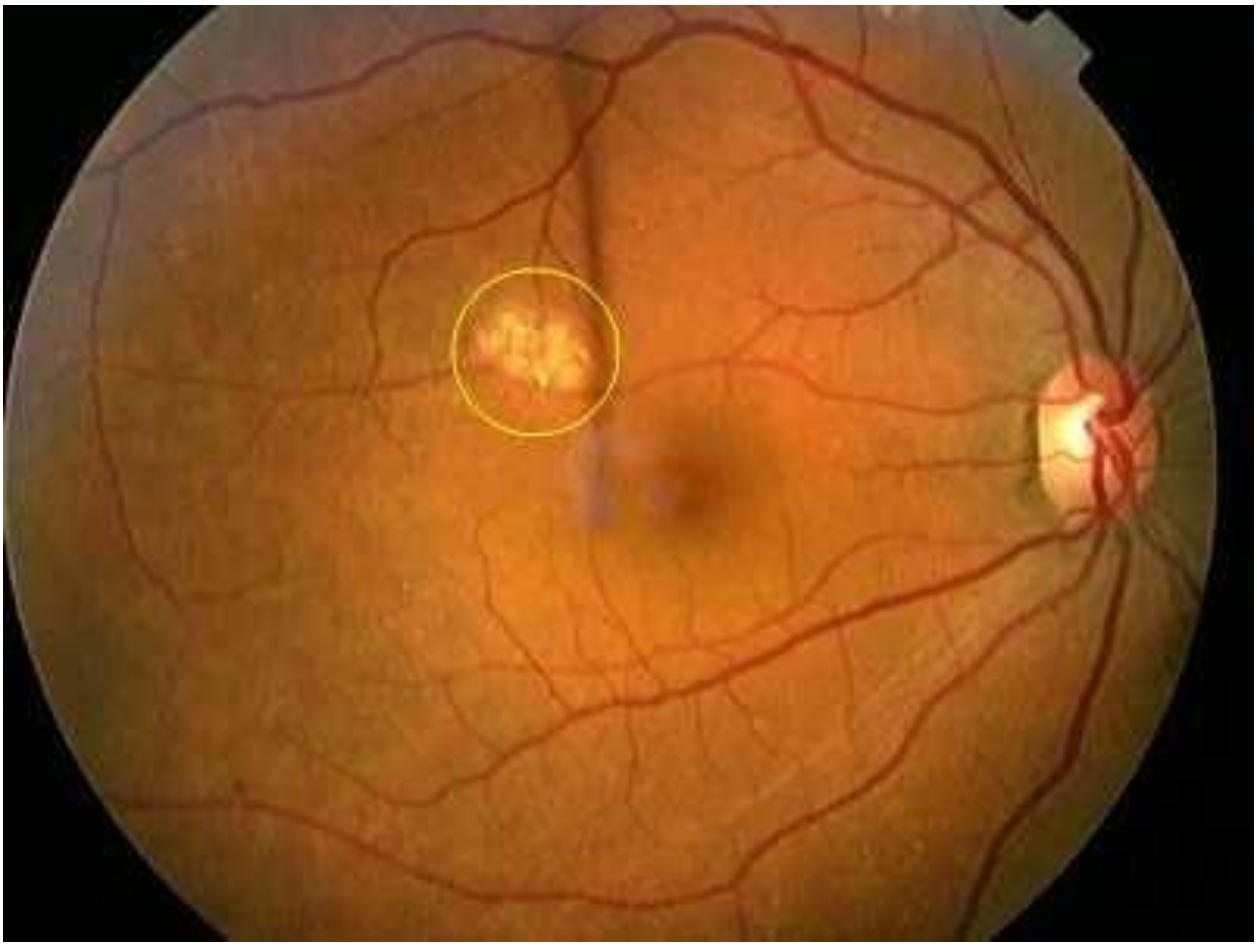


Fig.18. Focal Laser application.

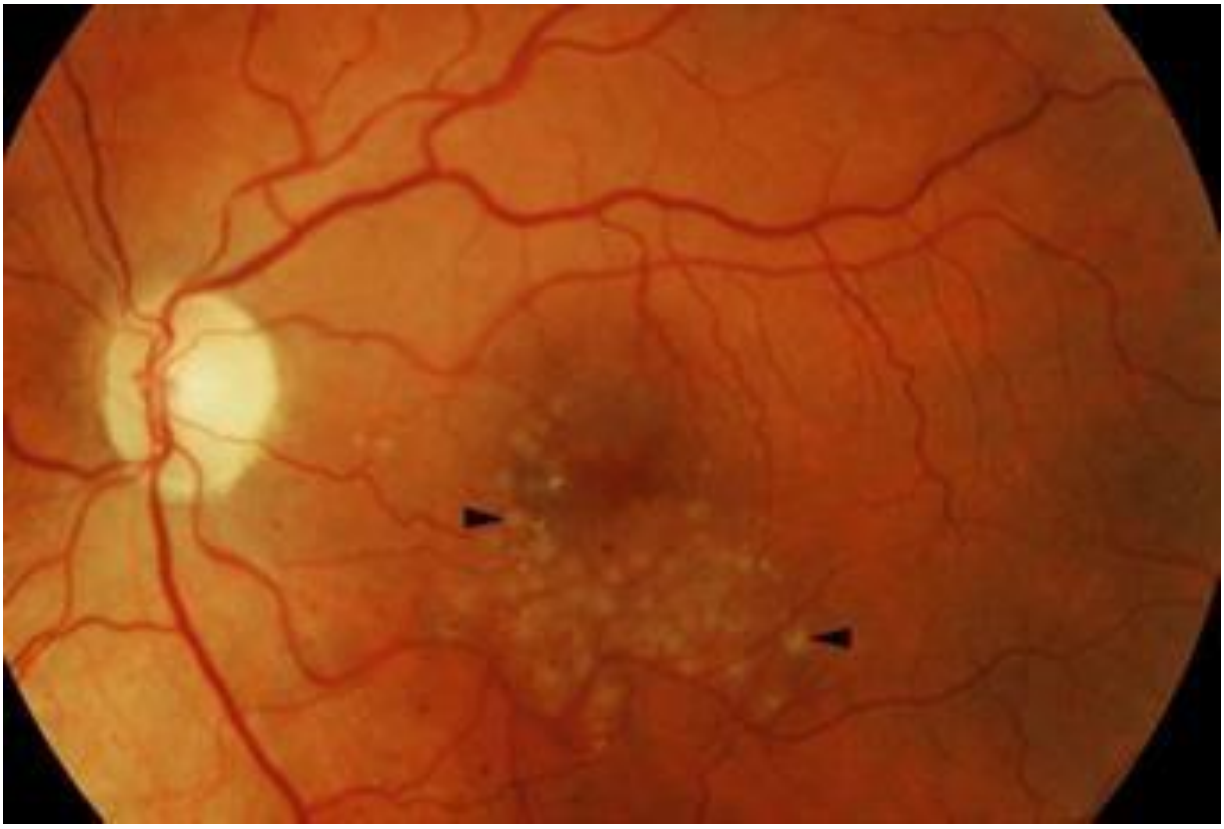


Fig.19. Fresh grid laser application.

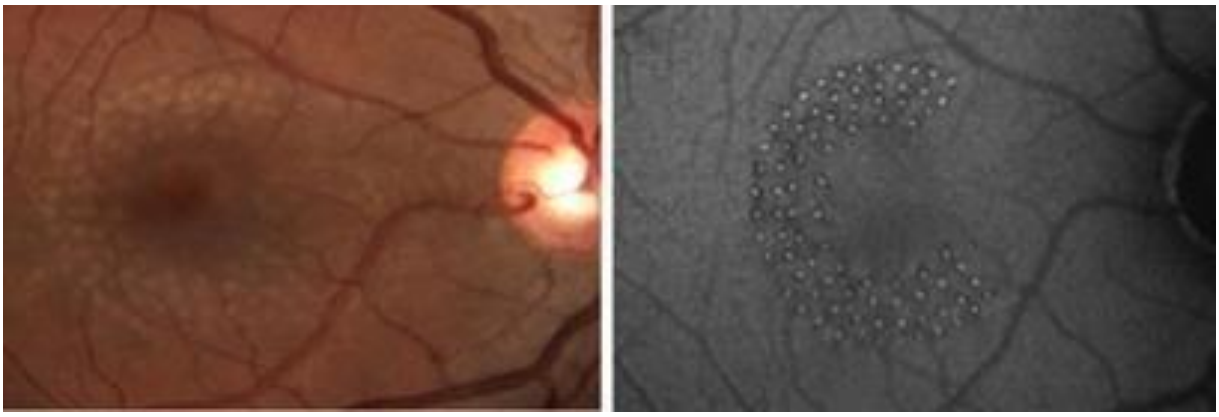


Fig.20. Fresh grid laser application through a pattern scanning laser system.

## *c) Intravitreal Corticosteroids*

Processes leading the Pathogenesis of DME, include increased levels of factors (like VEGF) that lead to vascular permeability, loss of endothelial tight junction proteins, and formation of

inflammatory mediators. Corticosteroids can effectively block these events so they are thought to have role in the treatment of DME.

Use of 4 mg preservative free intravitreal Triamcinolone with modified laser therapy has been found to have improved visual acuity at 4 months. As a monotherapy, it is inferior to laser and combined with laser, still inferior to intravitreal anti VEGF with immediate or delayed laser, except in pseudophakic patients. Slow release fluocinolone intravitreal implants have been found to be more effective, but there is a high rate of developing increased intraocular pressure and cataract. These are better suited for pseudophakic patients.

### *d) Laser Treatment of Maculopathy in the Presence of Retinal Neovascularization*

Diabetic maculopathy may exist with or without NVD or NVE. If these co-exist then which one to address first, depends on several factors as severity of retinopathy and age of the patient. This question arises when we are treating with laser alone or in combination. In young patients it is better to treat the new vessels first with PRP as these are more aggressive in young age. Concurrently macular laser may be done if deemed appropriate. Especially, peripheral retina should be treated as it has been found that peripheral retinal ischemia has important role leading to DME. PRP should preferably be fractioned in several session to avoid aggravation of macular edema. With the introduction of **pattern scanning laser systems**, the laser treatment has become more target specific (Fig.20) and spillover laser effects can be better avoided [100]. In lower risk PDR cases, it is better to treat macula first or concurrently.

### *e) Cataract surgery in presence of DME*

Fine and uncomplicated phacoemulsification surgery has reduced the risk of post operation aggravation of DR and DME [101], but pre-existing macular edema, severity of DR and diabetes mellitus do increase the risk of post-operation development or aggravation of macular edema. Ideally, macular edema should be fully treated before cataract surgery but in reality, some edema may persist despite all efforts (anti-VEGF, Laser) and cataract surgery may exacerbate it due to inflammation caused by surgery. Intravitreal triamcinolone has been proposed to be used at completion of surgery. Intravitreal anti VEGF injection may be given at the end of surgery depending upon the judgment of the surgeon. Patient should be informed of this risk and close monitoring after surgery is advisable.

Progression of DR has been seen in up to 20% of patients within twelve months following cataract surgery [102]. It is prudent to treat PDR with anti VEGF injection or laser PRP where possible if fundus view is adequate, around two weeks prior to surgery. If the fundus view is not adequate, laser may be applied just after conclusion of cataract surgery through indirect device. These patients are closely followed up after surgery to monitor for macular changes.

Cystoid macular edema (CME) is also seen more frequently in diabetics after cataract surgery . CME responds favorably to periocular or intraocular corticosteroids in addition to pre-operation topical non-steroidal anti-inflammatory agents [103,104,105].

## *f) Recommendations for treatment of Maculopathy with Clinically Significant Macular Edema*

Management of diabetic maculopathy depends on the location and extent of macular thickening. All indicated treatment modalities should be discussed with the patient so that they consider in the light of their individual circumstances and the treatment may then be tailored accordingly. Intravitreal injection should only be administered by an ophthalmologist experienced in this procedure. Treatment of clinically significant macular edema (CSME) may be done according to the following protocol.

| **CSME** | **Centre-involving** | **Visual acuity** | **Phakic /pseudophakic** | **OCT Finding** | **Treatment options** |
|---|---|---|---|---|---|
| Yes | No | Normal | Either | Off center Thickening | AntiVEGF/Photocoagulation |
| Yes | Yes | Normal or slightly reduced (better than 78 letters) >6/10 | Either | Off center /Mild central thickening | Anti VEGF according to the standard protocol.<br>Low intensity grid laser |
| Yes | Yes | Reduced (78-24 letters) 6/10-6/90 | Phakic | ≥250µm central subfield thickness | Intravitreal anti-VEGF treatment with or without laser . If the eyes are unresponsive to other treatments, intravitreal corticosteroid to be considered, bearing in mind the untoward effects. |
| Yes | Yes | Reduced. (78-24 letters) 6/10-6/90 | Pseudophakic | ≥250µm central subfield thickness | Intravitreal anti-VEGF or intravitreal triamcinolone (preservative – free) with or without laser. If the eye is not responding then intravitreal dexamethasone or fluocinolone slow release implant may to be considered depending upon availability. |
| Yes | Yes | < 24 letters 6/90 | Either | VMT | Vitrectomy with intravitreal anti-VEGF (with or without corticosteroid depending upon surgeon's judgement). |

## *g) Suggested treatment regime with anti VEGF*

Patients with center-involving macular edema and reduced vision will benefit most from intravitreal anti-VEGF. Start with monthly injections for 4-6 months, then follow treat & extend (preferable) or pro re nata (PRN) schedule with continuous follow up with OCT scan and visual acuity assessment and treatment during 1st year until the macula is dry or no further improvement is seen. If the patient becomes stable then in the 2$^{nd}$ year onwards, the follow up gap may be increased to 12-16 weeks unless there is some recurrence indicating frequent follow up again.
Patients with poor visual acuity (below 24 letters- 6/90) may be observed particularly if the macular edema is chronic and there is considerable macular ischemia unless the ophthalmologist expects some benefit of some intervention.

## *h) Laser treatment for Maculopathy*

Macular laser is reserved mostly for the patients who are unwilling for intravitreal injections.
Patients with clinically significant macular edema (CSME), not involving the center may be treated with laser photocoagulation.

## *i) Monitoring and Follow up schedule*

Patients undergoing anti VEGF therapy require monthly follow-up for at least one year while patients undergoing macular laser need follow-up every three to four months unless there is an indication for more frequent visits.

Regular monitoring of intraocular pressure is required for patients undergoing intravitreal steroid therapy.

Patients with early maculopathy without any CSME and early non proliferative DR (NPDR) may be followed up and monitored through colour fundus photographs (CFP) and OCT scans, at 4- 6 monthly intervals.

# Section 5

## Establishment of Diabetic Care Service

### Expected Features of a Diabetic Care Service

A diabetic eye care services should have:

1. Qualified and well trained ophthalmologists who can perform cataract surgery if needed and treat DR and DME with different available treatment modalities.
2. An adequate trained work force including paramedical and other staff to cater for all the needs of the service.
3. Adequate and purpose built building to cater for patients reception, registration, screening and adequate management.
4. An appropriate and sustained source of funding.
5. A process for screening for diabetic eye disease including pregnant women DM and gestational diabetes.
6. An on-line consultancy service should be available to engage experienced ophthalmologists in the country and abroad.
7. An efficient/smart record/data keeping system for recall and follow up of the patients.
8. All the relevant/modern diagnostic and treatment facilities including all the machines and appropriate space.
9. Facility to regularly monitor those who are already getting treatment.
10. A facility to address special people and those with psychosocial problems.
11. Provide education and information to the patient and family/caretaker about the disease and all its implications.
12. A well-developed network with other hospitals, voluntary social services and charity organizations to cover all the patients belonging to different strata and segments of the society.
13. An adequate, efficient and honest governance.

# Section 6

# Quick Guide

## 1. Intravitreal Injections:

| | |
|---|---|
| Ranibizumab | 0.3-0.5 mg /0.05ml |
| Bevacizumab | 1.25 mg/ 0.05ml |
| Aflibercept | 2.0 mg / 0.05ml |
| High- Dose Aflibercept | 8.0 mg / 0.05ml |
| Faricimab | 6 mg / 0.05 mL |
| Brolucizumab | 6mg / 0.050 ml |
| Triamcinolone acetonide | 1-4 mg / 0.05 ml |
| Dexamethasone | 0.7 mg (Posterior segment delivery system) |
| Fluocinolone | 0.19 mg |

## 2. Laser: [106]

532nm Argon-Green:

| | |
|---|---|
| PRP: | Spot size: 200-500µm, duration 10-100ms (0.01-0.1sec), spacing 1-1.5 burn apart.<br>Power: Adjust power to produce a gentle blanching burn.<br>Area to be lased: 510–1280mm2 (usually 2000–3000 laser burns)<br>Temporal barrier to be placed at least 2-3DD temporal to fovea.<br>If patient feels pain, reduce duration (0.05 sec) but increase the power to maintain burn intensity.<br>Review after three weeks for fill in burns according to the response. |
| Macular Focal Laser: | Spot size: 50-200µm, duration 80-100ms (0.08-0.1sec).<br>Power: Adjust power to produce a blanching burn.<br>Apply to leaking MAs 500-3000µm from center of fovea. Lesions as close as 300µm from center may be lased provided these are not inside FAZ. |
| Macular Grid laser: | Spot size: 50-200µm, duration 80-100ms (0.08-0.1sec), spacing 1-1.5 burn apart. At least 500µm from foveal center and the disc.<br>Power: Adjust power to produce a gentle blanching burn. |

# 3. Follow up and Treatment Schedule by an Ophthalmologist

| **DR Severity** | **Follow-up Schedule** | **Treatment Plan** |
|---|---|---|
| No apparent DR | 1-2 years | |
| Mild NPDR | 1-2 years | |
| Moderate NPDR | 6-12 months | |
| Severe NPDR | < 3 month | Consider early PRP |
| PDR | <1 month | Consider PRP/Anti-VEGF |
| Stable PDR (Treated) | 6-12 months | |
| **DME Severity** | **Follow-up Schedule** | |
| Non center involving DME | 3-6 months | Focal laser may be considered |
| Center involving DME | 1-3 months | Focal/Grid, Anti-VEGF, Steroids |
| DME with PDR | <1 month | Anti-VEGF +/- PRP |
| Stable DME | 3-6 months | |
| Vitreomacular traction (VMT) | | Pars plana vitrectomy (PPV) |

# 4. Management of risk factors; the ideal targets

Optimal control of blood sugar levels, hypertension and serum lipids is vital for the prevention and progression of diabetic retinopathy. Treating physician / diabetologist should be consulted in this regard. Suggested target ranges are:

**HbA1c**

<6.5% is the ideal
<7.0 or <8.0 may be acceptable

**Blood Pressure (BP)**

Patients with diabetic retinopathy should have a target BP of 130/80.

In the presence of nephropathy (even microalbuminuria) this should be lower.

**Lipids**

Desired lipid values

TC < 5.0 mmol/l

LDL-c < 3.0 mmol/l
TG < 2.3

It is recommended that statins to be started in:

Patients with diabetes aged 40 or over
Patients with diabetic retinopathy aged 19 or over

# Section 7

## Quick Labelling Guide for Screening & Action/Referral

### (Primary health care centers / Qualified opticians)[107,108]

### Retinopathy

| Label | Retinopathy Level | Action |
|---|---|---|
| R0 | No retinopathy | Annual screening at primary care center |
| R1 | Background / early NPDR (Fig.21) | Annual screening at primary care center |
| R2 | Preproliferative/ moderate to late NPDR (Fig.22) | Referral to the ophthalmologist. To be seen within 3 months (13 weeks) |
| R3A | Active Proliferative DR (Fig.23) | Referral to the ophthalmologist. To be seen within 2 weeks |
| R3S | Stable treated Proliferative DR (Fig.24) | Referral to the ophthalmologist. To be seen within 13 weeks |

### Maculopathy

| Label | Maculopathy Level | |
|---|---|---|
| M1 | a) exudate within 1 disc diameter (DD) of the center of the fovea (Fig.25).<br>b) circinate or group of exudates within the macula (Fig.26).<br>c) any microaneurysm or hemorrhage within 1 DD of the center of the fovea only if associated with a best VA of +0.3 logMAR (6/12) or worse | Referral to ophthalmology clinic for expert advice within 2 weeks |
| M0 | No lesion within 1DD (disc diameter) or<br>VA better than 0.3LogMAR with no exudates within 1dd<br>(i.e. does not meet any of the categories<br>of M1) | Annual screening at primary care center |

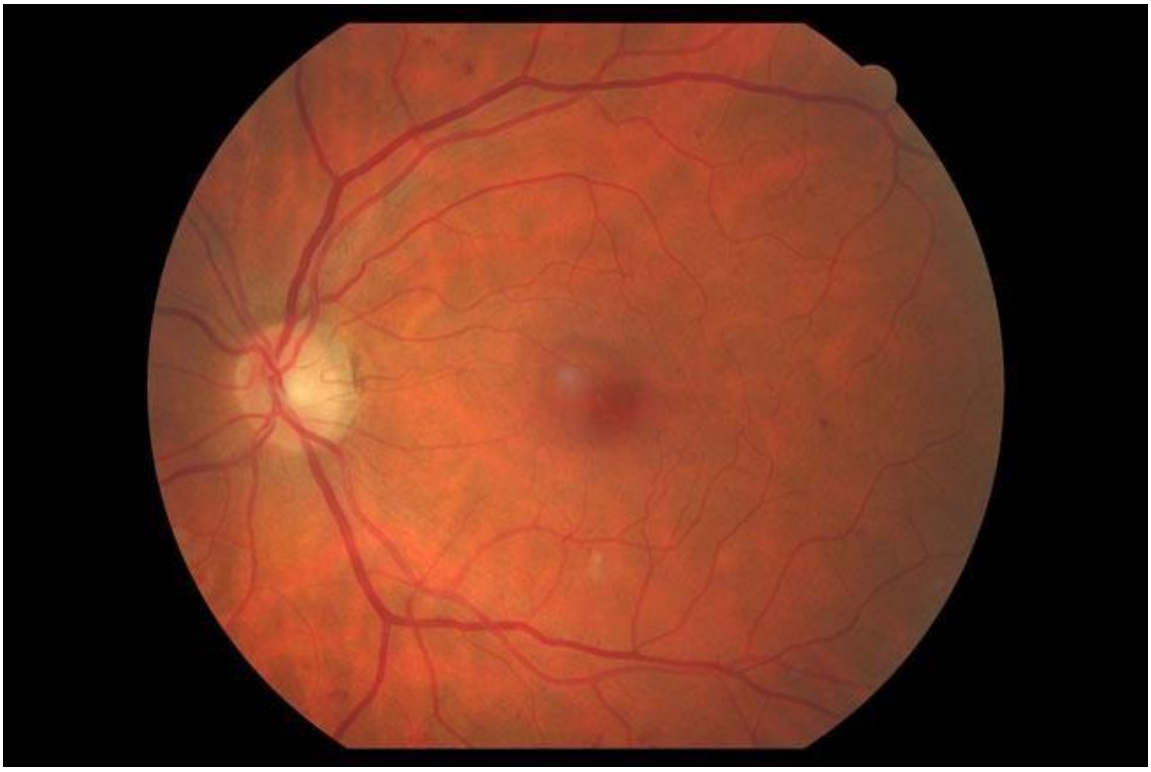


**Fig. 21. R1, M0**

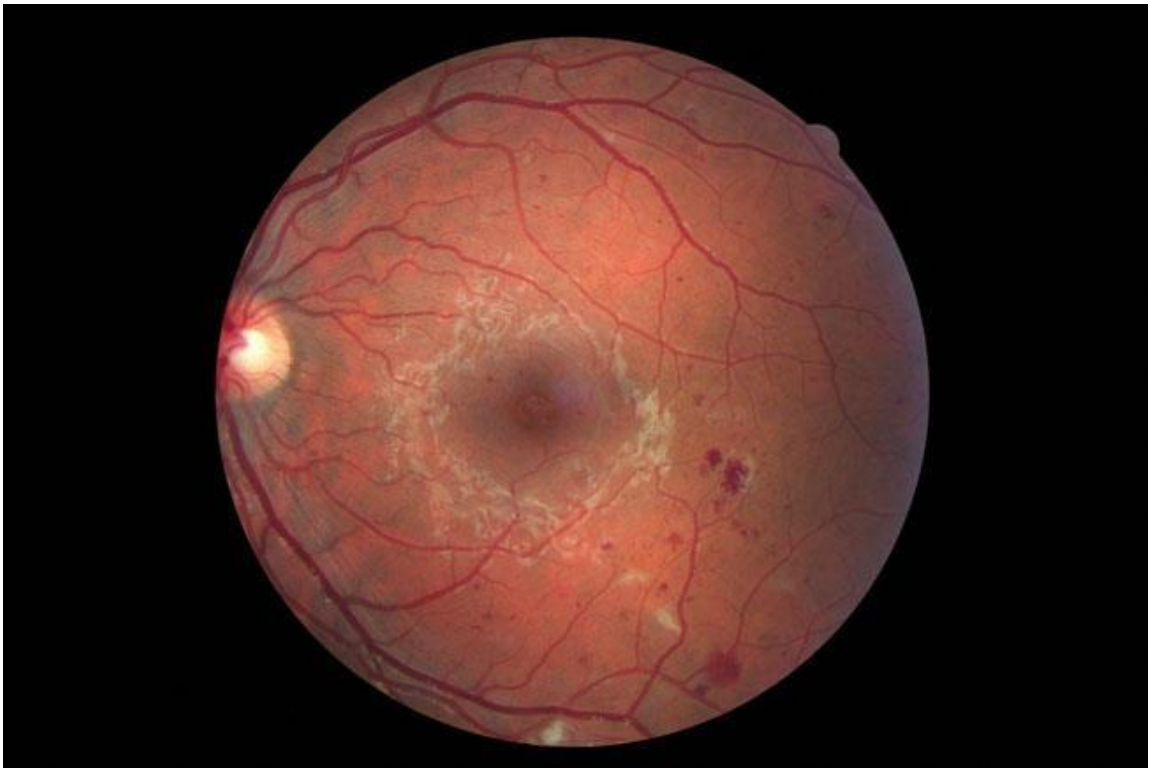


**Fig.22. R2, M0**

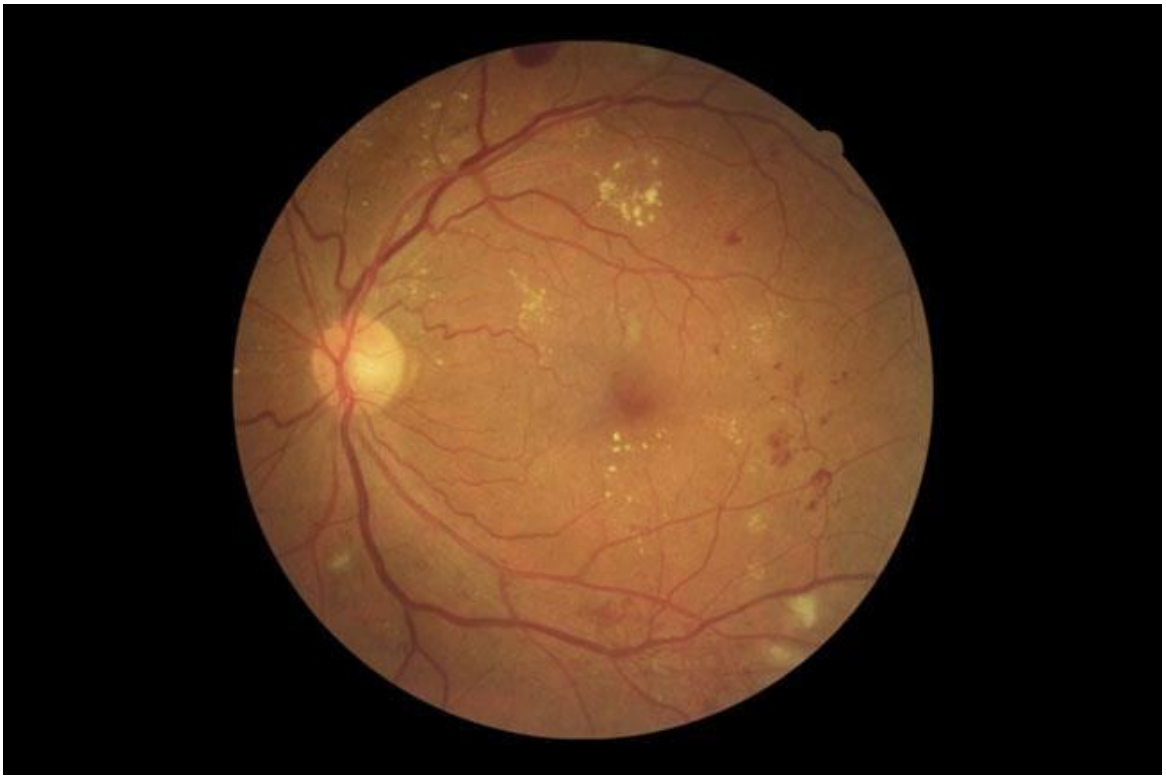


**Fig.23. R3A, M1**

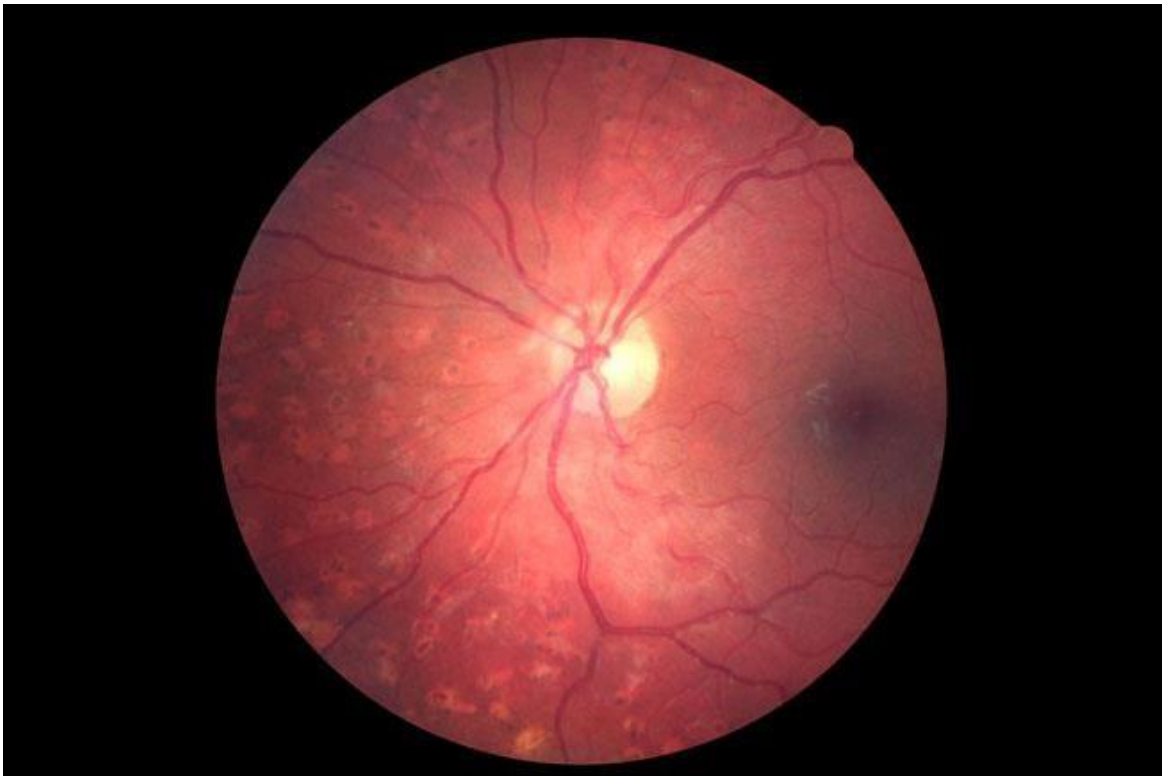


**Fig.24. R3S, M0, P1**

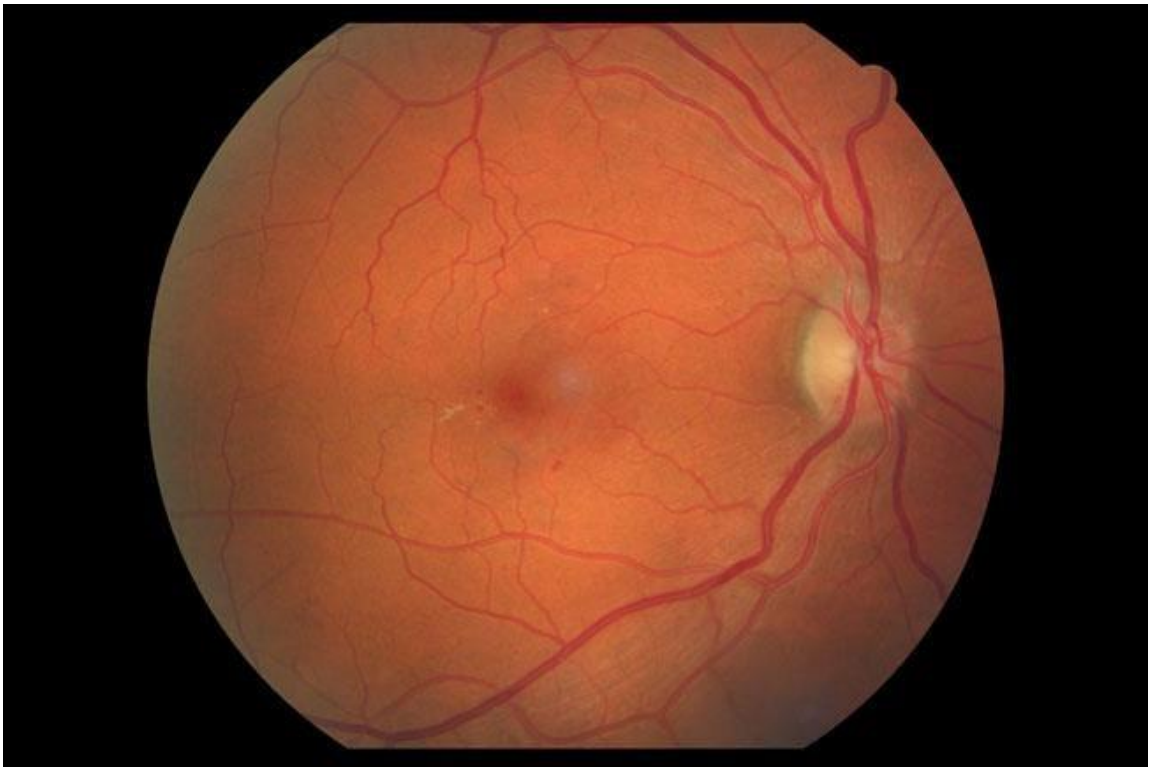


**Fig.25. M1, Exudates within 1DD**

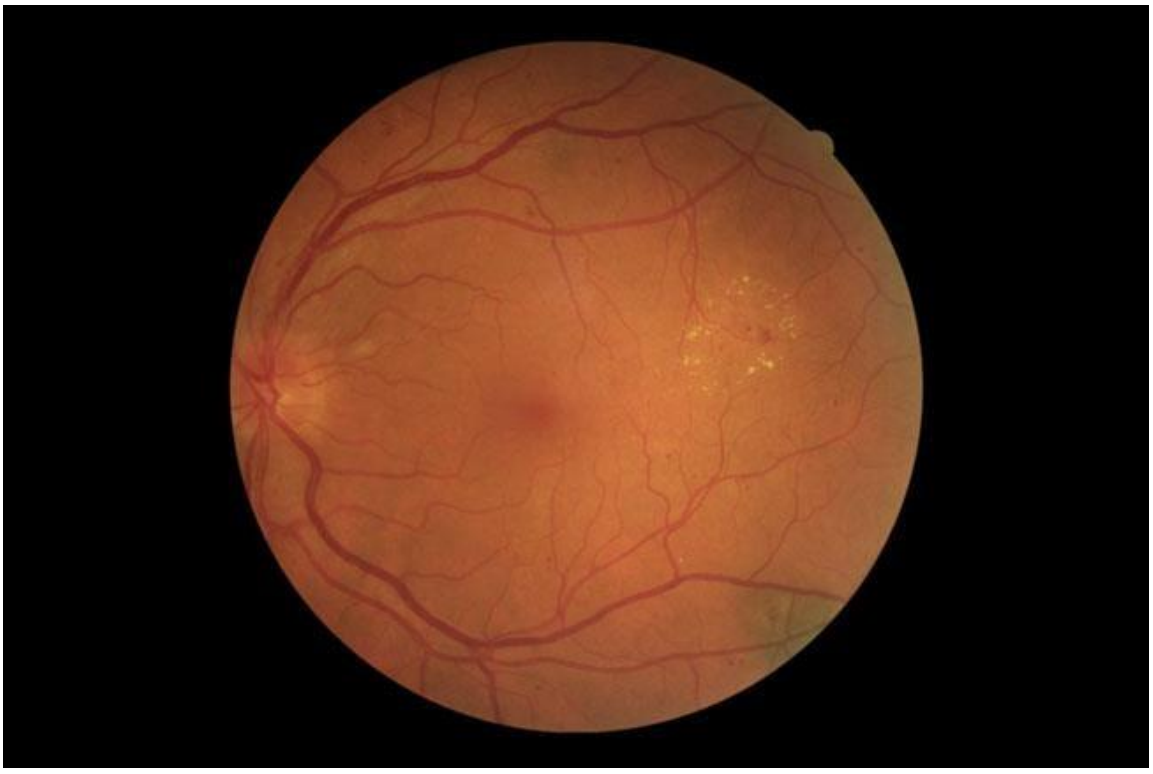


**Fig.26. M1, Exudates away from fovea but greater than 0.5 DD**

# Section 8

## References


1. SIGN Guideline 116. Management of diabetes. A national clinical guideline, available on line -http://www.sign.ac.uk/pdf/sign116.pdf (accessed 14/1/12)
2. The worldwide epidemic of diabetic retinopathy Yingfeng Zheng,1,2 Mingguang He,1 and Nathan Congdon1. Indian J Ophthalmol. 2012 Sep-Oct; 60(5): 428–431.
3. Diabetes Care 2012 Mar; 35(3): 556-564.).
4. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care*2001;24(11):1936-40.
5. 5.Type 2 diabetes epidemic: a global education. *Lancet* 2009;374(9702):1654.
6. Glen Y Ozawa, Marcus A Bearse Jr,Kevin W Bronson-Castain, Wendy W Harrison, Merilyn E Schneck, Schirin Berez, Anthony J Adams. Neurodegenerative Differences in the Retinas of Male and Female Patients with Type 2 Diabetes. Investigative Ophthalmology & Visual Science. May 2012, Vol.53, 3040-3045.
7. White N, Cleary P, WD. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the DCCT *J. Pediatr* 2001; 139:804-812.
8. Lueder G, Silverstein J, Section on Ophthalmology, Section on Endocrinology. Screening for Retinopathy in the Pediatric Patient with Type 1 Diabetes Mellitus. *Pediatrics*2005;116:270-273.
9. Stratton IM, Cull CA, Adler AI, Matthews DR, Neil HA, Holman RR. Additive effects of glycaemia and blood pressure exposure on risk of complications in type 2 diabetes: a prospective observational study. Diabetologia 2006; 49: 1761-1769.
10. Dodson PM. Medical treatment for diabetic retinopathy: do the FIELD microvascular study results support a role for lipid lowering? Practical Diabetes 2008; 25: 76-79.

11. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo- controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.
12. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, Taskinen MR, Simes RJ, Tse D, Williamson E, Merrifield A, Laatikainen LT, d'Emden MC, Crimet DC, O'Connell RL, Colman PG, FIELD study investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007; vol.370 (9600):1687-1697
13. ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, DanisRP,Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, Perdue LH, Goff DC Jr, Cushman WC,Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010 Jul 15;363(3):233-44. Epub 2010 Jun 29.
14. Wright AD, Dodson PM. Medical management of diabetic retinopathy: fenofibrate and ACCORD Eye studies. Eye (Lond) 2011; 25(7): 843-849.
15. Moss SE, Klein R, Klein BE. Association of cigarette smoking with diabetic retinopathy. Diabetes Care.1991;14(2):119-26.
16. 15.KaramanosB,PortaM,SonginiM,MetelkoZ,KerenyiZ,TamasG,RottiersR,StevensLK,Fuller JH. Different risk factors of microangiopathy in patients with type I diabetes mellitus of short versus long duration. The EURODIAB IDDM Complications Study. Diabetologia 2000; 43(3): 348-355.
17. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. Diabetes Care 2010; 33(8):1872-94.
18. Kaaja R, Loukovaara S. Progression of retinopathy in type 1 diabetic women during pregnancy. Curr Diabetes Rev. 2007; 3(2): 85-93.

19. Arun CS, Taylor R. Influence of pregnancy on long-term progression of retinopathy in patients with type 1 diabetes. Diabetologia. 2008; 51(6): 1041-5. Epub 2008 Apr 8.

20. Diabetic Retinopathy Guidelines. The Royal College of Ophthalmologists. 2012.

21. Chiarelli F, Spagnoli A, Basciani F. Vascular endothelial growth factor (VEGF) in children, adolescents and young adults with Type 1 diabetes mellitus: relation to glycaemic control and microvascular complications. *Diabetic Medicine* 2002;17:650-656.

22. John D. Ferris. Essential Medical Ophthalmology. Reed Educational and Professional Publishing Ltd. 2001. pp 225-227.

23. American Academy of Ophthalmology. Preferred practice pattern: Diabetic retinopathy. San Francisco CA., 2003.

24. American Diabetes Association. Diabetic Retinopathy.*Diabetes Care* 2002;25:s90-s93.

25. Lueder G, Silverstein J, Section on Ophthalmology, Section on Endocrinology. Screening for Retinopathy in the Pediatric Patient with Type 1 Diabetes Mellitus. *Pediatrics*2005;116:270-273.

26. Chakrabarti R, Harper C A, Keeffe J E. Diabetic Retinopathy Management Guidelines. Expert Rev. Ophthalmol.7(5)417-439(2012).

27. Commissioning Guidance for people with learning disability and diabetes. NHS Diabetes June 2011www.diabetes.nhs.uk

28. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA**)** Ophthalmologica 2017;237:185–222.

29. Wessel MM, Aaker GD, Parlitsis G. et al. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. Retina. 2012;32:785-791.

30. Kong M, Lee MY, Ham DI. Ultrawide-field fluorescein angiography for evaluation of diabetic retinopathy. Korean J Ophthalmol. 2012;26(6):428-431.

31. Silva PS, Cavallerano JD, Sun JK, et al. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. Ophthalmology. 2013;120(12):2587-2595.

32. de Carlo TE, Romano A, Waheed NK, et al. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous 2015;1:5.

33. Stanga PE, Papayannis A, Tsamis E, et al. New Findings in Diabetic Maculopathy and Proliferative Disease by Swept-Source Optical Coherence Tomography Angiography. Dev Ophthalmol 2016;56:113-21.
34. Spaide RF. Volume-Rendered Optical Coherence Tomography of Diabetic Retinopathy Pilot Study. Am J Ophthalmol 2015;160:1200-10.
35. Bresnick GH, Condit R, Syrjala S, et al. Abnormalities of the foveal avascular zone in diabetic retinopathy. Arch Ophthalmol 1984;102:1286-93.
36. Gozlan J, Ingrand P, Lichtwitz O, et al. Retinal microvascular alterations related to diabetes assessed by optical coherence tomography angiography: A cross-sectional analysis. Medicine (Baltimore) 2017;96.
37. Krawitz BD, Mo S, Geyman LS, et al. Acircularity index and axis ratio of the foveal avascular zone in diabetic eyes and healthy controls measured by optical coherence tomography angiography. Vision Res 2017;139:177-86.
38. Yoshitake S, Murakami T, Horii T, Uji A, Ogino K, Unoki N, *et al.* Qualitative and quantitative characteristics of near-infrared autofluorescence in diabetic macular edema. Ophthalmology 2014;121:1036-44.
39. Pece A, Isola V, Holz F, Milani P, Brancato R. Autofluorescence imaging of cystoid macular edema in diabetic retinopathy. Ophthalmologica 2010;224:230-5.
40. Vujosevic S, Casciano M, Pilotto E, Boccassini B, Varano M, Midena E. Diabetic macular edema: Fundus autofluorescence and functional correlations. Invest Ophthalmol Vis Sci 2011;52:442-8.
41. Chung H, Park B, Shin HJ, Kim HC. Correlation of fundus autofluorescence with spectral-domain optical coherence tomography and vision in diabetic macular edema. Ophthalmology 2012;119:1056-65.
42. Bessho K, Gomi F, Harino S, Sawa M, Sayanagi K, Tsujikawa M, *et al.* Macular autofluorescence in eyes with cystoid macula edema, detected with 488 nm-excitation but not with 580 nm-excitation. Graefes Arch Clin Exp Ophthalmol 2009;247:729-34.
43. Vujosevic S, Casciano M, Pilotto E, Boccassini B, Varano M, Midena E. Diabetic macular edema: Fundus autofluorescence and functional correlations. Invest Ophthalmol Vis Sci 2011;52:442-8.

44. Canning, C., P. Polkinghorne, A. Ariffin, and Z. Gregor.1991. Panretinal laser photocoagulation for proliferativediabetic retinopathy: the effect of laser wavelength onmacular function. *Br J Ophthalmol 75:608*.
45. McDonald, H. R., and H. Schatz. 1985. Macular edema following panretinal photocoagulation. *Retina 5:5*.
46. McDonald, H. R., and H. Schatz. 1985. Visual loss following panretinal photocoagulation for proliferative diabetic retinopathy. *Ophthalmology 92:388*.
47. Francois, J., and E. Cambie. 1976. Further vision deterioration after argon laser photocoagulation in diabetic retinopathy. *Ophthalmologica 173:28*.
48. Meyers, S. M. 1980. Macular edema after scatter laser photocoagulation for proliferative diabetic retinopathy. *Am J Ophthalmol 90:210*.
49. Antonetti DA, Barber AJ, Hollinger LA, Wolpert EB, Gardner TW: Vascular endothelial growth factor induces rapid phosphorylation of tight junction proteins occludin and zonula occluden 1. A potential mechanism for vascular permeability in diabetic retinopathy and tumors. J Biol Chem 1999; 274: 23463–23467.
50. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS: Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012; 119: 789–801.
51. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, Sutter F, Simader C, Burian G, Gerstner O, Weichselberger A: The RESTORE Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema. Ophthalmology 2011;118:
615–625.
52. Lang GE, Berta A, Eldem BM, Simader C, Sharp D, Holz FG, Sutter F, Gerstner O, Mitchell P: Two-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema: interim analysis of the RESTORE extension study. Ophthalmology 2013; 120:2004–2012.
53. Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, Gerstner O, Bouazza AS, Shen H, Osborne A, Mitchell P: Three-year outcomes of individualized ranibizumab treatment in patients with diabetic macular edema: the RESTORE extension study. Ophthalmology 2014; 121:1045–1053.

54. Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, Jampol LM, Stone TW: Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. Ophthalmology 2015; 122: 375– 381.
55. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, Schlottmann PG, Rundle AC, Zhang J, Rubio RG, Adamis AP, Ehrlich JS, Hopkins JJ: Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013; 120: 2013–2022.
56. Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW: Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015; 372:1193–1203.
57. Cilley JC, Barfi K, Benson AB 3rd, Mulcahy MF: Bevacizumab in the treatment of colorectal cancer. Expert Opin Biol Ther 2007; 7: 739–749.
58. Krohne TU, Eter N, Holz FG, Meyer CH: Intraocular pharmacokinetics of bevacizumab after a single intravitreal injection in humans. Am J Ophthalmol 2008; 146: 508–512.
59. Matsuyama K, Ogata N, Matsuoka M, Wada M, Takahashi K, Nishimura T: Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. Br J Ophthalmol 2010; 94: 1215–1218.
60. Zehetner C, Kirchmair R, Huber S, Kralinger MT, Kieselbach GF: Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with agerelated macular degeneration, and in patients with diabetic macular oedema. Br J Ophthalmol 2013; 97: 454–459.
61. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. British Journal of Ophthalmology 2008; 92(5): 667-668.
62. Do DV, Nguyen QD, Shah SM *et al.* An exploratory study of the safety, tolerability and bioactivity of a single intravitreal injection of vascular endothelial growth factor Trap-Eye in patients with diabetic macular oedema. The British Journal of Ophthalmology 2009; 93(2): 144-149.
63. Lanzetta P. Intravitreal aflibercept injection 8 mg for nAMD: 48-week results from the phase 3 PULSAR trial. Presented at American Academy of Ophthalmology 2022 annual meeting, September 30 to October 3, 2022. investor.regeneron.com/static-files/e3307e7d-d495-438c-b8bb-c62cdacdb37. Accessed July 9, 2023.
64. Brown DM. Intravitreal aflibercept injection 8 mg for DME: 48-week results from the phase 2/3 PHOTON trial. Presented at American Academy of Ophthalmology 2022 annual meeting, September 30 to October 3, 2022. investor.regeneron.com/static-files/da20405e-b843-402e-855b-d824a15dec60. Accessed July 9, 2023.

65. Jhaveri CD, Glassman AR, Ferris FL, et al. Aflibercept monotherapy or bevacizumab first for diabetic macular edema. N Engl J Med. 2022;387(8):692-703.

66. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Faricimab: expanding horizon beyond VEGF. *Eye (Lond)*. 2020;34(5):802-804. doi:10.1038/s41433-019-0670-1

67. Benest AV, Kruse K, Savant S, Thomas M, Laib AM, Loos EK, Fiedler U, Augustin HG. Angiopoietin-2 is critical for cytokine-induced vascular leakage. PLoS One. 2013 Aug 5;8(8):e70459. doi: 10.1371/journal.pone.0070459. PMID: 23940579; PMCID: PMC3734283.

68. Schaefer W, Regula JT, Bahner M, Schanzer J, Croasdale R, Durr H, et al. Immunoglobulin domain crossover as a generic approach for the production of bispecific IgG antibodies. Proc Natl Acad Sci USA. 2011;108:11187–92. doi: 10.1073/pnas.1019002108.

69. Regula JT, Lundh von Leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases [published correction appears in EMBO Mol Med. 2019 May;11(5):]. *EMBO Mol Med*. 2016;8(11):1265-1288. Published 2016 Nov 2. doi:10.15252/emmm.201505889

70. Vabysmo prescribing information - gene.com. https://www.gene.com/download/pdf/vabysmo_prescribing.pdf. Accessed April 17, 2022.

71. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. Ophthalmology. 2020;127(1):72-84.

72. Brown DM, Emanuelli A, Bandello F, et al. KESTREL & KITE: 52-week results from two phase III pivotal trials of brolucizumab for diabetic macular edema. Am J Ophthalmol. 2022;238:157-72.

73. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion–related events with brolucizumab: post hoc review of HAWK and HARRIER. Ophthalmology. 2021;128:1050-9.

74. Zhang X, Zeng H, Bao S, Wang N, Gillies MC: Diabetic macular edema: new concepts in patho-physiology and treatment. Cell Biosci 2014; 4: 27.

75. Chang-Lin JE, Attar M, Acheampong AA, Robinson MR, Whitcup SM, Kuppermann BD, Welty D: Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. Invest Ophthalmol Vis Sci 2011; 52: 80–86.

76. Aiello LP, Clermont A, Arora V, Davis MD, Sheetz MJ,Bursell S-E. Inhibition of PKC beta by oral administration of ruboxistaurin is well tolerated and ameliorates diabetes induced retinal hemodynamic abnormalities in patients. Invest Ophthalmol Vis Sci 2006; 47(1): 86-92.

77. 47. Harhaj NS, Felinski EA, Wolpert EB, Sundstrom JM, Gardner TW, Antonetti DA. VEGF activation of protein kinase C stimulates occludin phosphorylation and contributes to endothelial permeability. Invest Ophthalmol Vis Sci 2006; 47(11): 5106-5115.

78. Biosimilars. US FDA. Updated March 1, 2023. www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars. Accessed July 9, 2023.

79. FDA Approves First Biosimilar to Treat Macular Degeneration Disease and Other Eye Conditions. US FDA. Published September 17, 2021. www.fda.gov/news-events/press-announcements/fda-approves-first-biosimilar-treat-macular-degeneration-disease-and-other-eye-conditions. Accessed July 1, 2023.

80. CIMERLI™ (ranibizumab-eqrn) U.S. Prescribing Information, August 2022. www.accessdata.fda.gov/drugsatfda_docs/label/2022/761165s000lbl.pdf.

81. Ranade S V, Wieland MR, Tam T, Rea JC, et al. The Port Delivery System with ranibizumab: a new paradigm for long-acting retinal drug delivery. Drug Deliv. 2022;29(1):1326-34.

82. Holekamp NM, Campochiaro PA, Chang MA, et al. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. Ophthalmology. 2022;129(3):295-307.

83. Hutton D, Charters L. Genentech recalling ranibizumab injection ocular implant in US. Ophthalmology Times. Published October 17, 2022. www.ophthalmologytimes.com/view/genentech-recalling-ranibizumab-injection-ocular-implant-in-us. Accessed July 9, 2023.

84. Patel P, Sheth V. New and innovative treatments for neovascular age-related macular degeneration (nAMD). J Clin Med. 2021;10(11).

85. Crago SM. FDA Gives Clearance of IND for SK0106, Skyline Therapeutics AAV gene therapy candidate for nAMD. Modern Retina. Published July 6, 2023. www.modernretina.com/view/fda-gives-clearance-of-ind-for-sk0106-skyline-therapeutics-aav-gene-therapy-candidate-for-namd. Accessed July 9, 2023.

86. OTT166 in Diabetic Retinopathy (DR). Clinicaltrials.gov. Updated July 17, 2023. classic.clinicaltrials.gov/ct2/show/NCT05409235. Accessed July 9, 2023.

87. Hutton D. Efficacy and safety results of the ZETA-1 Phase 2 trial in diabetic retinopathy at the 83rd Scientific Sessions of the ADA. Modern Retina. Published July 3, 2023. www.modernretina.com/view/efficacy-and-safety-results-of-the-zeta-1-phase-2-trial-in-diabetic-retinopathy-at-the-83rd-scientific-sessions-of-the-ada. Accessed July 9, 2023.

88. *Retina Specialist*, January/February 2023 issue.

89. Local Anaesthesia in Ophthalmic Surgery 2012. Joint guidelines from the Royal College of Anaesthetists and the Royal College of Ophthalmologists. http://www.rcophth.ac.uk accessed 25th March 2012.

90. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS Report Number 9. Ophthalmology. 1991;98:766-785 (Start PRP?)

91. A screening approach to the surveillance of patients with diabetes for the presence of vision-threatening retinopathy. Bresnick GH, Mukamel DB, Dickinson JC, Cole DR. Ophthalmology 2000;107:19-24.

92. Relationship of hyperglycaemia to the long-term incidence and progression of diabetic retinopathy. Klein R, Klein BE, Moss SE Cruickshanks KJ. Arch Intern Med 1994;154:2169-78.

93. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus.The Diabetes Control and Complications Trial. Arch Ophthalmol 1995;113:36-51

94. UKPDS 50: Risk factors for incidence and progression of retinopathy in Type II diabetes over 6 years from diagnosis. Stratton IS, Kohner EM, Aldington SJ, Turnder RC, Holman RR, Manley SE, Matthews DR. Diabetologia 2001;44:156-163

95. Risk Factors for High-Risk Proliferative Diabetic Retinopathy and Severe Visual Loss: Early Treatment Diabetic Retinopathy Study Report Number 18. Davis MD, Fisher MR,

Gangnon RE, Barton F, Aiello LM, ChewEY, Ferris FL, Knatterud GL Invest Ophthalmol Vis Sci 1998;39:233-252.

96. The Diabetic Retinopathy Study Research Group. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study No.14 Int Ophthalmol Clin 1987;27:239-252.
97. Retinal laser lenses: magnification, spot size, and field of view. Mainster MA, Crossman JL, Erickson PJ, Heacock GL. Br J Ophthalmol 1990;74:177-179.
98. Volk Catalogue. www.volk.com/catalog accessed March 4th 2012.
99. Intravitreal bevacizumab combined with panretinal photocoagulation in the treatment of open angle neovascular glaucoma. Ciftci S, Sakalar YB, Unlu K, Keklikci U, Caca I, Dogan E. Eur J Ophthalmol. 2009;19:1028-33.
100. Muqit MM, Marcellino GR, Henson DB, Young LB, Patton N, Charles SJ, Turner GS, Stanga PE. Single-session vs multiple-session pattern scanning laser panretinal photocoagulation in proliferative diabetic retinopathy: The Manchester Pascal Study. Arch Ophthalmol. 2010 May;128(5):525-33.
101. D Squirrell, R Bhola, J Bush, S Winder, JF Talbot. A prospective, case controlled study of the natural history of diabetic retinopathy and maculopathy after uncomplicated phacoemulsification cataract surgery in patients with type 2 diabetes. Br J Ophthalmol 2002;86:565-571.
102. Greenberg PB, Tseng VL, Wu WC, Liu J, Jiang L, Chen CK, Scott IU, Friedmann PD. Prevalence and predictors of ocular complications associated with cataract surgery in United States veterans. Ophthalmology. 2011 Mar;118(3):507-14.
103. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology, May 2007, vol./is. 114/5(881-9), 0161-6420.
104. Endo, N., Kato, S., Haruyama, K., Shoji, M., & Kitano, S. (2010). Efficacy of bromfenac sodium ophthalmic solution in preventing cystoid macular oedema after cataract surgery in patients with diabetes. Acta Ophthalmologica, 88(8), 896-900.
105. Shimura M,Nakazawa T,Yasuda K,Nishida K. Diclofenac prevents an early event of macular thickening after cataract surgery in patients with diabetes. Journal of ocular pharmacology and therapeutics 2007,23/3;1080-7683.

106. Laser Procedures in Retina. Oxford Handbook of Ophthalmology.Oxford University Press. 3rd ED.2014.pp:964-5.

107. Optician. C42378: Diabetes part 3 - The English Grading Scheme. 2015.

108. Essential Elements in Developing a Diabetic Retinopathy Screening Programme, Workbook 4.3 Release 4.3, UK NATIONAL SCREENING COMMITTEE 16 June 2009.