“A Clinico-Angiographical Correlation in Grading of Diabetic Retinopathy- A one year hospital based cross sectional study.”

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This is to certify that the dissertation entitled **"A Clinico-Angiographical Correlation in Grading of Diabetic Retinopathy- A one year hospital based cross sectional study"**is a bonafide research work done by**REGISTRATION NO.BK0113003**

Dr. Rekha B.K.M.S, DOMS,Ph.D
Professor and Head,
Department of Ophthalmology,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi

Dr. N.S. Mahantashetti, MD
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi

ABBREVIATIONS

µm	micrometre
Ang-2	Angiopoietin2
bFGF	Basic fibroblast growth factor
BP	Blood pressure
CSME	Clinically significant macular edema
CWS	Cotton wool spot
CURES	The Chennai urban rural epidemiology study.
ERG	Electroretinography
DCCT	Diabetes Control and Complications Trial
DM	Diabetes mellitus
DME	Diabetic macular edema
DRP	Diabetic retinopathy
DRS	Diabetic Retinopathy Study
ETDRS	Early Treatment Diabetic Retinopathy Study
EURODIAB	The European Diabetes Study
FA	Fluorescein angiography
FBS	Fasting blood sugar.
FFA	Fundus Flourescein angiography
H	Haemorrhage
HbA_{1c}	Glycolysatedhaemoglobin
He	Hard exudate
HGF	Hepatocyte growth factor
IDDM	Insulin dependent diabetes mellitus
IGF-1	Insulin-like growth factor 1
IRMA	Intra retinal microvascular abnormality
k	Kappa
Ma	Microaneurysm
Mi	Microinfarct
MODY	Maturity onset diabetes mellitus.
NIDDM	Non-insulin dependent diabetes mellitus
NPDR `	Non-proliferative diabetic retinopathy

NVD	Neovascularization on the disc
NVE	Neovascularization elsewhere
PDR	Proliferative retinopathy
PEDF	Pigment epithelium-derived factor
PKC	Protein kinase C
PlGF	Placenta growth factor
PPDR	Preproliferative retinopathy
PRH	Preretinalhaemorrhage
S.D.	Standard deviation.
Sp	Standard photograph
STDR	Sight-threatening diabetic retinopathy
TGF	Transforming growth factor
UKPDS	United Kingdom Prospective Diabetes Study
VA	Visual aquity
VB	Venous beading
VEGF	Vascular endothelial growth factor
VH	Vitreous haemorrhage
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WHO	World Health Organization

ABSTRACT

TITLE:A Clinico-Angiographical Correlation in Grading of Diabetic Retinopathy- A one year hospital based cross sectional study

INTRODUCTION

Diabetes is the commonest metabolic abnormality in the world.. Diabetic retinopathy is a common and specific microvascular complication of diabetes, and remains the leading cause of preventable blindness in working-aged people. Delay in treatment is the main reason for visual loss and is largely preventable with proper screening. Among several studies that have been conducted for establishing a safe, cost effective and highly sensitive method for diabetic retinopathy screening and early detection, not many have compared FFA with slit lamp biomicroscopy.

AIMS AND OBJECTIVES

1. To establish a correlation between the findings of slit lamp ophthalmoscopy and fundus flourescein angiography in grading of diabetic retinopathy.

2. To study the association between duration of diabetes mellitus, blood pressure and glycosylated hemoglobin with severity of diabetic retinopathy.

MATERIALS AND METHODS

The present study was carried out as a one year cross sectional descriptive observational design between January 1, 2014 and December 31, 2014 at KLES Hospital and MRC. A total of 52diabetic patients (both T_1DM and T_2DM) with retinopathy changes were included. Participants with very hazy ocular media, with history of intravitreal injection or fundus laser photocoagulation were excluded. Informed consent were taken followed by relevant history, general

physicalexamination, complete ophthalmic examination. Diabetic retinopathy grading was done by slit lamp ophthalmoscopy using a Volk Superfield NC lens by an expert ophthalmologist.. The retinopathies were documented in accordance with the modified ETDRS classification. Fundus flourescein angiography were performed and grading by both methods compared.

RESULTS

There were 52 patients included in our study. Mean age of participants in was 55.88 ± 12.27 and out of the 52 participants, there were 29 males and 23 females with M:F ratio of 1.3 : 1. Our study included 9.8% mild NPDR, 35.3% moderate NPDR, 17.6% severe NPDR, 9.8% very severe NPDR, 16.7% early PDR and 10.8% high risk PDR. 28.3% participants had CSME. The mean at diagnosis of diabetes was 16.8 ± 6.8 years for types 1 diabetics, and 48.6± 10.2 years for type 2 diabetics. Mean duration of diabetic age was 10.37± 5.94. The age at diagnosis was not significantly associated with the severity of retinopathy. The severity of retinopathy and the duration of diabetes was found to be statistically significant (p=0.001). There was clinically significant association between concomitant hypertension in patients and the severity of retinopathy (p=0.161). The mean of Glycosylated haemoglobin (HbA1c) in the study population was 8.73.+ 1.5 %There was noted a highly significant increasing trend of severity of retinopathy with raise in HbA1c (p<0.001). The severity of retinopathy was significantly associated with treatment by insulin (p=0.030) . Slit lamp biomicroscopy had an excellent agreement with flourescein angiography for grading of diabetic retinopathy (k= 0.836). The sensitivity of slit lamp ophthalmoscopy for grading of diabetic retinopathy was 89.7%. The sensitivity and specificity for detection of CSME by slit lamp ophthalmoscopy were 100% .

CONCLUSION

Diabetic age, hypertension and high HbA_{1c} are clinically and statistically significant risk factors for diabetic retinopathy. Since there is excellent agreement of slit lamp ophthalmoscopy with fundus flourescein angiography in grading of diabetic retinopathy (k=0.836) findings of slit lamp ophthalmoscopy may be relied upon and need not be confirmed with fundus fluorescein angiography.

KEYWORDS: Diabetic retinopathy, Slit lamp ophthalmoscopy, Superfield NC, Fundus flourescein angiography, NPDR, PDR, CSME, HbA1c, Duration of diabetes, Age at onset of diabetes, Hypertension

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INTRODUCTION

Diabetes mellitus (DM) is a disorder of the carbohydrate metabolism characterized primarily by hyperglycaemia and glycosuria with secondary anomalies of metabolism of proteins and fats. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and in the health care system. [1]

Today diabetes mellitus is the systemic disease that most often leads to blindness. Diabetic retinopathy is a microvascular complication of diabetes wherein high blood glucose affects retinal blood flow and has a direct damaging effect on the cells lining the retinal blood vessels[2]. South India has a 1.3% prevalence rate of diabetic retinopathy among those aged >50 years.[3]

The most effective therapy for diabetic retinopathy is prevention. Intensive glycaemic control and blood pressure control will delay the development or slow the progression of diabetic retinopathy in patients. Delay in treatment is the main reason for visual loss and is largely preventable with proper screening. Because of the inadequacies of current screening programmes, many diabetic patients never receive treatment before developing severe visual loss and diabetic retinopathy remains the commonest cause of registrable blindness in people aged under 65.[4]

There is a latent period before the development of symptomatic disease and though the exact time period is not known, considerable evidence suggests that outcomes are substantially improved if latent disease is detected.[5]According to Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS), laser photocoagulation was beneficial in reducing the risk of further visual loss, but generally not beneficial in reversing already diminished acuity.[6,7] This preventive effect and the fact that patients with proliferative diabetic retinopathy or

macular edema may be asymptomatic provide strong support for accurate screening to detect the grade of diabetic retinopathy.

Today, retinal imaging is very advanced with technology like optical coherence tomography and multimodal imaging systems like confocal scanning laser ophthalmoscopy, ultrawidefield imaging, infrared reflectance imaging, fundus autoflourescence, flourescein angiography, indocyanine green angiography etc. `

The gold standard for diagnosing diabetic retinopathy itself is a matter of some debate. The candidate methods of screening are, direct and indirect ophthalmoscopy, slit lamp fundus biomicroscopy, slit lamp biomicroscopy, retinal photography and flourescein angiography.[8]

The initial sign of diabetic retinopathy is considered to be microaneurysm, determined by ophthalmoscopy. Early vascular changes can be elucidated by fluoresce in angiography, which embraces dye leakage, dilatation of capillaries, filling defects, and micro aneurysms.There are clear advantages for using fundus fluorescein angiography (FFA) to evaluate diabetic retinopathy. These include the improved ability to detect microvascular abnormalities, as well as the ability to assess regions of capillary dropout orcapillary remodelling.

FFA is however expensive, time consuming, invasive. Also, injection of flourescein may often be contraindicated in patients suffering from nephropathy. This may be frustrating to the ophthalmologist as diabetic retinopathy and nephropathy are frequently encountered in the same patient. Flourescein also carries a risk of hypersensitivity reaction in a minority of patients.

The slit lamp biomicroscope with fundus noncontact lenses is an alternate method of ocular fundus viewing for detection of diabetic retinopathy changes.

Among several studies that have been conducted world over for establishing a safe, cost effective and highly sensitive method for diabetic retinopathy screening and early detection, not many have compared FFA with slit lamp biomicroscopy. Only a few Indian studies have been undertaken on this comparison even when FFA is being routinely performed for plan of diabetic retinopathy treatment and most ophthalmologists use slit lamp biomicroscopy for ocular fundus viewing regularly as well.

Hence this study was undertaken to make a clinical and angiographical co-relation between the findings of FFA and slit lamp biomicroscopy in accurate detection and grading of diabetic retinopathy.

AIMS AND OBJECTIVES

- Primary objective - To establish a correlation between the findings of slit lamp ophthalmoscopy and fundus flourescein angiography in grading of diabetic retinopathy.

- Secondary objective – To study the association between duration of diabetes mellitus, blood pressure and glycosylated hemoglobin with severity of diabetic retinopathy.

REVIEW OF LITERATURE

Diabetes Mellitus results in considerable morbidity and mortality, affecting about 285 million people worldwide.[9]

It is a group of chronic metabolic conditions, all of which are characterized by elevated blood glucose levels resulting from the body's inability to produce insulin or resistance to insulin action, or both. This group of conditions can be subdivided into 4 clinically distinct types[10]:

1. Type 1, which results from autoimmune beta-cell destruction in the pancreas and is characterized by a complete lack of insulin production;
2. Type 2, which develops when there is an abnormal increased resistance to the action of insulin and the body cannot produce enough insulin to overcome the resistance;
3. Gestational diabetes, which is a form of glucose intolerance that affects some women during pregnancy; and
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), drug- or chemical-induced diabetes (such as in the treatment of HIV/AIDS or after organ transplantation)and diseases of the exocrine pancreas (such as cystic fibrosis)

   It is speculated that today 50% of diabetics in the population remain undiagnosed.[11]

The total number of people with diabetes is expected to rise to an estimated 300 million cases by the year 2025, with the most significant increase in developing countries, thought to be a result of population growth, aging, obesity, and sedentary lifestyles.[12]

Diabetic patients are at risk of developing a broad spectrum of irreversible complications. Complications of diabetes are chiefly divided into macrovascular and microvascular subtypes.

The macrovascular complications include coronary heart disease, cerebrovascular disease, and peripheral vascular disease. The microvascular complications include diabetic retinopathy (DR), diabetic nephropathy, and diabetic neuropathy. The prevalence of these complications is strongly related to prevalence,type, and duration of diabetes.[12]

Diabetes Control and Complications Trial (DCCT)and United Kingdom Prospective Diabetes Study (UKPDS) have concluded that good glycaemic control can prevent or retard the progression of microangiopathic complications.[13,14]

The Diabetic Eye

DM affects the eye in varying ways. Apart from hyperglycaemia-induced variations of the refractive power of the lens, cataract occurs earlier in patients with DM compared to persons without DM. Patients with DM have approximately a two-fold risk of cataract.[15,16] A special type of fast-maturing diabetic cataract involving both eyes that specially affects young people may occur.[17] Diabeticneuropathy can manifest itself as extraocular muscle palsies and also as autonomous neuropathy causing miosis.

The most important diabetes induced pathologic finding is, however, diabetic retinopathy (DRP). Advanced DRP withretinal non-perfusion may also lead to neovascularization in the anterior segment of the eyecausing therapy-resistant neovascular glaucoma.

People with diabetes are 25 times more likely than the general population to become blind.[11] According to a population based survey of 10, 033 participants, eight in ten

patients with diabetic retinopathy are undiagnosed, and importantly, over a quarter with vision threatening diabetic retinopathy are undiagnosed.[18]

Diabetic Retinopathy

History

The disease diabetes was well-known as long back as 2nd century AD, but this endocrine disorder was never linked with eye-pathology before the mid-19th century. In 1846, the French ophthalmologist and Professor of Hygiene, AppolinaireBouchardat reported the development of visual loss in the absence of cataract in diabetics. This was partly reversible and in most cases improvement was associated with better control of diabetes.[19]

In 1856, Eduard Jaeger used the recently developed direct ophthalmoscope to observe yellowish spots and extravasations in the macular region of few diabetic patients. He incorporated these into his drawings in an atlas of 21 fundus drawings which he painstakingly drew with upto 20-30 clinical session with each patient.[19]

Albrecht von Graefe, the pioneer of German ophthalmology disregarded Jaeger's findings by saying that there was no proof of a cause-effect relationship between diabetes and retinal complication.[20]

In 1872 Edward Nettleship published a paper "On oedema or cystic disease of the retina" giving histopathological proof of "cystoid degeneration of the macula" in patients with diabetes. In 1876, Wilhelm Manz described the proliferative changes occurring in diabetic retinopathy and the importance of tractional retinal detachments and vitreous haemorrhages. In the early years of the 20th century, the debate continued

whether macular changes were directly related to diabetes or whether they were due to hypertension and arteriosclerosis. It was not until the second half of the century that the work of Arthur James Ballantyne in Glasgow provided more evidence that suggested that diabetic retinopathy represents a unique vasculopathy.[20]

`After the Second World War the German ophthalmologist Meyer-Schwickerath reported treatment of retinal diseases with light coagulation. Today laser photocoagulation for proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) are well-documented treatment modalities.

In 1968 an international symposium, the Airlie HouseSymposium, was held in the USA to evaluate the current knowledge of the natural history of DRP. It brought together leading American, British and Scandinavian ophthalmologists interested in retinal disease and DM. This symposium emphasized the need for standardized classifications of DRP, which was an important step towards quantifying the natural history of DRP and documenting the value of varying therapeutic interventions. Since then several multicentre studies, such as the Diabetic Retinopathy Study (DRS), Early Treatment Diabetic Retinopathy Study (ETDRS), Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), Diabetes Control and Complications Trial (DCCT), United Kingdom Prospective Diabetes Study (UKPDS), have provided evidence that now are considered the foundations of not only laser and surgical therapy but also of the general management, screening for and follow-up of DRP.[21]

Aspects of pathogenesis

Retina has a sparse vascularity and low PO_2, but has one of the highest metabolic demands of any tissue. This combination of increased metabolic demand and minimal vascular supply limit the retina's ability to adapt to the metabolic stress

of diabetes. To date, several possible mechanisms including the polyol pathway, non-enzymatic glycation, oxidative stress and activation of PKC have been implicated in the development of DRP. [22-27]

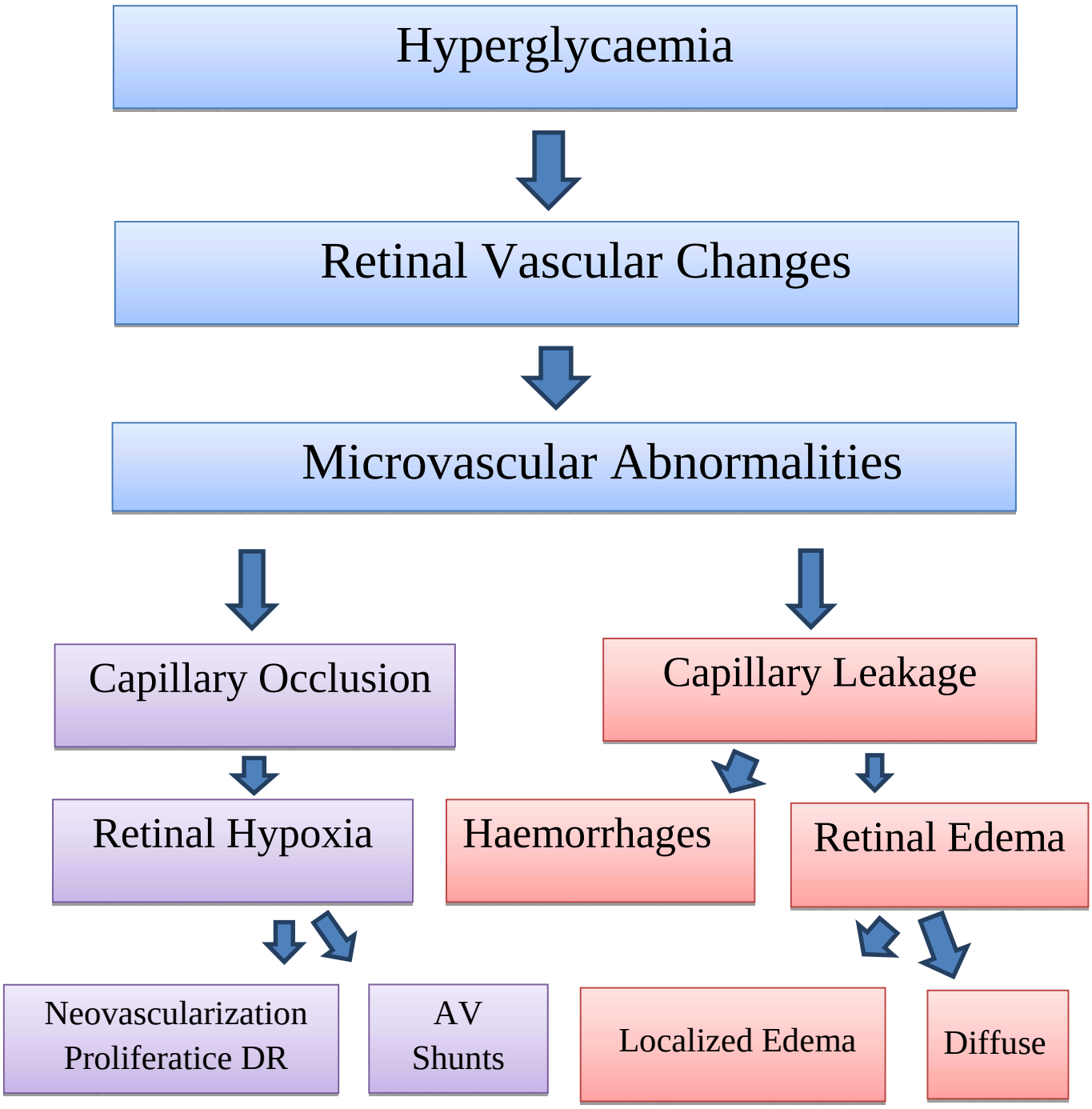


Figure No. 1: Pathogenesis of diabetic retinopathy lesions

Functional as well as structural changes take place.

The functional changes comprise of an increase in and heterogeneity of the distribution of retinal blood flow. The retinal circulation is controlled locally in response to local and systemic influences and this auto-regulation is impaired in DM. (Sinclair *et al.*1982, Harris *et al*. 1998, Kohner*et al*. 1995).[28-30] So far at least ten humoral regulating substances have been proposed for the control of retinal blood flow (Chen *et al*. 2000).[31] They fall into two main categories: firstly endothelium derived relaxing factors such as nitric oxide, prostaglandin and endothelium-derived hyperpolarizing factor and secondly endothelium-derived contracting factors such as endothelin and cycloxygenase products.

In retinal blood vessels both endothelial cells as well as pericytes are affected in DRP. Furthermore the basement membrane is thickened which in turn may contribute to capillary closure (Stitt*et al*.1995).[32] The endothelial cells constitute the blood-retinal barrier and the pericytes regulate the vascular blood flow. The tight junctions of the endothelial cells, essential for the inner blood-retinal barrier, are dependent on an assembly of different proteins such as occludins, claudins and zonula occludens-1, -2 and -3 (Antonetti*et al*.1999, Gardner *et al*.1999).[33]Morover, cytokines, such as VEGF altering the tight junction proteins, induces increased vascular permeability (Aiello 1997, Gupta *et al*. 2013).[34,35] Other cytokines such as IGF-1 and bFGF may also be involved.

Apart from the well-known microvascular functional and structural lesions, hyperglycemia also induces retinal neurodegeneration which affects the macroglial, neuronal and microglial cells (Gardner *et al*. 2002).[36] The macroglial cells, Müller cells and astrocytes are support cells that regulate retinal metabolism and modulate the function of neurons and blood vessels (Abbott *et al*. 1992).[37] Astrocytes extend

end-feet that wrap around blood vessels of the inner retina. This interaction is important to induce the expression of tight junction proteins and to maintain the blood-retinal barrier (Abbott *et al*.1992, Gardner *et al*.1997).[37,38] In addition, Müller cells proliferate in the formation of epiretinal membranes in PDR (Hiscott*et al*. 1984).[39]

Furthermore, many studies have shown that glial cells as well as neurons produce cytokines as VEGF, which increase blood vessel permeability (Gilbert *et al*. 1998, Cooper *et al*. 1999, Gupta *et al.* 2013).[40,41,35]

Microglial cells also become activated by DM and become phagocytic (Broderick *et al*. 2000).[42] Furthermore, cytokines and chemokines, such as VEGF and tumor necrosis factor, are released from the affected microglial cells and increase retinal vascular permeability.

Neuronal cells, of which there are four primary types, photoreceptors, bipolar cells, amacrine cells and ganglion cells, are influenced by DM as well. Pathologic ERG, impaired colour vision and contrast sensitivity, in fact, may precede the clinically detectable DRP (Daley *et al*1987, Di Leo M 1992, Parisi*et al*. 2001, Pescosolido *et al.* 2015).[43-46] In fact retinal ganglion cells and inner nuclear layer cells die by apoptosis early in DM, explaining these findings. This may explain why some patients lose vision even if DME is successfully treated or in patients with clinical manifestations of DRP but without any signs of macular thickening in ophthalmoscopy, fluorescein angiography or optical coherent tomography.

However, it is still unclear which cells, vascular or glial and neuronal cells, are primarily affected in DM. Moreover, other systemic conditions such as hypertension and renal and cardiac failure affecting the hydrostatic pressure and colloid osmotic

pressure are of importance as etiologic factors for DME (Aiello *et al*. 2001, Gardner *et al*. 2002).[47,36]

Besides increased vascular leakage, microvascular occlusion is the other important component of DRP. The mechanisms behind vascular closure are many: microthrombosis, leucostasis and the invasion of Müller cells into the vascular lumen all contribute to the occlusion (Bek 1997, Barouch*et al*2000, Boeri*et al*. 2001,).[48-50] Occluded vessels cause retinal hypoxemia, which in turn increases the excretion of angiogenic factors as VEGF, bFGF, IGF-1, HGF, PlGF, Ang-2, TGF-α and TGF-β which stimulate the formation of new vessels (Boulton et.al.1997, 1998, Cai and Boulton 2002).[51-53] PEDF, on the other hand, seems to inhibit the formation of new vessels (Chader 2001).[54]

Individual DRP lesions

The previously described functional and structural changes of the retina and retinal vessels in DM lead to vascular abnormalities, which in turn cause retinal hypoxia and oedema.

Microaneurysms

The first signs of DRP are usually small, 10 μm-100 μm sized, saccular capillary extensions called microaneurysms (Mas), which may disappear in early DRP (Kohner 1999).[55]these were first described by Mackenzie in 1879. They are a characteristic feature of DR but not pathognomic for diabetes. As the microaneurysms enlarge they become visible as small red dots, it follows an atypical life cycle of gradual enlargement, thickening, hyalinization of it's walls and eventually auto occlusion by the encroachment of the thickened wall into the lumen.

Hypothesis for microaneurysms formation: 1) pericyte degeneration which leads to weakening of the capillary wall and saccular outpouching at the site of degeneration.

2) They represent a proliferative cellular response to focal retinal hypoxia supported by preferential location of the patent capillary bed surrounding the zone of capillary nonperfusion.

Only a small part of the Mas detected on FA are seen in a clinical examination or on fundus photography (Friberg*et al*. 1986, Hellstedt*et al*. 1996).[56,57]

Duration of life cycle of aneurysm varies considerably from patient to patient, ranging in length from a few months to several years. Their rate of appearance and disappearance is used as a measure of activity of the retinopathy (Hellstedt*et al.* 1996).[58]

Haemmorhages

Intraretinal haemorrhages (Hs) may appear on various levels in the retina: superficial flame shaped Hs are oriented in the direction of the nerve fibre layer, small dot Hs usually lie in the superficial capillary plexus of the retina and can be indistinguishable from Mas, while larger blotch and cluster Hs lie deeper in the retina and are a hallmark of capillary damage.

Hard Exudates

Leaking lipoproteins are seen as white streaks, clusters or circinate rings called hard exudates(Hes). They usually appear in the posterior pole with a preference for the macula. The factor which determines the dotted exudates arranged in a circular manner depends on the degree of ischemia. The stimulating factor in haemorrhage or

leaked plasma attracts macrophagic cell which diffuse through the tissue until capillaries are reached. Because the interface between the ischaemic and relatively normal areas are circular, the deposition of the hard exudates is circular. Greater the zone of ischaemia, larger will be the circle.

Cotton Wool Spots

Capillary closure leads to microinfarcts (Mi), also called cotton wool spots (CWS). These are localswellings of the nerve fibre layer due to disturbed axoplasmic flow, which appear as white fluffy spots. They may appear early as isolated lesions but in combination with other abnormalities are a sign of a more advanced DRP. They are more common where nerve fibre layer is thickest around the disc and along the temporal arcade. These are frequent findings in both normotensive and hypertensive diabetics with retinopathy. Cotton wool spots should be considered as one of the indications of worsening and impending neovascularization. Kohnersuggested that eyes with 8 or more cotton wool spots (in the absence of systemic hypertension) are likely to develop proliferative retinopathy within the next 6 to 18 months.[55]

Venous Changes

Venous dilation occurs early in DM, often before the clinical DRP, whereas venous beading (VB), which appears as focal areas of segmental venous dilation andnarrowing, is a sign of advanced DRP.[59]Other venous abnormalities are omega loops and segmental reduplication.

IRMAs

Intraretinal microvascular abnormalities (IRMAs), indicating sight threatening diabetic retinopathy (STDR), are seen as pathologicnetworks of dilated and teleangiectatic capillaries. The morphology of IRMAs is consistent with the features of blood vessels in general in DRP: pericyte degeneration, thickening of basement membranes and endotehelial cell loss, but there are also histopathologic features indicating intraretinal neovascularization (Imesch*et al*. 1997).[60]

Macular Edema

DME, the most common cause of decreased vision in non-proliferative diabetic retinopathy (NPDR), arise when plasma constituents accumulate in the extra cellular space. It can be seen as a local or a diffuse thickening of the retina or as a cystoid swelling in the centre of the fovea.

There are four main types of maculopathy according to clinical examination and fluorescein angiography. These are:

● Focal: Leakage from dilated segments of capillaries and microaneurysms.

● Diffuse: Characterized by the presence of diffuse oedema.

● Ischaemic: Capillary shut down results in retinal non-perfusion and ischaemia. It ischararacterized by the presence of large blot haemorrhages, multiple cotton wool spots and IRMAs.

● Mixed: It is not uncommon to see a combination of focal, diffuse and ischaemic maculopathy.

Neovascularization

When the capillary nonperfusion proceeds, it results in increased excretion of varying angiogenicfactors and new blood vessels develop, on the retina (NVE) and/or on the optic disc (NVD). Neovascular vessels are fragile and may bleed either in the retrohyaloid space or in the vitreous and can be seen as either a preretinal haemorrhage (PRH) or vitreous haemorrhage (VH). The spontaneous regression of these new vessels is known as 'Involutional diabetic retinopathy'.[61]When the ischaemia which was responsible for the proliferation of new vessels becomes very severe, such regression is supposed to occur. In advanced DRP fibrous tissue develops in connection with neovascularizations. Fibrovascular proliferations may adhere to the undetached posterior surface of the vitreous body, the contraction of which can cause traction to the retina and finally retinal detachment.

Classification of DRP and maculopathy

DRP is classified in two main categories: non-proliferative (NPDR) and proliferative (PDR) with neovascular vessels. DME is the other type of STDR involving the macular region. One of the main tasks for the international Airlie House Symposium held in 1968 was to create an uniform, internationally adopted, detailed grading-scale for DRP (Davis *et al*.1969).[62] This grading-scale became the foundation for later modified classifications used in epidemiological and therapeutic intervention studies such as ETDRS (1980)[63], DRS (1981)[6], WESDR (Klein *et al*. 1984a,b, 1986)[64,65], DCCT (1986)[66], and the UKPDS (1991)[67]. The grading was based on seven-field stereoscopic 30º photographs using colour transparencies. The severity level of individual lesions was assessed field-by-field comparing them with 30º

standard photographs. The overall DRP for each eye was obtained by summarizing the findings. This detailed grading-scale for DRP is still considered the Gold Standard with which other methods should be compared.

The DRS identified the special characteristics of PDR with a high risk for severe visual impairment (VA< 0.025) in the following years. High-risk PDR as defined below, if untreated, leads to severe visual impairment in about one half of the affected eyes within the next four years (DRS 1981).[6]

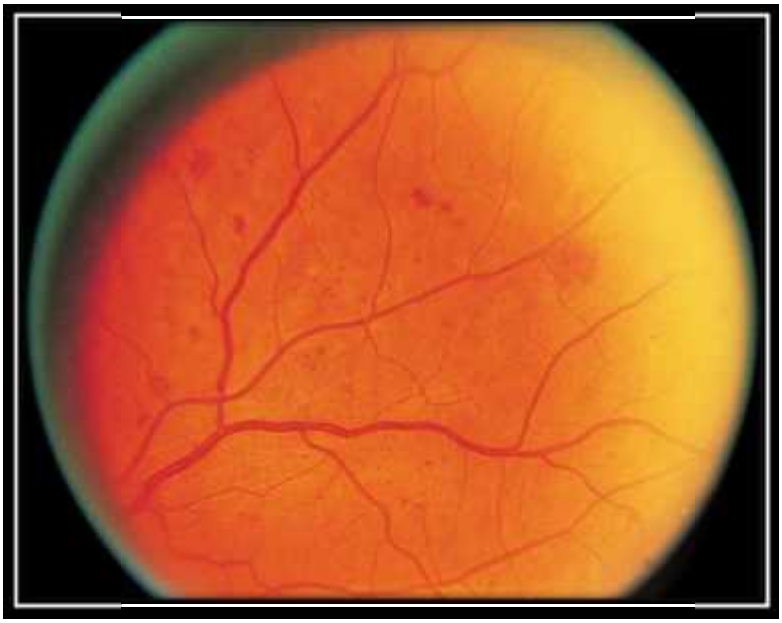
High-risk PDR

- **NVD**≥ Sp 10A or
- **NVD**< Sp 10A plus VH or PRH
- **NVE**≥ 0.5 disc area plus VH or PRH
- **VH orPRH** obscuring ≥ 1 disc area

In the ETDR study Nr12 (1991c)[68], gradings of baseline 30º seven-field stereoscopicfundus photographs of eyes with NPDR assigned to deferral of photocoagulation, were used to examine the power of various lesions and the combination of lesions to predict the progression to PDR. The severity and extent of IRMAs, Hs and/or Mas and VB were the most important factors in predicting progression. A detailed 12-level DRP severity scale was developed based on these findings.

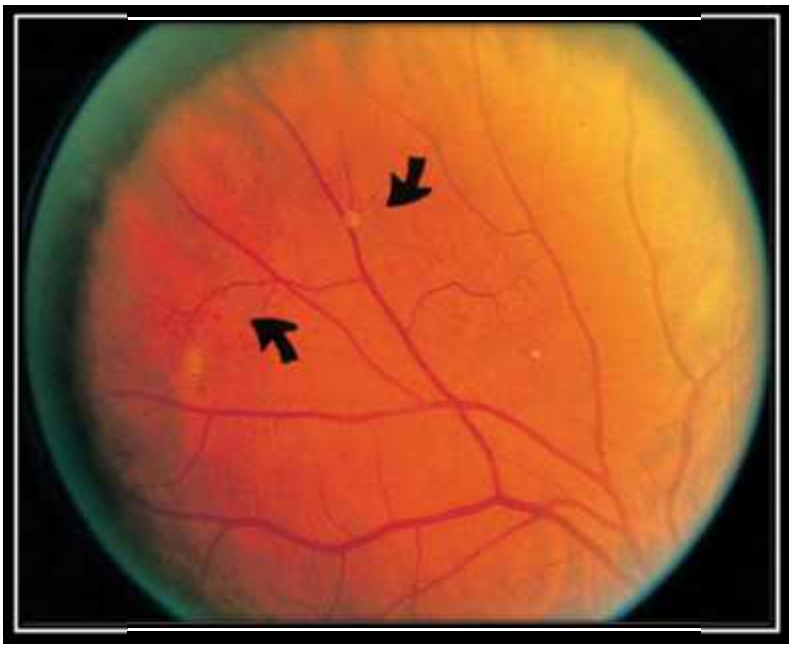
The grading scale consists of 12 levels (ETDRS 1991c)

Level 10	DRP absent
Level 14-15	Questionable DRP
Level 20	Minimal DRP
Level 35	Mild DRP
Level 43	Moderate DRP
Level 47	Moderately severe DRP
Level 53	Severe DRP
Level 61	Mild PDR
Level 65	Moderate PDR
Level 71-75	High-risk PDR
Levels 81-85	Advanced PDR
Level 90	Cannot grade

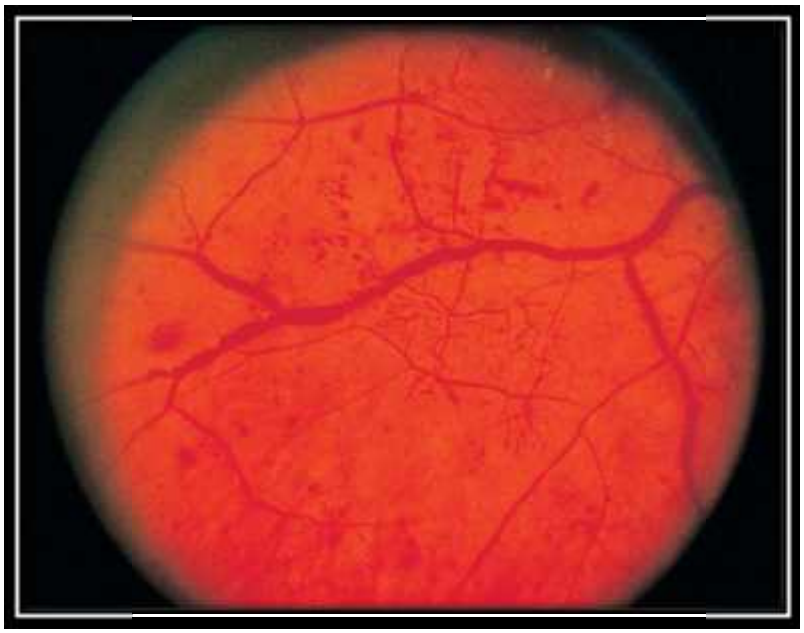


Standard photograph No. 2A of the Modified Airlee House Classification of Diabetic Retinopathy demonstrating a moderate degree of hemorrhage or microaneurysms, or both.

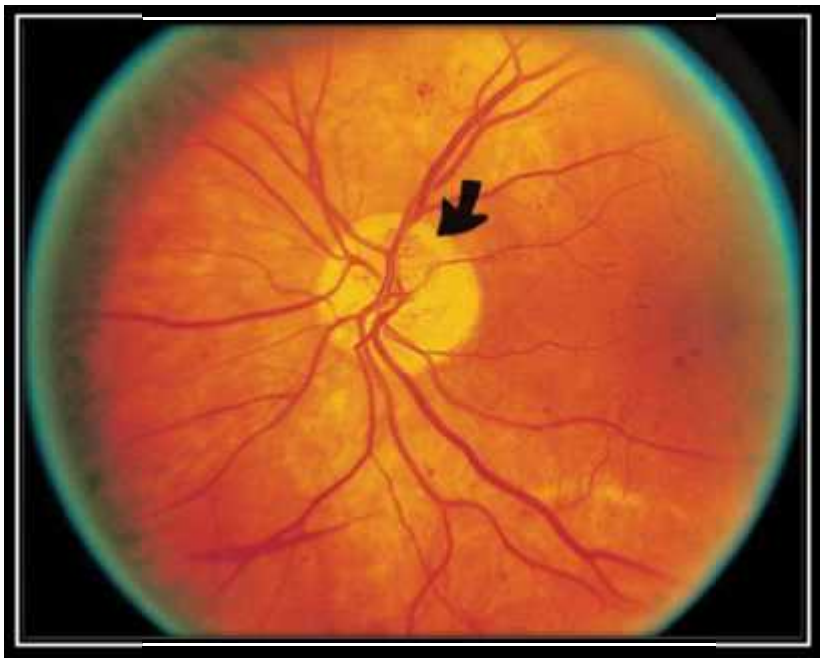
Courtesy of the Early Treatment Diabetic Retinopathy Study [ETDRS].



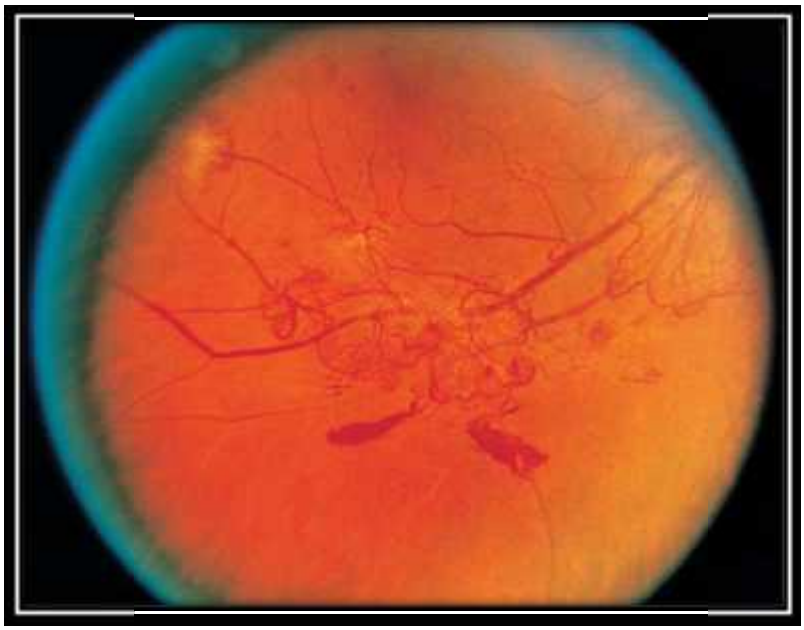
Standard photograph No. 8A of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating intraretinal microvascular abnormalities (IRMAs) (*arrows*). *Courtesy of the ETDRS.*



Standard photograph No. 6B of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating venous beading.
Courtesy of the ETDRS.



Standard photograph No. 10A of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating neovascularization of the optic disc (NVD) (*arrow*),covering approximately one quarter to one third of the disc area. *Courtesy of the ETDRS.*



Standard photograph No. 7 of the Modified Airlie House Classification of Diabetic Retinopathy demonstrating neovascularization elsewhere (NVE) in the retina greater than one half disk diameter with a fresh hemorrhage present. *Courtesy of the ETDRS.*

Of special interest is the concept of moderately severe and severe DRP levels which are crucial for further prognosis. The definitions in general are complex, as demonstrated below, and they are not easily applied to wide-field photography as they are based on 30º fields.

Definitions for minimal to severe (levels 20-53) DRP (ETDRS 1991c)

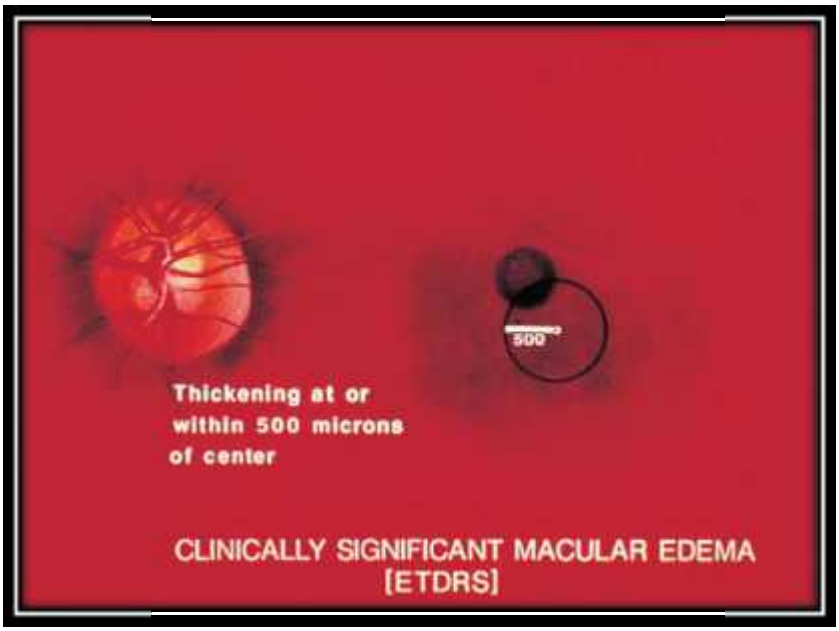
Level 20	Mas only
Level 30	One or more of the following:
	Venous loops ≥ D /1*;
	CWS, IRMA or VB = Q;
	Retinal Hs present;
	He ≥ D/1;
	CWS ≥ D/1
Level 43	H/Ma = M/4-5 – S/1 or Irma=D/1-3 (not both)
Level 47	Both characteristics for moderate DRP and/or 1 only of the Following:
	IRMA = D 4-5
	H/Ma = S/2-3
	VB = D /1
Level 53	One or more of the following:
	≥2 of the 3 of level 47 characteristics
	H/Ma ≥ S/4-5
	IRMA ≥ M/1
	VB ≥ D /2-3

*) D=definite, M=moderate, S=severe. The number after the letter indicates number of 30º standard fields (3-7) affected

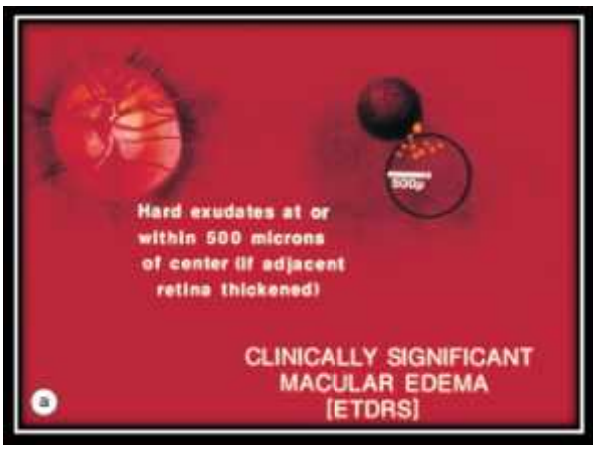
For the classification of maculopathy the concept of DME and CSMO has been presented. The latter is relevant for the ophthalmic clinician, as it defines treatment-needing, sight-threatening DME according to ETDRS studies (ETDRS 1985, ETDRS 1987a,b)[69-71]

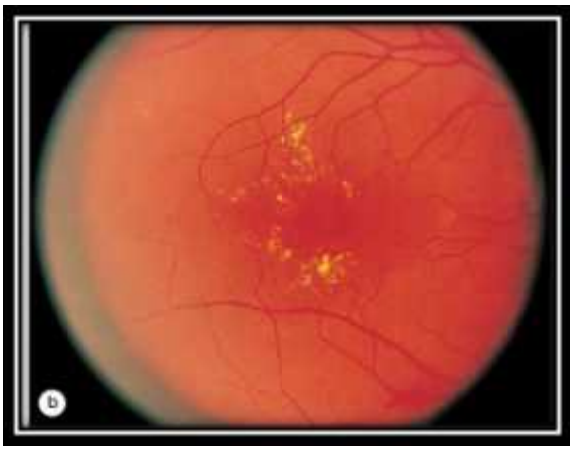
CSMO as defined by the ETDRS is one or more of the following:

- Retinal thickening at or within 500µm of the foveal avascular zone.
- He at or within 500 µm of the center of the foveal avascular zone, if associated with thickening of the adjacent retina.
- Retinal thickening > 1,500 µm within 1,500µm of the center of the foveal avascular zone.

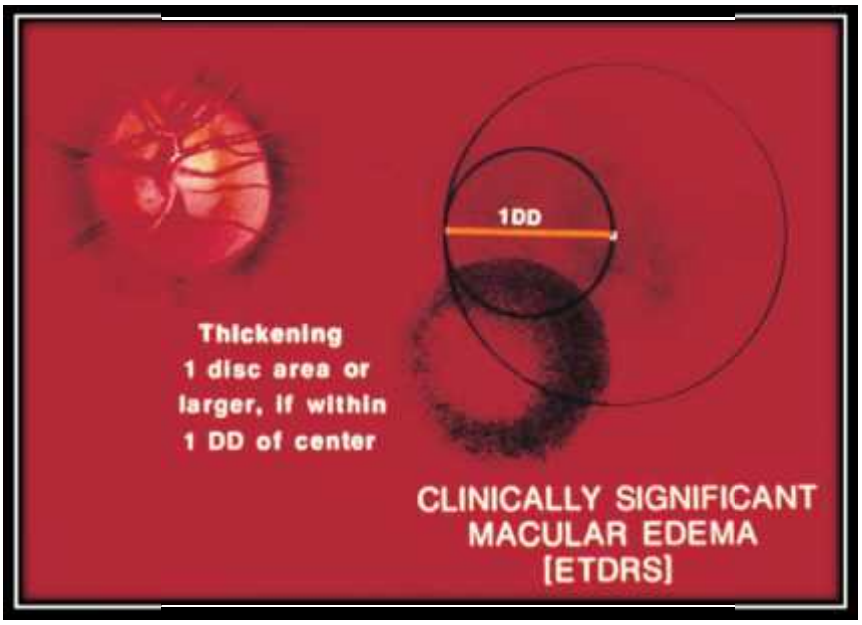


Schematic Representation of Clinically Significant Macular Edema (CSME),With Thickening Of The Macula Less Than 500 Mm From The Center Of The Macula





Schematic representation of CSME with hard exudates at or within 500 µm of the center of the macula, with thickening of the retina adjacent to the exudates. (b) Clinical appearance of hard exudates less than 500 µm from the center of the macula. There is thickening of the adjacent retina, which is not appreciated without stereoscopic observation



Schematic representation of area of thickening, 1 disk diameter in size, part of which is within 1 disk diameter of the center of the macula.

ETDRS investigators recognized that some diabetic features could be assessed better with fluorescein angiograms than clinical fundus photographs. Thus the ETDRS also classified DR from FA. The protocol consisted of stereoscopic FA of two 30° fields that extended along the horizontal meridian from 25° nasal to the disc to 20° temporal to the macula. In the early-mid phase of the FA, the foveal avascular zone (FAZ), capillary loss, capillary dilatation, arteriolar and RPE abnormalities were assessed. Fluorescein leakage, fluorescein leakage source and cystoid changes were graded during the late FA phase.[72] This fluorescein angiographic classification scheme is time consuming, complex and ideal for the research setting but not for regular clinical use.

Although the Early Treatment Diabetic Retinopathy Study (ETDRS) staging system is recognized as the gold standard for grading in clinical trials, in everyday clinical practice, it has not proven to be easy or practical to use. There are too many levels, required correlations with standard photographs and additional complicated grading rules for the different stages, and these are difficult to remember.

Contemporary studies have documented that the ETDRS grading system is not employed by the vast majority of physicians managing patients with diabetes. It is also useful to have a common disease severity scale for DME, because it is an important cause of visual loss.

Therefore, a system that can be used globally was needed to facilitate communication between retina subspecialists and general ophthalmologists, and also among general ophthalmologists, retina subspecialists, endocrinologists/diabetologists and primary care physicians.

Thus came into establishment a system is based on an evidence-based approach, combining the findings of the Early Treatment of Diabetic Retinopathy Study (ETDRS) and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). This came to be known as International Clinical Disease Severity Scale for DR.[73] The foundation of understanding of diabetic retinopathy progression, risk factors, and outcomes of treatment came from the two earlier landmark studies.

There are five stages that are recognized. The first is “no apparent retinopathy”. As the name implies there are no diabetic fundus changes. The second stage is “mild non-proliferative retinopathy” (NPDR). This stage is characterized by the presence of a few microaneurysms. The third stage is “moderate NPDR” which is characterized by the presence of microaneurysms, intraretinal haemorrhages or venous beading that do not reach the severity of the standard photographs 2A and 8A.[74]

“Severe NPDR”, the fourth stage, is the key level to identify. Data from the ETDRS has shown that eyes in patients with DM type 2 that reach the grade of severe NPDR have a 50% chance of developing high risk characteristics if laser treatment is not instituted .[75]The diagnosis of severe NPDR is based on the 4:2:1 rule of the

ETDRS. Using standard photographs 2A, 6A and 8A to compare with the fundus findings, one can easily diagnose severe NPDR. If hemorrhages of at least the magnitude of standard photograph 2A are present in all 4 quadrants, then by definition severe NPDR is present. If 2 quadrants or more have venous beading (VB) of the same magnitude or greater than standard photograph 6A, then by definition severe NPDR is present. If one or more quadrant has intraretinal microvascular abnormalities (IRMA) of the same magnitude or greater than standard photograph 8A, then by definition severe NPDR is present.

The final stage is "proliferative diabetic retinopathy" (PDR). PDR is characterized by neovascularization of the disc, neovascularization of the retina, neovascularization of the iris, neovascularization of the angle, vitreous haemorrhage or tractional retinal detachment.[73]

With regards to macular edema, it should be noted if macular edema is present or absent. If it is present then it can be further classified as mild, moderate and severe depending on the distance of the exudates and thickening from the center of the fovea.[76]

International Clinical Disease Severity Scale for DR

Proposed Disease Severity Level	**Findings Observable upon Dilated Ophthalmoscopy**
No Apparent Retinopathy	No abnormalities
Mild Non-Proliferative Diabetic Retinopathy	Microaneurysms only
Moderate Non-Proliferative Diabetic Retinopathy	More than just microaneurysms but less than Severe NPDR
Severe Non-Proliferative Diabetic Retinopathy	Any of the following: • More than 20 intraretinal hemorrhages in each of 4 quadrants • Definite venous beading in 2+ quadrants • Prominent IRMA in 1+ quadrant And no signs of proliferative retinopathy
Proliferative Diabetic Retinopathy	One or more of the following • Neovascularization • Vitreous/preretinal hemorrhage

Comparison of the International Clinical DR Scale and the Early Treatment Diabetic Retinopathy Study (ETDRS) Scale of Diabetic Retinopathy

International Classification Level of DR	ETDRS Level of DR
No apparent retinopathy	Level 10: DR absent
Mild NPDR	Level 20; very mild NPDR
Moderate NPDR	Levels 35, 43, 47; moderate NPDR
Severe NPDR	Levels 53A-E; severe to very severe NPDR
PDR	Levels 61,65,71,75,81,85; PDR, high-risk PDR, very severe or advanced PDR

Prevalence and incidence of DRP

Type 1 DM

Generally the prevalence of DRP at diagnosis of Type 1 DM has been reported to be low, between0 to 3% (Klein *et al*. 1997, Wan Nazaimoon*et al*. 1999).[77,78] In theDCCT study from Canada and the USA involving 29 centres, however, photographic evidence ofDRP was found in 54% at baseline (DM < 5 years duration) and 67% within five years of diabetesduration (Malone *et al*. 2001).[79] In the WESDR, the prevalence of DRP was strongly correlated with the duration ofDM. In the WESDR, prevalence of DRP rose sharply from 2% in those with DM less than twoyears to 98% after 15 years (Klein *et al*.1984a).[64]Children with the onset of DM before the age of ten do not usually have DRP and definitely nottreatment needing lesions.

These results confirm the necessity of regular retinal screening examinations among IDDMchildren after ten years of age. Patients with Type 1 DM diagnosed later should be examinedregularly from the onset of the disease.

Type 2 DM

From 13% to 39% of patients with Type 2 DM have some DRP at baseline ophthalmologicexamination (two to five years from diagnosis of DM) and these patients are at risk to developSTDR in the follow-up period of ten years (Henricsson *et al*.1996a, UKPDS1998b).[80,81] Twenty years from the onset of DM more than 60 % of people with Type 2 DM will havesome kind of DRP (Henricsson *et al*.1996a).[80] The prevalence of DRP is higherfor those patients needing insulin treatment compared to those maintaining diet or oral agents only,62% and 36%, respectively (Klein *et al*1985a).[82]

Patients with Type 2 DM and with a normal baselinestatus or with minimal DRP (Ma in one eye only) are not likely to develop treatment-needing lesions in the next three years (UKPDS 2001a).[83] Notably, patients who aremaintaining on diet-treatment only and who at baseline examination have a normal retinal status,are at low risk to develop treatment-needing retinopathy in the next four to five years (Henricsson*et al*.1996b, Hansson-Lundblad *et al*.1997).[84,85]

In the UKPDS study, the number of Mas and level of DRP at baseline examination stronglycorrelated with the risk for STDR in the next nine years (Kohner*et al*.1999).[81] Interestingly, about50% of single Mas disappeared over the course of three years (Kohner*et al*. 1999).[81]These findings suggest that the screening interval for DRP, for patients with Type 2 DM with agood glycaemic control without or with minimal DRP (1-2 Mas) at baseline examination, could betwo or even three years instead of one year, if screened with a reliable screening method. Likewisepatients with a normal baseline retinal status, maintaining on diet-treatment only, could be

screened every fourth to fifth year.

Prevalence and incidence of STDR and blindness

In developed countries DRP is one of the leading acquired and treatable causes of visualloss in people of working-age as well as in people older than 65 years (Kocur*et al*. 2002).[86] STDR comprises DME, which is the more frequent cause of visual impairment inpatients with Type 2 DM, and PDR which is the more common cause of visual impairment amongpatients with Type 1 DM (Klein *et al*.1984d, Fong *et al*. 1999).[87,88] The prevalence of PDR and DMEare both related to the duration of the disease.[89.90]

None of the patients with Type 1 DM in the WESDR had DME with disease duration of less thanfive years, compared with 29% after 20 years. Corresponding figures for Type 2 diabetic patientswere 3% and 28% (Klein *et al*.1984c).[91] Prevalence of DME varies also, depending on whether thedisease is insulin treatment-needing.

The prevalence of PDR in the WESDR for patients with Type 1 DM was 4% when the diseaseduration was nine to ten years and 51% after 20 years disease duration. In patients with Type 2 DMwith disease duration less than four years the prevalence was 4% versus 3% depending on whetherthe patients were insulin dependent or not. With disease duration of more than 15 years corresponding figures were 20% versus 4% (Klein *et al*. 1987).[92] Again the patients who were insulin dependent had a higher prevalence of PDR compared with the non-insulin dependent ones, 25% versus 5%, respectively (Klein *et al*. 1985a).[88]

Klein and co-workers (1984c)[91] found a four-year risk of developing PDR in 42% of those patients with level 41 baseline DRP characteristics.In the WESDR the four-year incidence of blindness was 1.5% for patients Type 1 DM and 3.2% versus

2.7% for insulin-treated and oral medication or diet-treated patients with Type 2 DM, respectively (Moss *et al*. 1988).[98]

Risk factors for DRP

Glycaemic control

Apart from the duration of DM, the most important risk factor for DRP is unsatisfactory glycaemiccontrol. Normoglycaemia, or blood glucose values as close to normoglycaemia as possible, protectthe eye from DRP as such or the progression of pre-existing DRP in patients withboth Type 1 andType 2 DM.

The DCCT multicentre study (1993)[13] from the USA involved altogether 1441 patients with Type 1 DM, 726 patients without DRP (primary prevention cohort) and 715 patients with mild DRP (secondary prevention cohort) at baseline. The patients in both groups were randomly assigned to intensive therapy or to conventional therapy. The mean follow-up time was 6.5 years. The average HbA1c value in the intensive treatment group was 2% lower than that in the conventional treatment group (7% versus 9%). In the primary prevention cohort intensive therapy reduced the adjusted mean risk for the development of DRP by 76% and in the secondary invention cohort intensive therapy slowed the progression of DRP by 54% as compared with conventional therapy. In another large prospective complication study including 3250 Type 1 diabetic patients, the EURODIAB study, HbA1c value was the strongest predictor of progression to PDR (Porta*et al*. 2001).[94]

The UKPDS study, a multicentre randomised intervention study, included 3867 newly diagnosed patients with Type 2 DM who were randomly assigned to two groups, one on intensive treatment and one on diet-therapy only (UKPDS 1998a).[95] The target fasting blood glucose in the intensive therapy group was 6 mmol/l. In ten years the average HbA1c value was 11% lower in the intensive therapy group as

compared to the conservative treatment group (7% versus 7.9%). The risk for DRP and the need for photocoagulation treatment were reduced by 25% in the former group.

Rapid improvement of glycaemic control might cause an early worsening of DRP (DCCT 1993, Henricsson *et al*. 1999).[13,96] However, long-term outcomes in the intensively treated group who had an early worsening, were similar or more favourable than outcomes in conventionally treated patients. (DCCT 1993).[13]

Blood pressure

Strictly controlled blood pressure appears to reduce the risk of clinical complications from diabetic eye disease.

The UKPDS (2004)[97] included 1148 patients with Type 2 DM and arterial hypertension, of whom 758 patients were allocated to a tight BP control either with angiotensin-converting enzyme inhibitor or β-blocker as the main therapy and 390 patients were allocated to a less tight BP control. The mean BP during the study over nine-year follow-up was 144/82 mm Hg in the tight BP therapy group and 154/87 mm Hg in the conventional therapy group. It became evident that there was a statistically significant reduction in the progression of DRP and a reduced need of lasertreatment due to maculopathy in the tight BP treatment group. After 7.5 years the relative risk forat least a two-step progression of DRP in the tight BP therapy group was 0.66 ($p<0.001$).

For patients with Type 1 DM similar results have been obtained. In WESDR systolic BP was found to be a significant and independent predictor of the four-year incidence of DRP (Klein *et al*1989a).[98] Diastolic BP was associated with DRP progression but the relationship did not reach statistical significance.

Blood lipids

Contradictory results regarding dyslipidaemia as a risk factor for DRP have been presented. In the observational data from the ETDRS (1996) patients with an elevated baseline serum total cholesterol or LDL-cholesterol were twice as likely to have hard exudates as patients with normal levels.[99] The risk of decreased visual acuity (loss of three lines) was associated with the extent of hard exudates. EURODIAB found a positive correlation between total cholesterol, LDL-cholesterol as well as trigycerides and the severity of DRP (Chaturvedi *et al*. 2001).[100] However, part of the association could be accounted for by the association of an increased albumin excretion rate from nephropathy.

In the DCCT study, the association between the severity of DRP and conventional lipid measureswas shown in univariate analyses but they were lost in multivariate analyses (Lyons *et al*. 2004).[101]

Other risk factors

Pre-existing DRP is always a risk for the progression of DRP (Klein *et al*. 1989b, UKPDS 1998b, UKPDS 2001a)[102,81,83]. Klein *et al*. (1995) showed that an increase of 16 or more Mas over a four-year period increased the risk of PDR by 4.6 and the risk of CSME by 9.1 times at the ten-year followup.[103]

Hormonal alterations in puberty and pregnancy are risk factors for the development of or the progression of pre-existing DRP. Murphy and co-workers (1990) showed that puberty is a risk factor for the development of DRP. The relative odds of having DRP, after adjusting for DM duration and gender, was 4.8 in the post-pubescent group as compared to the prepubescent or pubescent groups of patients with Type 1 DM.[1104] The mechanisms behind the acceleration of microvascular

disease is anticipated to be due in part to the combination of the deterioration of glycaemic control and an increase in growth and sexual hormones. In the DCCT study, pregnantwomen with Type 1 DM and conventional treatment had a 2.48-fold greater risk of any worseningof DRP during pregnancy compared with nonpregnant women. The risk for the pregnant women with better glycaemic control in the intensive treatment group was 1.63-fold (DCCT 2000).[105]

Prevention of visual impairment

Apart from minimizing risk factors for DRP, the most important tool to reduce visual impairment caused by DM is regular screening examinations of the ocular fundus in order to detect treatment needing, usually asymptomatic, lesions early enough to achieve optimal treatment results. Laser photocoagulation for high-risk PDR and CSME is of proven benefit (DRS 1981, ETDRS 1985).[6,69]Older patients with DM, in particular those with Type 2 DM and PPDR, also benefit, from photocoagulation before high-risk features develop (Ferris 1996).[75]

Treatment for DME has not been as successful. Focal photocoagulation and grid photocoagulation may reduce the risk of moderate vision loss by 50 % (ETDRS 1985).[69] However, a small number of patients end up visually impaired despite regular photographic screening mainly due to an unsuccessful outcome after laser treatment of DME (Hansson- Lundblad *et al*. 2002).[107]

Screening for diabetic retinopathy

Criteria of a disease suitable for screening : DRP fulfils the criteria for a screening programme according to WHO (1971): The disorder which should be screened is well defined, there is available knowledge about the prevalence and the progression of the disorder, there are effective treatment modalities, there are simple and safe screening

methods and the screening programme is cost effective.[108]

Methods

Screening for DRP is generally performed by a variety of health professionals usingophthalmoscopy or non-stereoscopic retinal photography. There is a wide variability in screening services both in coverage and methods used.Seven-field 30º stereoscopic photography, considered as the Gold Standard, is not usually a feasible method when performing large scale screening and is therefore not always used as the reference standard. An ophthalmologist's examination using slit lamp biomiscroscopy compares favourably with seven-field stereophotography and can therefore also be used as a reference standard (Scanlon *et al*. 2005).[109]

FA is the most sensitive method for the detection of DRP lesions. Only a small part of the Mas as detected with FA are perceived when using colour or red-free photography, 7% and 13%, respectively, according to Hellstedt and co-workers (1996).[57] However, as an invasive examination method, FA is time-consuming and expensive, and also prone to fatal risks (Yannuzzi *et al*. 1996, Beleña *et al.*2013).[110,111]It is therefore not suitable as a screening or as a reference method for screening purposes.

Direct Ophthalmoscopy, especially in the hands of a non-ophthalmologist, but even when used by experts, has proven to be insensitive (Buxton *et al*1991, Hutchinson *et al*. 2000)[112,113]

When screening for any STDR using direct or indirect ophthalmoscopy, the achieved specificity was over 91% but the sensitivity was poor in the hands of ophthalmologists (43-79%) as well as diabetologists (27-73%) and General practitioners (25-66%) (Hutchinson *et al*. 2000).[114] Fundus photography has proven to

be more reliable in detecting DRP than ophthalmoscopy (Klein *et al*. 1985b, Moss *et al*.1985, Kinyoun*et al*.1992, Harding *et al*.1995)[114-116, 4]

Slit Lamp Fundus Biomicroscopy

Biomicroscopy of the fundus with the slit lamp incorporates together two of the most important examination techniques in clinical ophthalmology -namely biomicroscopy with the slit lamp and fundoscopy.

Fundus examination with slit lamp was first done by Koeppe (1918) by attaching a mirror in front of the iluminating lens of slit lamp which brought the axes of illumination and observation nearly parallel and led to abolishing the refractive power of cornea by employing a contact lens with a flat anterior surface. Goldmann (1937) showed better methods of visualizing the posterior portions of the eye, he reduced the angle of observation illumination to 5^0(the Goldmannreduktion-prisma) on the slit lamp and visualized the fundus by placing a very light contact lens flat on the eyeball.[117]

Lemoine and Valois (1923) described the use of high power concave lens for fundus examination. Karl Hruby through a hand held lens with a refractive power of -58 dioptres created the first fundus noncontact lens which was held near but not in contact with the cornea and thus eliminated the problem of using a contact lens which was discomforting.[118]

Fundus examination with the Hruby lens was easy, but had some limitations, even with widely dilated pupil the field was view was small hardly larger than the diameter of the optic disc and the field of view was very small. Examinationwith high magnification and visualization of the periphery of the funduswere also difficult.[118]

In today's slit lamps, the source of light can be moved across the axis of observation. The illumination-observation angle can be reduced to 0° with no need of

sides of the slit-lamp in the central portion. The slit lamp in the central position the patient's eye is made highly myopic by using a strong convex lens placed in front of the patient's eye so that the emergent rays from an area of the fundus are brought to focus as a real inverted image which is formed between the condensing lens and the objective lens of slit lamp. The final image observed through the slit lamp is areal image of the fundus that is laterally reversed and inverted

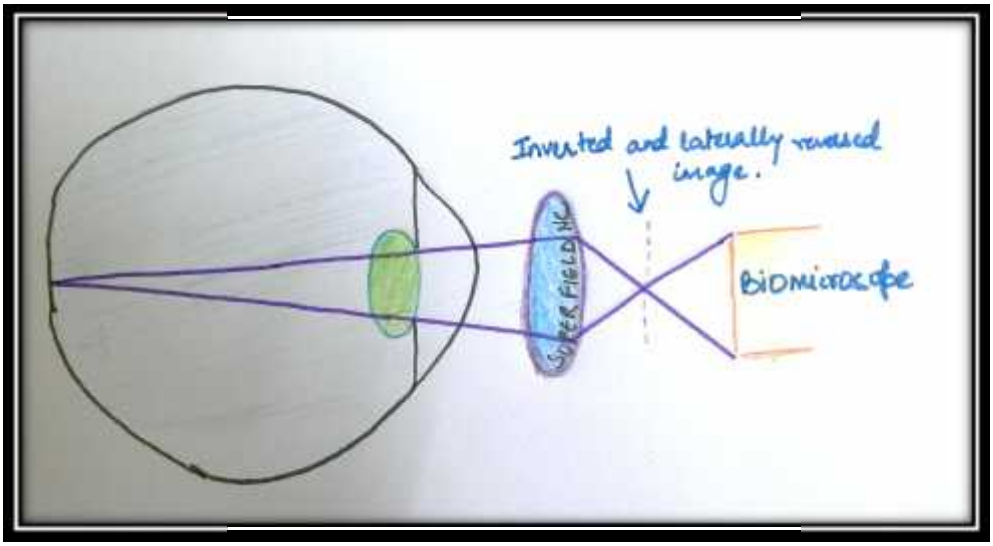


Figure 11: Optics of Slit Lamp Biomicroscopy using Fundus Non Contact Lens.

The higher the dioptric power of the lens, the greater the field of view; however, the working distance is then reduced. Each lens produces a stereoscopic fundus view that is only marginally magnified, with the greatest magnification being achieved with the lower powers. The slit lamp's optical system also allows additional magnification of the image. With stronger fundus lens, the focal length becomes short and less drawback of the slit lamp is required to bring into focus the fundus image.

Magnification is inversely related to dioptric power of lens. The Super Field lens gives a wider view of the fundus than a conventional 90D which is helpful for a multifocal lesion disorder such as diabetic retinopathy.Condensing lenses described with the 'super' prefix, such as SuperField and the SuperPupil, are not equi-convex so

need to be held with the tapered edge towards the patient. The other lenses may be held with either side towards the patient.

Field of view, magnification, working distance and primary applications of Fundus Non Contact Lenses

Lens	Field of view	Image Magnification	Working Distance	Primary Application
60 D	68°/81°	1.15x	13mm	High magnification view of posterior pole
78 D	81°/97°	0.93x	8mm	General diagnosis and treatment
90 D	74°/89°	0.76x	7mm	General diagnosis/ small pupil examination
SuperField	*95°/116°*	*0.76x*	*7mm*	*General retinal scanning situations*
SuperPupil XL	103°/124°	0.45x	4mm	Examination through small pupil (2-3 mm)

Examination technique

- For the best results, pupil should be dilated with appropriate pharmaceutical agent(s)
- The patient is instructed on the need for maximum compliance and asked to fixate the slit lamp fixation target if available. Alternatively, when viewing the right eye the patient may fixate on the practitioner's right ear and vice versa
- The illumination-observation angle is reduced to a minimum. The magnification is set to its lowest position and the slit height and width adjusted to around 5mm and 3-4mm respectively (to fill the pupil diameter)
- The slit is focused on the patient's cornea or iris and centred. The lens is then introduced close to the patient's eye. Condensing lenses have a working distance

varying typically from 4-11mm, at which it should be ideally held from the patient's eye. To offer a binocular view, it is important to maintain a distance.

- To focus the inverted image of the retina, the slit lamp is moved away from the patient. Finer movements of the joystick allows finer focussing. The rheostat and slit width may now be adjusted to optimize the view and minimize patient discomfort.
- Investigation of the vitreous is done by focussing just before the retinal surface. This is useful in posterior vitreous detachment (PVD).
- The field of view can be increased by bringing the lens closer to the eye. Slightly tilting the lens either vertically or horizontally helps minimise or eliminate the reflections from the slit lamp.
- Adjusting the magnification and slit width/height on the slit lamp brings optimal image into view.
- With the lens repositioned to optimize the view each time, the eye is examined in various positions of gaze. The lens is moved in the same direction as the desired movement of the image.

  Asking the patient to look up allows viewing of the superior retina. Once they look up their pupil will obviously move up too so the lens will accordingly have to be moved up in front of the pupil at which point a retinal view will again be seen. By tilting the lens top away from the patient slightly, excessive reflections may be minimised by maintaining coaxial illumination. The same should be repeated for all eight positions of gaze

  This technique provides 3 dimensional viewing of the fundus with excellent magnification that allows evaluation of macular oedema and neovascularization over a wide field. The disadvantageis that performing the technique with accuracy requires much experience.

Flourescein Angiography

Fluorescein angiography refers to photographing fluorescein dye in the retinal vasculature following intravenous injection of fluorescein solution. Use of flourescein was initiated by Erlich in 1882. The earliest description of flourescein angiography was given by Chao and Flocks in 1958.

Definition of fluorescence:

It is a type of photoluminescence created when fluorophores absorb electromagnetic energy leading to temporary excitation to a higher energy state.When the molecules return to original level, the light emitted will usually be different and belongs to a longer wavelength.

Phosphorescence will continue even after the removal of excitation source, whereas fluorescence requires continuous excitation. Emission of fluorescence will stop almost immediately (10^{-8} s) when the excitation source is removed.

The visualization of this fluorescence in the intravascular and extravascular compartments is the essence of fluorescein angiography.

Dye Used:

Sodium Fluorescein: Chemical composition- $\mathbf{C_{20}H_{10}Na_2O_5}$. It is a weak dibasic acid of the xanthine group chemically related to phenolphthalein..It's low molecular weight of 332.31 g/moland high water solubility allows rapid diffusion in the vascular compartment.

Adolf von Baeyer, a Nobel Laurette in Chemistry first synthesized this in 1871.It's low molecular weight of 332.31 g/moland high water solubility allows rapid

diffusion in the vascular compartment.

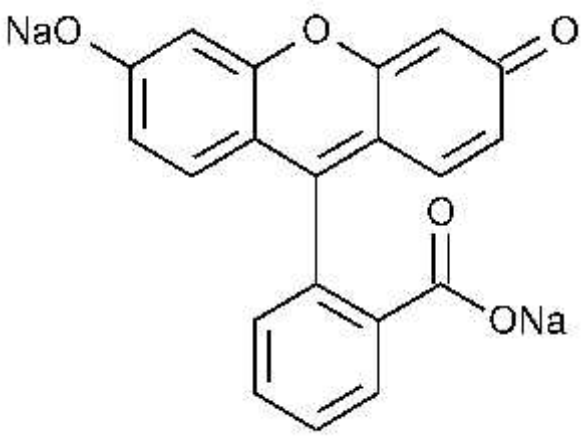


Figure 12: Chemical Structure of Sodium Flourescein

Topical application of fluorescein sodium is routinely used for documentation of ocular surface disorders such as abrasions, ulcers or other epithelial defects and for applanation tonometry.

It is also used to determine tear film breakdown time, verify the lacrimal passageway patency, check the fit of contact lenses or for detection of aqueous leakage through conjunctival wounds using Seidel Test.

Intensity of fuorescence can be affected by pH and concentration of the dye. pH needed for maximum fluorescence is 7.4, where as the pH of fluorescein sodium used for angiography is adjusted between 8 – 9.8 for stability.

Appearing orange–red in colour in powered or concentrated solution form, flouorescence is detectable between 0.1% and 0.0000001% in concentration. Diluted fluorescein sodium appears bright yellow-green colour in broad spectrum illumination. This yellow-green colour intensifies dramatically when illuminated with blue light.

Excitation and emission. Representative excitation and emission curves of fluorescein sodium. Peak excitation occurs at wavelengths between 465 and 490 nm

(blue–green). Peak fluorescence occurs at wavelengths of 520-530 nm (green–yellow).

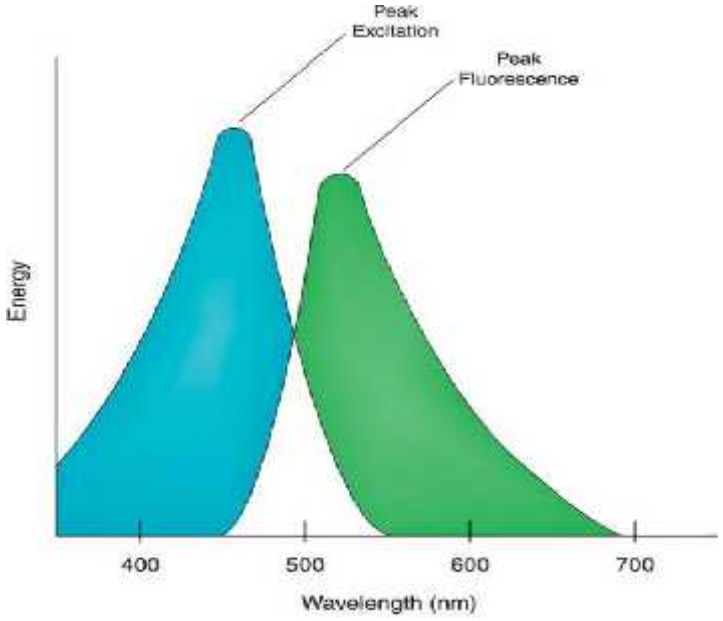


Figure 13:Excitation and emission. Representative excitation and emission curves of fluorescein sodium. Peak excitation occurs at wavelengths between 465 and 490 nm (blue–green). Peak fluorescence occurs at wavelengths of 520-530 nm (green–yellow).

Metabolism: It can be given by the intravenous route or by the oral route. 40% to 60% of the dye becomes bound to plasma proteins mainly albumin and to lesser extent to globulins. It also attached to the surface of the RBC's (15 to 17%). Further part of the emitted fluorescence is absorbed by haemoglobin.

Thus it requires a smallvolume high concentration bolus injection into the largest available peripheral vein so as to saturate the plasma proteins and avail maximal fluorescence. Dye is rapidly distributed throughout the intravascular and extravascular compartments of the body staining the skin and mucous membrane within minutes. This reaches its peak in 10 minutes and fades over 4 hours: Sodium fluorescein does not form a firm bond with any vital structures. It is largely eliminated by the liver and kidneys within 24 hours, however traces may however be detected upto 10 days after injection. Impaired renal function leads to considerable dye

retention.[119]

Preparations available:

Intravenous: 3ml of 20% is ideal, but there is an increased risk of crystallization, 5ml of 10% or 10ml of 5% solution are preferred.

Oral: 25–30 mg/kg body weight of fluorescein flavoured with lemon.[120]

Intra-arterial injection:

It has an advantage of widely separating the arterial and venous phases, and gives better photographs with greater definition.

The following is recommended in case of history of allergy:

1. Written consent

2. Test dose- 0.05 ml of dye injected intradermally and observing for wheal, however recent studies suggest allergy due to release of histamines therefore Non immunological reactions cannot be predicted by allergy skin tests, but their utility remains substantial in predicting anaphylaxis. Therefore these must be performed in patients reporting risk factors in their past medical history. [121]

Side effects:

The common side effects are nausea and vomiting, 5 to 10% develop urticarial and allergic skin conditions, rarer complications are bronchospasm, laryngeal oedema, pulmonary oedema, apnoea, respiratory arrest, myocardial infarction, syncope, seizures, cardiac arrest etc.[122]

Extravasation of the dye is very painful creating an idiosyncratic reaction which is treated by cold compresses and local infiltration of 2% xylocaine.

The principles of FFA are based on:

1. Outer blood retinal barrier

2. Inner blood retinal barrier

3.Phenomenon of fluorescence

4.Absorption and emission characteristics

5. Recording technique

Outer blood Retinal Barrier: The major choroidal vessels are impermeable to both bound and free fluorescein. However, the walls of the choriocapillaries contain multiple fenestrations through which free fluorescein molecules escape into the extravascular space. They then pass across Bruch membrane but on reaching the retinal pigment epithelium (RPE) are blocked by intercellular complexes termed tight junctions or zonula occludentes.[122]

Inner blood–retinal barrier is composed principally of the tight junctions between retinal capillary endothelial cells, across which neither bound nor free fluorescein can pass the basement membrane and pericytes play only a minor role in this regard. Disruption of the inner blood–retinal barrier will permit leakage of both bound and free fluorescein into the extravascular space.[122]

Instrumentation for FFA :

1. Fundus camera
2. Filters
3. Photography

Fundus camera:

Fundus cameras utilize an aspheric design and match the plane of focus to the curvature of the fundus, when combined with the optics of the subject eye,Refractive errors in the subject eye are compensated using focus control of the fundus camera.

Fundus cameras equipped for fluorescein angiography have a timer that records the angiographic sequencing on each frame of the study, a matched pair of

exciter and barrier filters and an electronic flash tube that recycles quickly so that acapture rate of up to one frame per second is made possible. The exciter filter transmits blue–green light at 465-490nm, the peak excitation range of fluorescein. The barrier filter transmits a narrow band of yellow at fluorescein's peak emission range of 520-530nm. The barrier filter effectively blocks all visible wavelengths but the specific colour of fluorescein.

Filters: Functionally classified as :

1. Exciterfilter: The exciter band should be in the range of 480 to 530 to achieve maximal excitation.
2. Barrier filter: It should screen out all the light except that emitted by fluorescences, it must block the reflector exciter light.

Types:

1. Absorption filter: Consisting of organic dyes coated on an acetate or glass substrate they selectively absorb certain wavelengths and transmit others.
2. Interference filters: They create ‘interference’ between layers as they are coated withmultiple thin coatings of materials with known refractive indices. This results in rejection of specific wavelengths. Interference filters offer efficient and precise light transmission capabilities with more linear spectral transmission gradients. Narrow-band interference form an essential component for modern retinal angiography.

Other filters are:

Red free filter : It provides valuable information about preretinal and superficial retinal lesions.

Infrared filters: Provides better details of choroidal circulation. Since they are of longer wavelength, they penetrate better through opacities and is of value in immature cataracts and vitreous opacities.

Digital Imaging:

Current retinal imaging systems have a spatial resolution varying from 800 x 600 to over 3000 x 2000 pixels. Monochrome digital backs are considered better for angiography than their colour counterparts since they are usually more light sensitive, and all pixels are available for exposure to fluorescence.

There are many advantages of digital imaging over traditional film-based angiography. Diagnostic information may now be enhanced with so many powerful tolls using computer technology. Brightness, contrast and sharpness may all be adjusted using software. Digital analysis may be used to measure pathologic structures, and digital overlays can be used to identify potential changes in lesion size in serial photographs, while multiple fields can be linked together to form composite wide-field images. Images can be stored on optical media like CD or DVD and transmitted electronically across computer networks for remote viewing or storage on servers. The easy availability of these stored images helps increase work efficiency and the ability to review these images in the monitor with the patient enhances patient education.

Technique:

After taking a detailed history and after a general examination, ocular examination is carried out, these are carried out with the help of slitlamp, direct and indirect ophthalmoscope,fundus non contact lenses and Goldmann’s three mirror lens. These help the ophthalmologists to know more in detail about the lesions and also to

have an idea of where they should look for and for what type of lesions while doing FFA.

1. Explain to the patient about the procedure and prepare him mentally to co-operate for the procedure.
2. Written informed consent should be taken to avoid legal problems.
3. Pupils are dilated maximally with suitable pharmacologic agent.
4. Patients name/ initials / registration numbers are entered into the system
5. Patient is seated comfortably in front of the camera with chin on the chin rest and the head touching the headrest.
6. Routine colour and the red free photographs are taken.
7. The camera is adjusted to catch the finest details. The light source should be of sufficient power for exposure of high resolution and should be of variable intensity which can be adjusted manually or automatically, the timing of exposure should be automatic to get 3 to 4 exposures/ second.
8. The scalp vein is put and its position into the vein is confirmed by injecting saline, the dye is then injected, the assistant notes time of the completion of the bolus so that the timer is started.
9. Photographs are started after 5 to 7 seconds after injection, and are taken every second for 5 to 25 seconds, later pictures are taken after 2.5 and 10 minutes , and at the end of one hour . Photos are taken of the less involved eye first , because they give better definition of early phases, but sometimes it may be necessary to take the more acutely involved eye first e.g. neovascularisation.

Interpretation

Fluorescein angiography records the dynamic interaction of fluorescein with

both normal and abnormal anatomic structures of the ocular fundus. A thorough understanding of the circulation phases and appearance of the dye in a normal eye is essential for interpretation of abnormalities.

Normal fluorescein Fundus angiogram

Arm to Retina Circulation Time:

This time is about 8.5 to 11 seconds. The dye appears in choriocapillaries in about 8 to 10 seconds, 0.5 to 1 second later it appears in the retinal arteries at the disc. This value in turn depends on cardiac output, blood viscosity, blood volume etc. It also depends on the way the dye is injected. Difference between the two eyes about this timing suggests carotid or ophthalmic artery disease.

Choroidal Circulation:

This is visualized as a 'flush' except in albinotic fundus. The pigment epithelium acts as a diffuse filter impairing the choroidal vascular reflexes and reduces the fluorescence. The other reason for such appearance is anatomical. The retina has true capillaries with a blood tissue barrier. The capillaries are separated by large intercapillary spaces. But the choriocapillaries have large sinusoids with little extracellular spaces. Therefore the dye extravasates freely and so a homogeneity is seen and this appears as the background fluorescence.

The dye reaches the branches of the choroidal vessels at different times resulting in patchy filling of the choriocapillaries in normal eyes. The position of arteries and venules supplying the capillary lobules is controversial. The margins of these lobules become clear cut until the dye perfuses to the neighbouring lobules. Visualization of choroidal vasculatureis usually not possible because of the masking effect of the dye filled choriocapillaries and the dye passing into the extracellular spaces. This phase typically occurs 9-15 seconds after dye injection.

Retinal Pigmentary Epithelium:

The pigmentary epithelial cell contains two forms of pigment melanin in the apical region and lipofuscin in the intermediate region. Those pigment act as a filter to obscure the details of the choriocapillaries in a normal fundus. It acts as a barrier to the passage of the dye. But in a pathological state like after photocoagulation, the tight junctions between the epithelial cells is broken and so the dye passes into the potential subretinal space or into the outer retinal layers.

Retinal Circulation:

Arterial Phase:

Within a fraction of a second after the choroidal phase, the dye appears in the retinal arteries. Initially only the midstream of the arterial blood fluoresces. Later the plasma adhering to the vessel wall takes up the stain. At this stage the vessel looks bigger in size as seen by ophthalmoscope, because the plasma circulating near the vessel wall is not seen by naked eye. This increase in the size is about 25% in the veins and 33% in large arteries. This phase starts about a second after the onset of choroidal fluorescence

Capillary or the arteriovenous phase:

In this phase there is complete filling of the arteries and capillaries with early laminar flow in the veins in which the dye appears to line the venous wall leaving an axial hypofluorescent strip.

The radial peripapillary capillaries which branch perpendicular to the disc with a few connecting loops originate from intraretinal arterioles. They are very much longer than other capillaries. They are involved in glaucoma, papilledema, cotton wool spot formation, diabetic retinopathy, Behcet’s disease and sarcoidosis.

Capillaries at the macula form irregular vascular loops around the avascular central foveal area. These form a fine lacy network. The capillaries at the border of the avascular area form a scalloped edge. The avascular area is approximately 500 microns or 1/3 - ½ disc diameter. Usually it is round in shape, sometimes it may be oval.Peripheral retina contains more tortuous capillaries and contains an arborizing network.

Retinal venous phase:

Laminar venous flow progresses to complete filling, with late venous phase featuring reducing arterial fluorescence. The time of onset of venous outflow depends on the particular area of the fundus, and on the retinal circulation time.

By definition, retinal circulation time is the duration between first detection of the dye in the arterial systems until the detection of the dye in the tributary venous system.

Maximal perifoveal capillary filling is reached at around 20–25 seconds in patients with normal cardiovascular function, and the first pass of fluorescein circulation is generally completed by approximately 30 seconds. These are calculated by photoelectric determination of dye dilution techniques.Hemicirculation phase: This phase begins within the first minute after intravenous injection of the dye. At this stage both the arteries and the veins show a homogenous fluorescence. Later phases become weaker with with each succeeding wave. Late staining of the vessel walls takes place, veins staining more than the arteries. This staining is due to the fluorescein – albumin complexes adhering loosely to the endothelial cells without penetrating them.

Optic disc- Fluorescence of the optic disc shows 4 stages

Stage I – Deep hazy fluorescence

Stage II – Prelaminar capillary fluorescence

Stage III – Epipapillary capillary florescence

Stage IV – Late diffuse staining and peripapillary halo

First three stages originating from three separate vascular plexuses cannot be easily differentiated. But in conditions of increased intraocular pressure or by increasing the intra-ocular pressure artificially it can be differentiated.

Stage I – Occurs during the choroidal phase or concomitant with the arrival of dye at the optic disc. The dye first appears at the disc margins in the centripetal branches from the posterior ciliary arteries supplying the region of the lamina cribrosa and possibly the pre – laminar region. This deep posterior laminar capillary plexus is not influenced by intraocular pressure and fluoresces in increased IOP.

The fluorescence reaches its maximum in a few seconds, becomes homogenous in nature filling the entire optic disc and outlines the empty major vessels by retro fluorescence. This effect is best seen when there is a deep physiological cup.

Stage II – this stage involves pre laminar capillaries which are clearly visible filling during choroidal and early retinal phase. When a cilioretinal artery is present, it fills simultaneously with this plexus. There is a dispute weather cilioretinal artery arises from choroidal or pre laminar vessels.[123]Prelaminar capillaries are seen as polygonally arranged small vessels within the papilla and receive their major blood supply from posterior ciliary arteries. This is confirmed by the fact that cilioretinal artery gets filled in central retinal artery occlusion. Filling of these vessels depends on intraocular pressure. It does not get filled when intra ocular pressure is more than the systolic pressure in the retinal artery.

Stage III – This stage is best observed when the disc vessels are congested. The filling is particularly dense on the temporal aspect and when the capillaries are

dilated in papilledemaand central retinal vein occlusion. The epicapillary vessels drain directly into central retinal vein whereas peripapillary capillaries drain primarily into intra retinalvenules. The two capillary beds can get affected separately. Some of the epicapillary capillaries originate from central retinal artery at the optic disc passing irregularly through nerve fibre layer before merging into the peripapillary vessels of the retina. Others arise from peripapillary arterioles and traverse back to the disc in the nerve fibre layer supplying the superficial layers. Peak fluorescence occurs during retinal venous phase concomitant with the perifoveal capillary phase.

Stage IV- Late fluorescenceThis stage of the optic disc is multifactorial in origin, with contributions from the deep capillary plexus of the disc, extravasation from the choriocapillaries at the disc margin and scleral flow in the lamina cribrosa.

Stage I to III may show sectoral filling even in a normal fundus.Clinically fluorescein angiography of the optic disc is of greatest value in differentiating pailloedema, drusen of optic nerve and hypermetropic disc to differentiate from pailloedema and optic neuritis.

Abnormal Flourescein Angiogram:

The terminologies used to describe abnormailities in an fluorescein angiogram are:

1. Hyperflourescence: this means increased fluorescence when compared to the normally expected or when compared to the normal areas of fluorescence surrounding this region. This is brought about by three mechanisms.

i) Increased quantity of extravascular fluorescent leaking into the serous or haemorrhagic areas or leaking into and staining abnormal materials.

   Eg- neovascularisedsubretinaldisciform fibrous tissue.

ii) Through an increased quantity of intravascular fluorescein as in a vascular tumour or neovascularization of tissue.

iii) Increase in the normal filter effect of pigment epithelium with enhanced visualization of otherwise normal choriocapillary fluorescence. This is called the window effect.[124]This does not increase in size during the late stages of angiography.

2. Hypofluorescence: This is a condition wherein there a decreased fluorescence compared to normal. This brought about by two mechanisms.

i) Obstruction to visualization of normal intravascular fluorescein as in haemorrhage, pigment accumulation or abnormal tissue proliferation.

ii) Decrease in vascularity of retina or choroid or both as in retinal vascular occlusion or choriocapillary atrophy.

3. Retrofluorescence – occurs when non-fluorescent structures are silhouetted against background fluorescence. It is most striking in the late phase (15 to 60 minutes)

4. Fluorescein leakage – Leakage of the dye out of physiological barriers of retinal vessels into the extracellular space or between tissue layers.

5. Flourescein pooling – Accumulation of the dye in spaces between cells or tissue layers.

6. Fluorescein staining – occurs when the dye gets attached to tissues causing fluorescence. This is a later phenomenon than leaking and pooling seen in 3 minute pictures and increased in 5 to 15 minutes and 30 minutes exposure. This occurs in abnormal structures as drusen, fibrous scar tissue . Normally this staining is seen in the optic disc, sclera.

7. Pseudofluorescence – This is normally seen in every angiogram. The term should be reserved for the artifact of reflected florescence of structures due to inadequate

barrier filters that allow light waves other than activated fluorescein to reach the film. It is a late process.[125]

8. Autofluorescence – It is thought to derive from lipofuscin in retinal pigment epithelial (RPE) cells, reflecting some aspect of RPE function andintegrity.[126]It is not of much importance in fluorescein angiography.

Fluorescein Angiography in Diabetic Retinopathy

The earliest papers on flourescein angiography in diabetic retinopathy were by Scott, Dollery, Hill in 1994.[127]Norton and Gutmann[128] described many of the structural and functional abnormalities in diabetic retinopathy. Thus many more capillary aneurysms were seen, than were visible on ophthalmoscopy, focal leakage from aneurysm and dilated vessels were described and areas of nonperfusion noted. Dilated channels connecting arteries to veins across areas of nonperfusion were observed and the sluggish circulation and extensive leakage from new vessels became apparent.[128]

Studying fluorescein angiogram in diabetic maculopathy,Patz, Schatz (1973)[129] found that patients with large areas of perifovealnonperfusion did badly,whether treated or not treated. Kohnerand Charg (1970)[130] found that prognosis for vision in untreated maculopathy could be predicted in 75.5%of patients from FFA. An important observation in this study was that large areas of peripheral nonperfusion preceded new vessel formation not only in the periphery but also on the disc.[130]Fluorescein angiography provides more information than ophthalmoscopy, and helps one to perform photocoagulation in a more proper and safer manner.[76]

Individual Diabetic Lesions as Seen on FFA

MICROANEURSYM (MA):

Flourescein angiography can highlight their onset in relationship with arteriolar micro-occlusions. They may be isolated or form clusters and often, if fluid is spreading through the altered walls, they may cause retinal oedema and later actual exudates. Microaneurysms may increase, disappear in a given point and then reappear in other places.

They may be subdivided depending on their developmental stage.

- Incipient microaneurysms are small,clearly seen on flourescein angiography; flourescein does not leak out through their walls
- Developed microaneurysms leak flourescein leaks through their walls.
- More developed microaneurysms vary in size, with slightly irregular walls and marked leakage of flourescein.
- The last degree of evolution is towards atrophy. The thrombosed microaneurysm does not fill the dye.

RETINAL HAEMORRHAGES:

They appear as areas of blocked fluorescence result of the faulty transmission of normal fluorescence, the so-called “blocking/masking effect”.[131]

HARD EXUDATES:

Hard exudates that that are evident by the ophthalmoscope are almost invisible with flourescein angiography. However, when they are very thick and dense, their images provide imperfect masking. Late leakage of dye may occur from the centre to the periphery of lipid and forms an advancing border which compromises the visual acuity as the sensory elements are distorted by oedema.

CAPILLARY NONPERFUSION:

Focal capillary obstructions perifoveal or regional are seen as areas of Hypofluorescence, irregular in shape in between areas of normal fluorescences. Often located close to these areas are patent dilated capillaries (IRMA) which stand out in contrast against the non perfused areas. These dilated capillaries may only rarely show leaks.

VENOUS CHANGES:

Venous changes are the same as in ophthalmoscopy i.e dilation, tortuosity , looping , kinking, sausaging and reduplication. There is usually a lack of capillary bed in the region of abnormal veins.

COTTON WOOL SPOTS:

Seen as blocked fluorescence, usually in areas of capillary nonperfusion. The involved arterioles show multiple fluorescent stumps marking origin of the occluded arterioles. There may be narrowing of the lumen of proximal arterioles.On FFA, the occluded arteriole is evident as a " pinching off" side branch with gross non perfusion of entire capillary bed in the distribution of the arteriole.[132]

LARGE ARTERIOLAR OBSTRUCTION:

It is a late finding seen as a white sheathed arteriole and a "featureless" retina in the distribution of occluded arteriole ophthalmoscopically. Later these are the sites for the development of neovascular fronds.

IRMA

Dilated,tortuous capillary segments are often noticed in flouroangiographies that may mimic new formed vessels. These pathological aspects are generally visible where the capillary network is sparser. These lesions are intraretinal and some authors consider them to be the beginning of an intraretinal neovascularization whereas other authors think that these are only the localized lesions of pre-existing capillaries.In any

case, these abnormal dilated and tortuous vessels have altered walls with marked leakage of the flourescein but they never lead to vitreous haemorrhages.[131]

PROLIFERATIVE PHASE:

The most common site for neovascular frond are along the course of major retinal vessels within three to four disc diameters. They accompany areas of large arteriolar obstruction with a predilection for superotemporal quadrant.

All new vessels leak profusely and can hence be seen clearly only in the early phases of FFA before leak obscures the individual fronds. The new vessels can be seen on the surface of the retina or may extend into the vitreous.[133]

DIABETIC MACULOPATHY

With FFA, maculopathy can be graded on the basis of extent of fluorescein leakage during the entire course of angiographic study.

Clinically FFA images affected with diabetic maculopathy can be classified into – focal, diffuse and ischemic maculopathy.[128]

Focal maculopathy- FFA image reveals leakages which are focal with adequate perfusion in the macular region.[128]

Diffuse maculopathy- Early phase angiography show ischeamic foci which tend to be both larger and more numerous than in focal maculopathy. Late phase fluorescein angiography show leakage from focal nests of aneurysms. There is generalized leakage of diffuse beds or leakage microaneuurysms and shunt vessels at the borders of large and numerous ischaemic foci.[128]

Ischemic maculopathy- is characterized by micro-vascular blockage FFA images shows non-perfusion areas which are associated with enlargement of Foveal

Avascular Zone (FAZ) in preliminary stage and areas with capillary dropouts in middle stage and pre capillary arterioles in the advanced stage.[128]

Comparison of Methods for Diabetic Retinopathy Screening

Several studies have attempted to find a simple, safe, and cost effective technique for mass screening for diabetic retinopathy.

Harding *et al*conducted a study to evaluate the different methods of community based screening for sight threatening diabetic eye disease. Community based photography with mydriasis and direct ophthalmoscopy through dilated pupils by an experienced ophthalmologist, both Compared with reference standard of slit lamp biomicroscopy by a consultant specialist in medical retinal disease was done. The main outcome measures were sensitivity and specificity of screening method and prevalence of sight threatening diabetic eye disease. Sensitivity of detection of eye disease by photography was 89%, which was significantly better than direct ophthalmoscopy which was 65%. Photography missed 5 patients with sight threatening eye disease, all with maculopathy. Patients with sight threatening retinopathy who were missed by photography tended to have peripheral venous beading or cotton wool spots with artefacts that rendered grading of peripheral retina difficult. The serious error rate for missed sight threatening eye disease was 1-5% (5/320) for photography and 50% (16/320) for direct ophthalmoscopy. Specificity of detection of sight threatening eye disease was 86% for photography and 97% for direct ophthalmoscopy.[4]

It was concluded that since high specificity is essential for an effective screening programme, a photographic method should be considered as preferred option in national, community based screening programme.[4]

Kinyoun*et al*studied three examination methods to detect and grade diabetic retinopathy in 124 subjects with T_2DM. These three examination methods included ophthalmoscopy (indirect and direct) by a retina specialist, seven standard field fundus photographs read by the same retina specialist, and the same photographs read by a trained photographic grader at the fundus photograph reading center. For the 59 subjects examined with all three methods, results indicated fair to good (kappas, 0.69-0.84) agreement between the retina specialist's and trained grader's reading of photographs, fair to good (kappas, 0.58-0.79) agreement between the retina specialist's ophthalmoscopic findings and the specialist's reading of photographs, and fair (kappas, 0.49-0.62) agreement between the retina specialist's ophthalmoscopic findings and the trained grader's reading of fundus photographs. Analysis of the disagreements confirmed earlier reports that ophthalmoscopy misses approximately 50% of eyes with microaneurysms only. Other disagreements resulted from the trained grader's overreading photographs of eyes with lesions simulating diabetic retinopathy. Of the 393 total subjects (diabetic and nondiabetic) in this study, such lesions were seen with ophthalmoscopy in six eyes of six subjects (2.4% of diabetic patients and 1.1% of nondiabetic subjects).[116]

Lee *et al*compared fundus photography with ophthalmoscopy in the detection of diabetic retinopathy. Ophthalmoscope and fundus photographs with a non mydriatic camera, both performed thorough dilated pupils were compared to diagnose retinopathy in a cohort of 410 Indians with T2DM. A total of 795 eyes were

examined using both methods. The mean age of participants was 60.3 years, with a mean duration of diabetes 17.3 years, an overall agreement of 86.3% with a kappa of 0.74 was found between ophthalmoscopy and fundus photography with a non mydriatic camera. For the diagnosis of proliferative diabetic retinopathy, kappa = 0.84 with an agreement of 98.1%. With a total of 61 cases of proliferative retinopathy diagnosed by either method, ophthalmoscopy alone detected 88.5% and fundus photography 78.7%. When compared on a lesion by lesion basis, agreement between the two diagnostic methods was highest for non proliferative diabetic retinopathy, as well as fibrous proliferation. The conclusion of the study was that fundus photography with a non mydriatic camera, performed with mydriasis is comparable to ophthalmoscopy for the detection of retinopathy. It may prove to a suitable, cost effective method for routine screening in diabetes clinic, provided ophthalmological referral is ensures for those with a diagnosis of any form of retinopathy, questionable retinopathy, non diabetic retinopathy, those with poor quality photographs, as well as those with acute changes in visual acuity.[134]

Moss *et al*conducted a study comparing ophthalmoscopy and fundus photography in determining severity of diabetic retinopathy in a population based Study of 2708 diabetic persons in South Wisconsin. The retinopathy levels as determined by ophthalmoscopy and by the grading of stereoscopic fundus photograph were compared. Ophthalmoscopy was performed by an ophthalmologist and a specifically trained optometrist and ophthalmic technician. There was exact agreement between ophthalmoscopy and grading for detecting retinopathy (none, non proliferative, proliferative) 85.7% of the time. The kappa statistic, which corrects for chance agreement was 0.749. There was no significant difference among the three ophthalmologists. Ophthalmoscopy was more likely disagree with fundus

photography reading in eyes with less severe forms of retinopathy and in patients examined early in the study. Other factors found to influence the degree of agreement were age, visual acuity and duration of diabetes. The authors concluded that with proper training ophthalmoscopy can be an acceptable alternative to fundus photography in certain situations.[115]

Several studies have reported the cost effectiveness of screening of retinopathy. They have established that screening for DR saved vision at a relatively low cost and this cost is many times less than the disability payments provided to people who go blind in the absence of screening programme. Many modalities of screening are in use depending on local availability of facility. These variables include number of available ophthalmologists, other trained Healthcare professionals, equipment and the sources available for screening. However, whichever method is used should have sufficient sensitivity more than 80% for a single modality screening process. Combining two modalities of screening provides excellent sensitivity but increases the cost per case screened and is often only possible in hospital based settings .[135,136]

In a two centre prospective study conducted in United Kingdom by Scanlon *et al*it was shown that slit lamp biomicroscopy, by an ophthalmologist, experienced in retinal examination, can compare favourably as a reference standard when assessing different methods of screening for diabetic retinopathy (sensitivity 87.4%). However, one cannot necessarily conclude that this examination, with different ophthalmologists, will produce consistently high quality results.[109]

A prospective analytic study conducted in Jordan Khalaf *et al*, compared grading obtained from clinical slit lamp biomicroscopy and fundus fluorescein

angiography found slit lamp biomicroscopy to be highly sensitive (91.2%) for diabetic retinopathy grading in diabetic patients with a degree of agreement kappa 0.87 with FFA and concluded that ophthalmologists do not need to confirm a suspected clinical diagnosis of proliferative diabetic retinopathy using FFA as ophthalmoscopy proved to be comparable to angiography.[137]

Several studies have been done to bypass the invasiveness of intravenous flourescein angiography by substituting it with oral flourescein angiography. Squirell*et al*found this was found to be significantly reliable for detection of macular leakage (kappa 0.78) and identification of microaneuryms (kappa 0.83) and neovascular complexes (kappa 1.0) but the foveal ischaemic zone was unreliably visualized (kappa 0.1%) and profuse dye leakage from neovascular complexes obscured the view of the peripheral retina.[120]

Nisic*et al*, in a study involving 90 subjects emphasised that for the diagnosis of macular edema stereo bio-microscope fundus examination, recording and analyzing computerized tomography of the retina (OCT), fundus images and fluorescein angiography should be performed. They concluded that for the accurate and in time diagnosis of CSME it is necessary to apply multiple methods and tests within the ophthalmological examination.[138]

A telemedicine approach has also been used for screening for diabetic retinopathy. Several studies have been done on this and found nonmydriatic photography, combined with tele-transmission to a reading centre, to be a feasible valid method for detection of diabetic retinopathy and this screening method allows the identification of patients requiring prompt referral to an ophthalmologist for further eye examination.[139-141]

MATERIALS AND METHODS

STUDY DESIGN:

The present study is a cross sectional, descriptive Study.

Source of Data:

All patients attending the out-patient, in-patient and referrals to Ophthalmology department at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum who were known diabetics and had evidence of diabetic retinopathy on direct/indirect ophthalmoscopy.

Study period:

One year-1st January 2014 to 31st December 2014.

Sample size: calculated as per -

$$n = \frac{(Z\alpha)^2 * \text{Sensitivity} * (100 - \text{sensitivity})}{L^2 * \text{Prevalence}}$$

where n = Sample Size

Z= Power of the study

α = Error

(for a confidence limit of 99% , Zα= 2.58)

L= absolute error (5%)

Prevalence= Prevalence of Diabetic Retinopathy in Diabetic patients at the time of presentation, 5%)

Substituting all,

$$n = \frac{2.582 * 89 * 11}{5^2 * 5} \sim \mathbf{52}$$

Selection Criteria

***Inclusion Criteria*:**

Participants who were known case of Diabetes and showed some evidence of Diabetic Retinopathy on Indirect Ophthalmoscopy

Exclusion *criteria:*

1. Patients with significant changes in ocular media transparency (cataract, corneal leukoma, vitreous hemorrhage)
2. Patients with other degenerative lesions of the fundus, as the presence of these wouldmask the fundus appearance of diabetic retinopathy.
3. Patients who had received intravitreal injections of anti vascular endothelial growth factor for diabetic retinopathy.
4. Patients who had received Laser Treatment for Diabetic Retinopathy.
5. Patients in whom injection of fluorescein dye was contraindicated. (renal insufficiency, history of drug allergies)
6. Patients who refused to give consent for participating in the study.

Study Participant Selection:

Since this is a cross sectional study, all patients who satisfied the inclusion-exclusion criteria were invited to participate in the study without the involvement of a sampling process. Participation was voluntary and participants could exercise their right to pull out of the study at any stage.

Procedure:

After taking informed consent [Annexure 1] a detailed history of the study participants was taken, they were asked regarding

- Duration of diabetes
- Past glycaemic control (HbA_{1c})
- Medications
- Medical history (e.g., obesity, renal disease, systemic hypertension, serum lipid levels
- Ocular history(e.g., trauma, ocular injections, surgery, including laser treatment and refractive surgery)

A general physical examination was performed followed by a complete ophthalmic examination [Annexure 2]

Ocular Examination included:

1. Visual Acuity Assessment
    a. Uncorrected visual acuity (UCVA)
    b. Best Corrected visual acuity (BCVA)
    c. Near vision
2. Torch Light Examination of eye
3. Slit Lamp Examination of anterior Segment
4. Intraocular Pressure measurement (IOP)

These patients were then, after mydriasis (using Tropicamide 0.8% + Phenylephrine 5%) subjected to 5. Slit Lamp Biomicroscopy on a Zeiss slit lamp using Volk Superfield NC lens.

The posterior pole was examined for

- Microaneurysms, retinal haemorrhages, venous beading, and IRMA
- Optic nerve head neovascularization and/or neovascularization elsewhere
- Vitreous or preretinal hemorrhage
- Presence of macular edema

This examination was captured by anterior segment videography. Retinopathy and maculopathy were also documented by a drawing on the proforma sheet and graded according to the ETDRS criteria

Nonproliferative Diabetic Retinopathy (NPDR)

A. Mild NPDR
At least one microaneurysm
Definition not met for B, C, D, E, F

B. Moderate NPDR
H/Ma ≥ standard photograph No. 2A
Soft exudates, VB, and IRMA definitely present
Definition not met for C, D, E, F

C. Severe NPDR
H/Ma ≥ standard photograph No. 2A (Fig. 133.1) in all 4 quadrants
VB in 2 or more quadrants (Fig. 133.3)
IRMA > standard photograph No. 8A in at least 1 quadrant (Fig. 133.2)

D. Very Severe NPDR
Any two or more of C.
Definition not met for E, F

Proliferative Diabetic Retinopathy (PDR)

(Composed of:(1) NVD or NVE, (2) preretinal or vitreous hemorrhage, (3) fibrous tissue proliferation)

E. Early PDR
New vessels
Definition not met for F

F. High-risk PDR
NVD (1/3 – 1/2 disc area (Fig. 133.4) *or*
NVD and vitreous or preretinal or vitreous hemorrhage (Fig. 133.5) or
NVE ≥ ½ disc area and vitreous or preretinal hemorrhage

Clinically Significant Macular Edema (CSME)

1. Thickening of the retina at or within 500 μm from the center of the macula *or*

2. Hard exudates with thickening of the adjacent retina located at or within 500 mm from the center of the macula *or*

3. A zone of retinal thickening, 1 disc area or larger in size located at or within 1 disc diameter from the center of the macula.

They were then positioned comfortably at the fundus camera with the chin in the chin rest and forehead against the bead bar and subjected to-6. FundusPhotography and seven field images taken as

1. Centered on the Optic Disc
2. Centered on the Fovea
3. Nasal edge on the Fovea
4. Superior Temporal overlapping images 1, 2 and 3
5. Inferior temporal overlapping images 1, 2 and 3
6. Superior nasal overlapping image 1 with temporal edge touching nasal edge of image 4
7. Inferior Nasal overlapping image 1 with temporal edge touching nasal edge of image 5

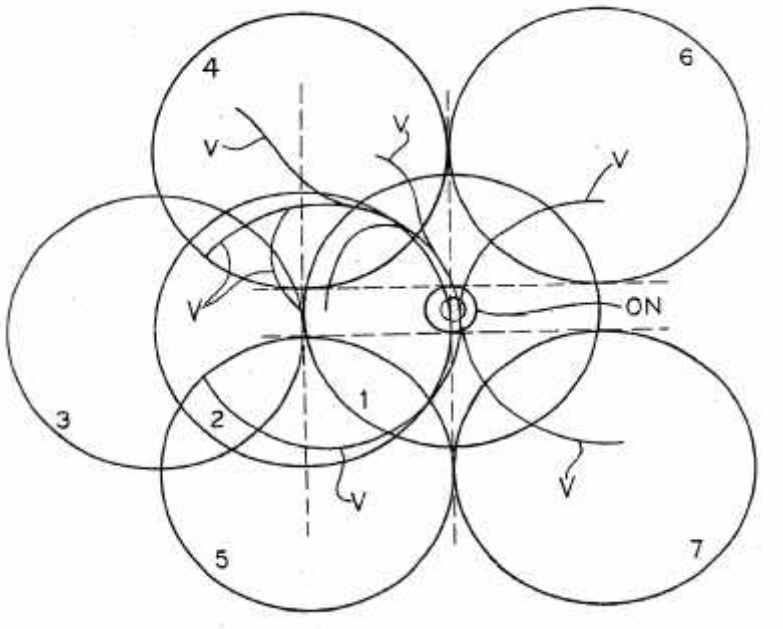


Figure 14: 7 fields of retinal photography

Once the patient's renal profile was assessed to be normal, they were once again explained regarding the risks of flourescein angiography and they were they were subjected to:

7. Fundus Fluorescein Angiography

Patient was given clear explanation regarding the procedure to make them less anxious and more co-operative. A 23 guage scalp- vein needle was inserted into anti-cubital vein and strapped into position. It's position in the vein and patency were verified by injecting 2cc of normal saline. 3ml of 20% fluorescein sodium dye was then rapidly injected by the assistant, and the timer simultaneously started and the first photograph taken, rapid series of photographs were then taken. Flourescein injection may rarely have adverse effects, in preparation the angiography room was kept equipped with emergency oxygen source, stethoscope, sphygmomanometer, intubation kit, intravenous needles, fluids, intravenous medication, epinephrine and an antihistamine

FFA findings were read and graded according to the ETDRS grading criteria.These photographs were also recorded on CD and documented by a diagram on the proforma sheet.

8. Both, the slit lamp fundus biomicroscopy and flourescein angiography findings were then compared.

Statistical analysis

Statistics were carried out using the SPSS program version 20.

The relationship between the quantitative variables was performed by Pearson correlation coefficient analysis.

Interpretation of P value-

p> 0.05 – Not significant

p< 0.05 – Significant

p< 0.01 – Highly significant

Sensitivity of slit lamp biomicroscopy in grading of diabetic retinopathy was calculated. kappa was used to measure the degree of agreement between slit lamp biomicroscopy and FFA grading. Association of Diabetic age, Hypertension and HbA_{1c} with severity of diabetic retinopathy was also determined.

Kappa statistics wereinterpreted as kappas over 0.75 as excellent, 0.40 to 0.75 as fair to good, and below 0.40 as poor.

Data representation was performed using pie charts, bars charts, charts with bars grouped for association.

Descriptive statistics (mean value and standard deviation) was used to show the basic features. Statistical analysis, data processing, the graphs and tables were made using the Microsoft Office computer programs.

RESULTS

The present study is an observational study. It was conducted on 52 patients with diabetic retinopathy, meeting the inclusion criteria, who presented to the ophthalmology department of KLES Dr. Prabhakar Kore Hospital and Medical research Centre between 1st January 2014 to 31st December 2014.

Table.1.Study InclusionData

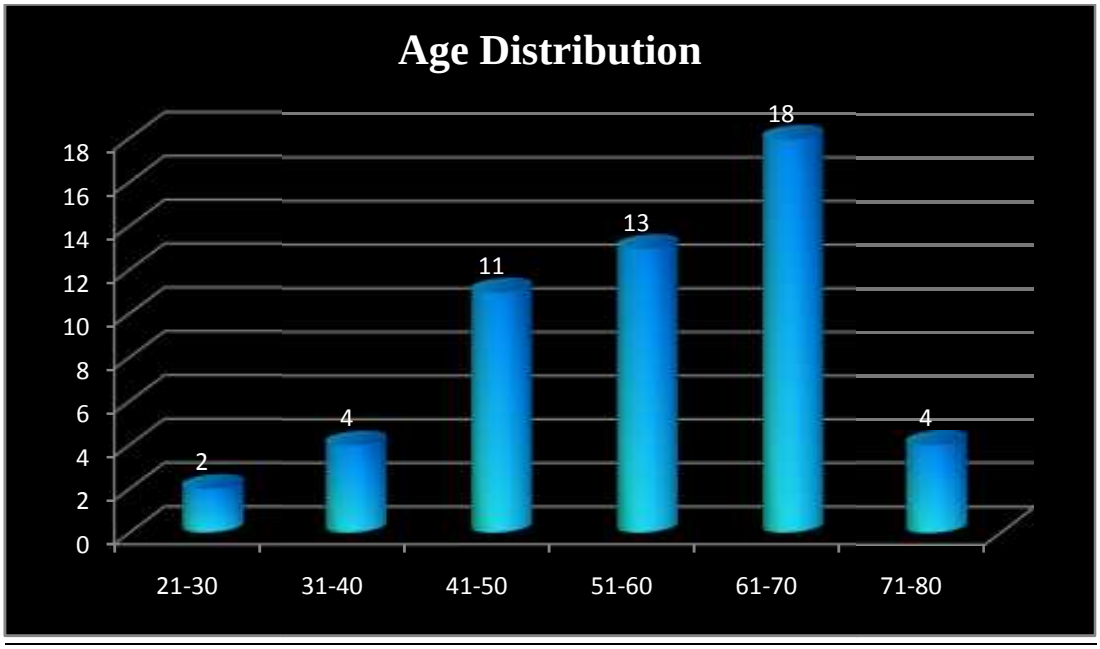
Parameters	Observation
Total number of patients	52
Type 1 Diabetics	5
Type 2 Diabetics	47
Total number of eyes included	102

Table 2: AGE DISTRIBUTION

AGE	NUMBER OF CASES	PERCENTAGE
20-30yrs	2	3.8%
31-40yrs	4	7.6%
41-50yrs	11	21.2%
51-60yrs	13	25%
61-70yrs	18	34.6%
71-80yrs	4	7.8%
Total	52	100%

Mean Age Distribution- 55.88 years; Std. deviation - 12.21

Graph 1. Age Distribution



In our study, the youngest patientwas 21 years old and the oldest patient was 77 years old, themaximum number of patients i.e. 34.6%, belonged to the age group of 61 – 70 years .

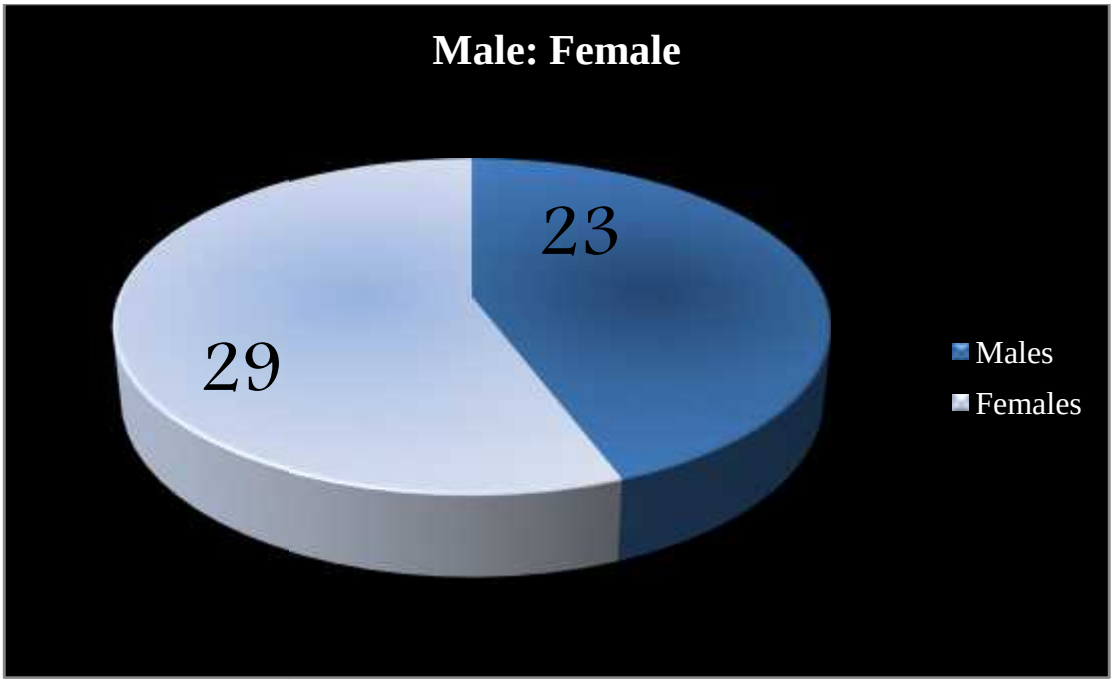
The mean age of participants was 55.88 ± 12.2 years

Table 3: Gender Distribution

SEX	NUMBER	PERCENTAGE
MALES	29	55.7%
FEMALES	23	44.3%
Total	52	100%

Male: Female = 1.3:1

Graph 2.Male: Female



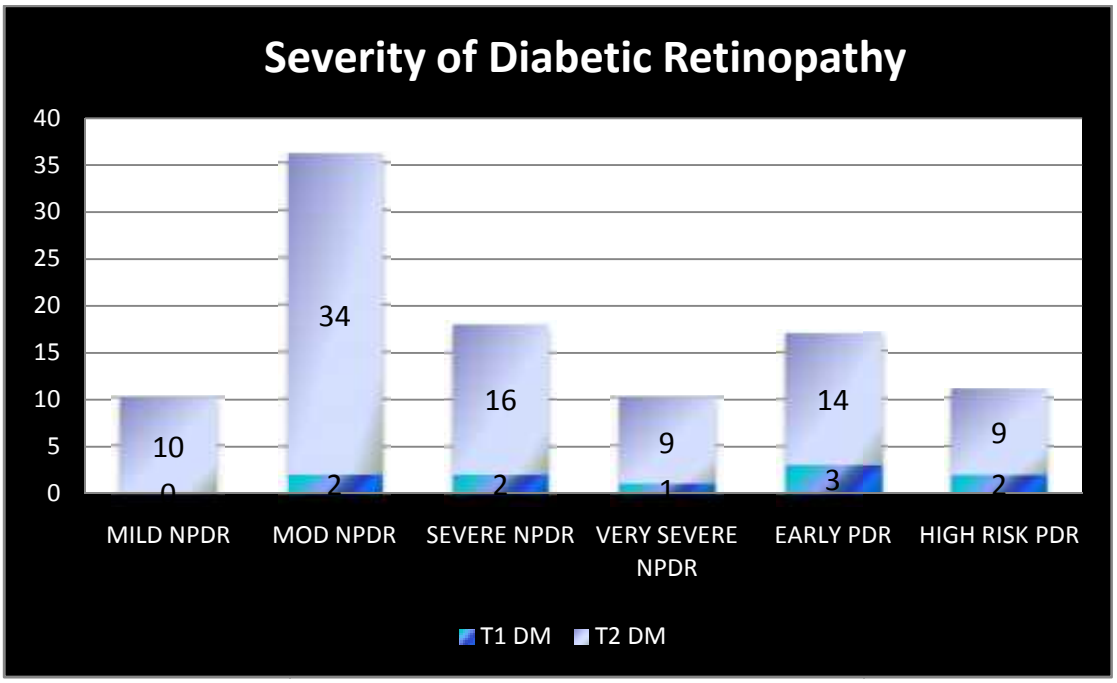
There were 29 males and 23 females in our study group, revealing a malepreponderance in our recruited study population. The male: female ratio was 1.3 : 1.

Table 4A: Severity of Diabetic Retinopathy (FFA Grading)

Retinopathy	Number of Eyes		Total	%
	T_1DM	T_2DM		
MILD NPDR	0	10	10	9.8
MODERATE NPDR	2	34	36	35.3
SEVERE NPDR	2	16	18	17.6
VERY SEVERE NPDR	1	9	10	9.8
EARLY PDR	3	14	17	16.7
HIGH RISK PDR	2	9	11	10.8

Total	10	92	102	100

Graph3. Severity of Diabetic Retinopathy

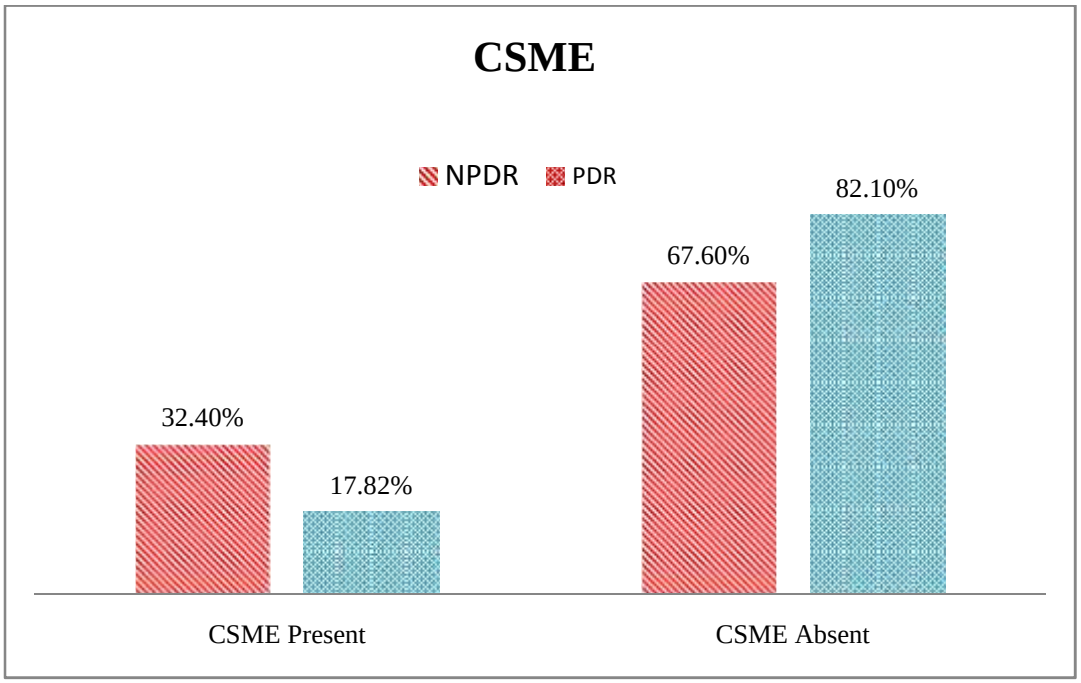


The present study constituted 10% mild NPDR, 35% moderate NPDR, 18%severe NPDR, 10% very severe NPDR, 17% PDR and 11% high risk PDR. Out of 52 retinopathy patients studied moderate NPDR accounted for more than one-third the patients.

TABLE 4B: Prevalence of CSME

CSME	Non Proliferative	Proliferative	Total	%
Present	24	5	29	28.43
Absent	50	23	83	71.5
Total	74	28	102	100

Graph 4.CSME



A total of 28.43% of eyes with diabetic retinopathy had CSME.

32% of eyes with NPDR had CSME

21.7% of eyes with PDR had CSME.

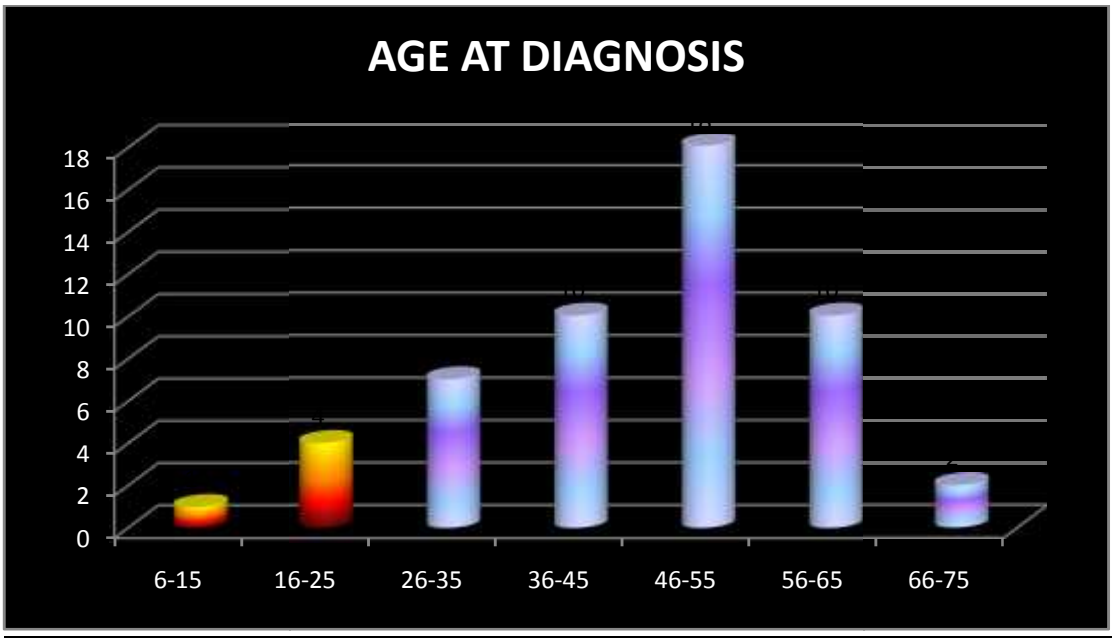
All 29 of the CSME cases had T_2DM. None of the T_1DM participants had CSME.

Table 5A: Age at Diagnosis of Diabetes

	AGE	NUMBER OF CASES	PERCENTAGE
T_1DM	6-15 yrs	1	1.9%
	16-25 yrs	4	7.7%
T_2DM	26-35 yrs	7	13.5%
	36-45 yrs	10	19.2%
	46-55 yrs	18	34.6%
	56-65 yrs	10	19.2%
	66-75 yrs	2	3.8%
	Total	52	100%

Mean Age at Diagnosis for T_1DM – 16.8; Std. deviation 6.8
Mean Age at Diagnosis for T_2DM – 58.5; Std. deviation 5.0

Graph 5: AGE AT DIAGNOSIS



Age at diagnosis was calculated as patient's age at point of examination minusduration of diabetes. The range of age of onset in our study was 6 – 72 years

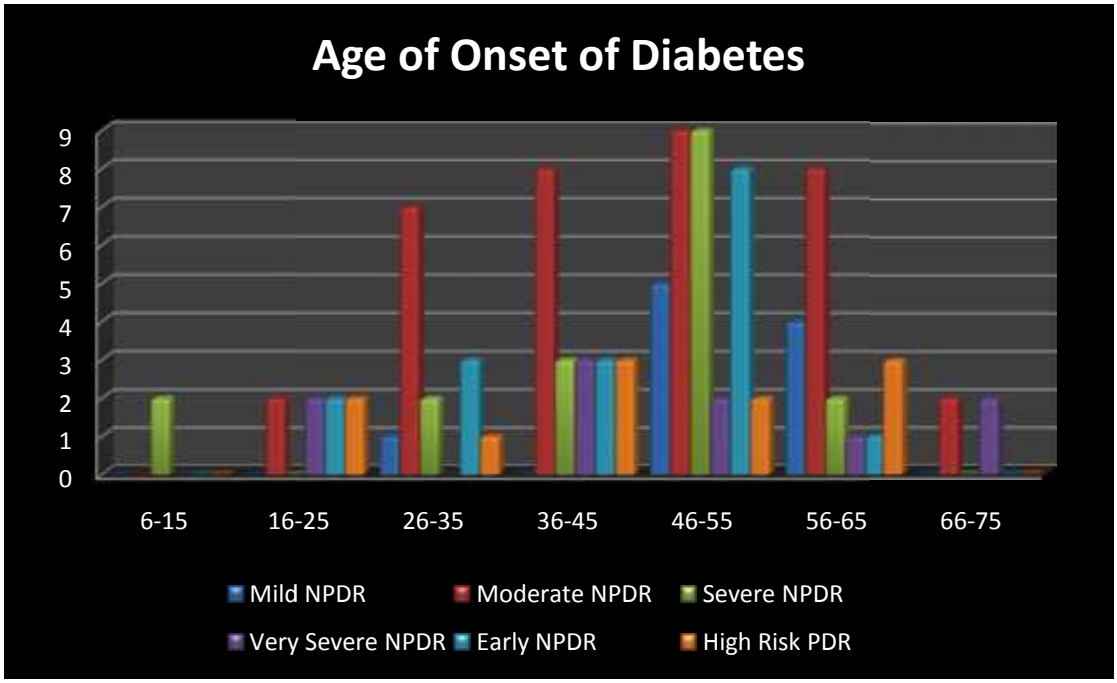
Table 5B: Association ofAge at Diagnosis with Severity of Retinopathy (by FFA)

AgeofOnset * DiabeticRetinopathyGrade Crosstabulation

		DiabeticRetinopathyGrade						Total
		Mild NPDR	Moderate NPDR	Severe NPDR	Very Severe NPDR	Early PDR	High Risk PDR	
Ageof Onset	6-15	0	0	2	0	0	0	2
	16-25	0	2	0	2	2	2	8
	26-35	1	7	2	0	3	1	14
	36-45	0	8	3	3	3	3	20
	46-55	5	9	9	2	8	2	35
	56-65	4	8	2	1	1	3	19
	66-75	0	2	0	2	0	0	4
Total		10	36	18	10	17	11	102

p= 0.8 (NS)

Graph 6.Age of Onset of Diabetes



The above table shows that around 6 out of 10 (60%) cases withmild NPDR were had age of onset at less than 55 years, 61% of moderate NPDR patients were had age of onset less than 55 years, 61% cases with severe NPDR had age of onset after 45 years. 50% of cases of PDR had age of onset more than 45 years.

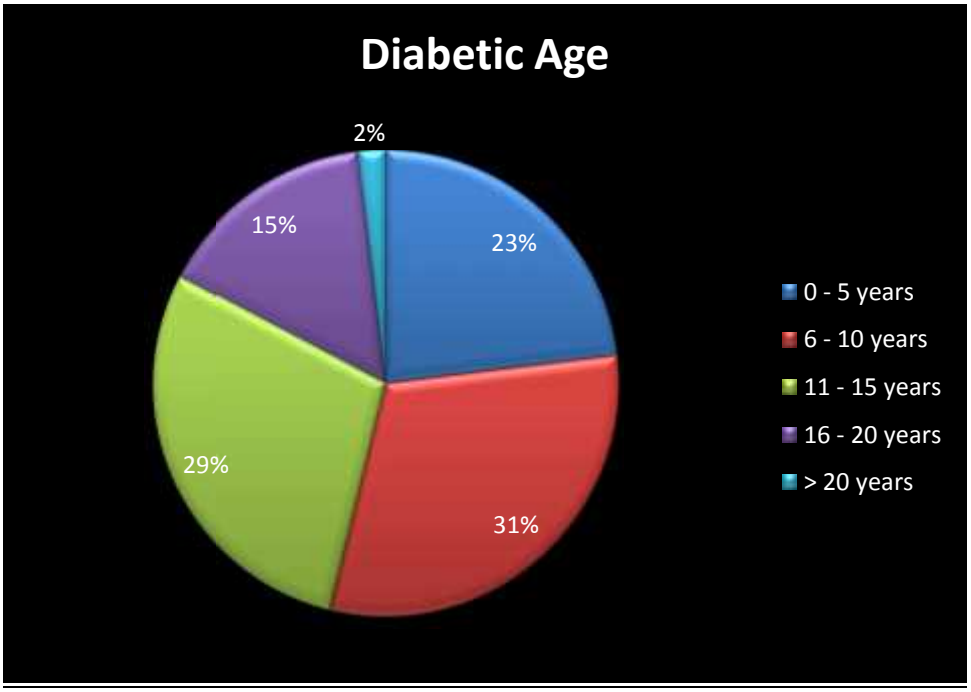
Table 6A: Diabetic Age

DURATION (YEARS)	NUMBER	PERCENTAGE
0 - 5	12	23.1%
6 – 10	16	30.8%
11 – 15	15	20.8%
16 – 20	8	15.4%
>20	1	1.9%

Total	52	100%

Mean= 10.37 Std. dev= 5.94

Graph7.Diabetic Age



The rage of duration of diabetes in our study was from 0 – 22 years with maximum participants having a diabetic age between 6 – 10 years duration.

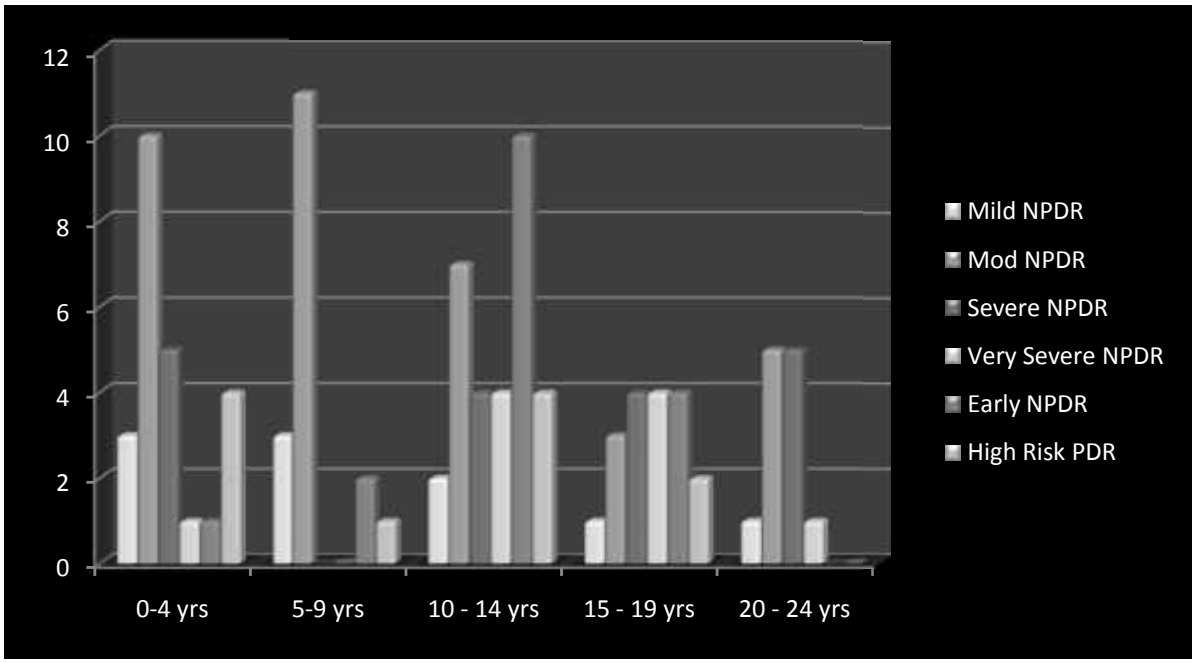
Table 6B: Correlation of Severity of Retinopathy (by FFA) with Diabetic Age
Diabetic Age * Grade of Diabetic Retinopathy

		FFA						Total
		Mild NPDR	Mod NPDR	Severe NPDR	Very Severe NPDR	Early PDR	High Risk PDR	
Diabetic Age	0-4 yrs	3	10	5	1	1	4	24
	5-9 yrs	3	11	0	0	2	1	17
	10-14 yrs	2	7	4	4	10	4	31
	15-19 yrs	1	3	4	4	4	2	18

	20-24 yrs	1	5	5	1	0	0	12
Total		10	36	18	10	17	11	102

p =0.001 (HS)

Graph 8. Correlation of Severity of Retinopathy (by FFA) with Diabetic Age



60% cases of mild NPDR cases had a diabetic age of less than 10 years, 77% of moderate NPDR cases had a diabetic age less than 15 years, 72% cases of severe NPDR had diabetic age more than 10 years and 72% of PDR cases had diabetic age more than 10 years.

Table 7: Correlation of Severity of Retinopathy (by FFA) with Treatment

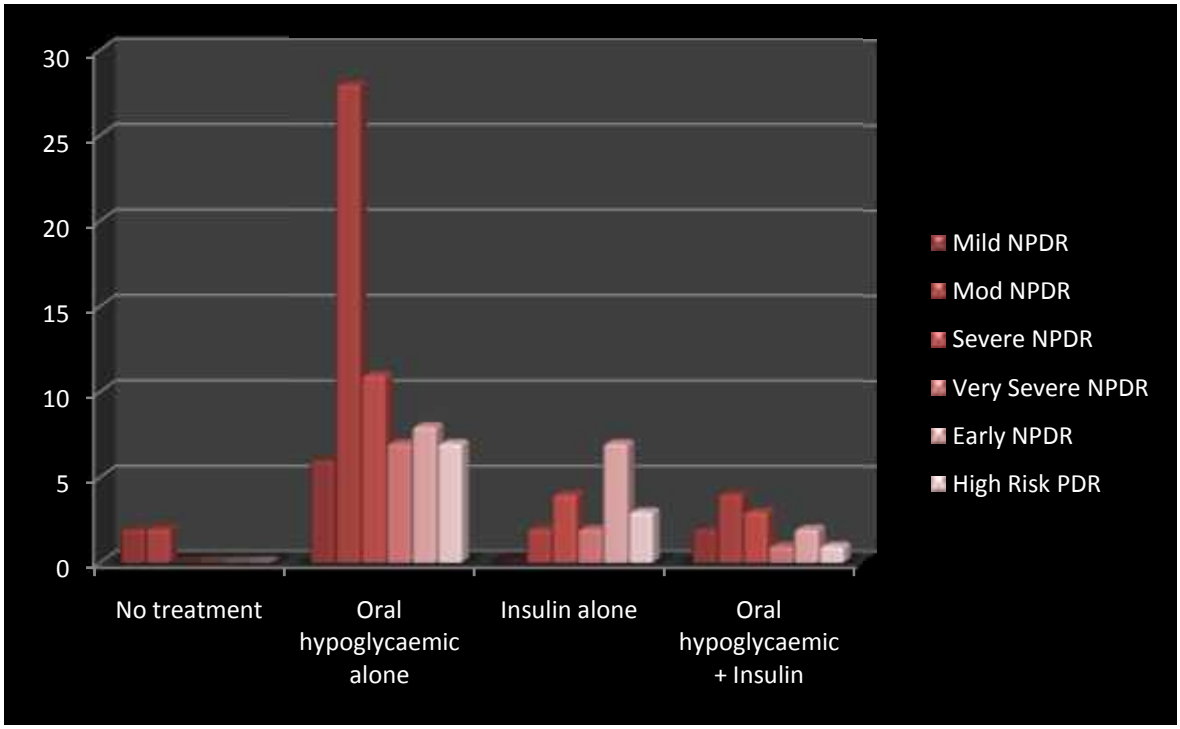
Treatment * Severity of Diabetic Retinopathy

		FFA						Total
		Mild NPDR	Mod NPDR	Severe NPDR	Very Severe NPDR	Early PDR	High Risk PDR	
Diabetic Age	No treatment	2	2	0	0	0	0	4
	OHA alone	6	28	11	7	8	7	67
	Insulin alone	0	2	4	2	7	3	18

	OHA + Insulin	2	4	3	1	2	1	13
Total		10	36	18	10	17	11	102

p = 0.091(NS)

Table 9. Correlation of Severity of Retinopathy (by FFA) with Treatment



65.8% participants were on treatment using only oral hypoglycaemic agents, 18% were on insulin alone, 13% were on OHA + insulin, 2 participants (3.8%) were not on any treatment.

Table 8: Correlation of Severity of Retinopathy (by FFA) with Hypertension

	Diabetic Retinopathy Grade						Total
	Mild NPDR	Moderate NPDR	Severe NPDR	Very Severe NPDR	Early PDR	High Risk PDR	
Normotensive	5	16	10	3	9	1	44
Hypertensive	5	20	8	7	8	10	58
Total	10	36	18	10	17	11	102

p = 0.161 (NS)

Graph 10. Correlation of Severity of Retinopathy (by FFA) with Hypertension

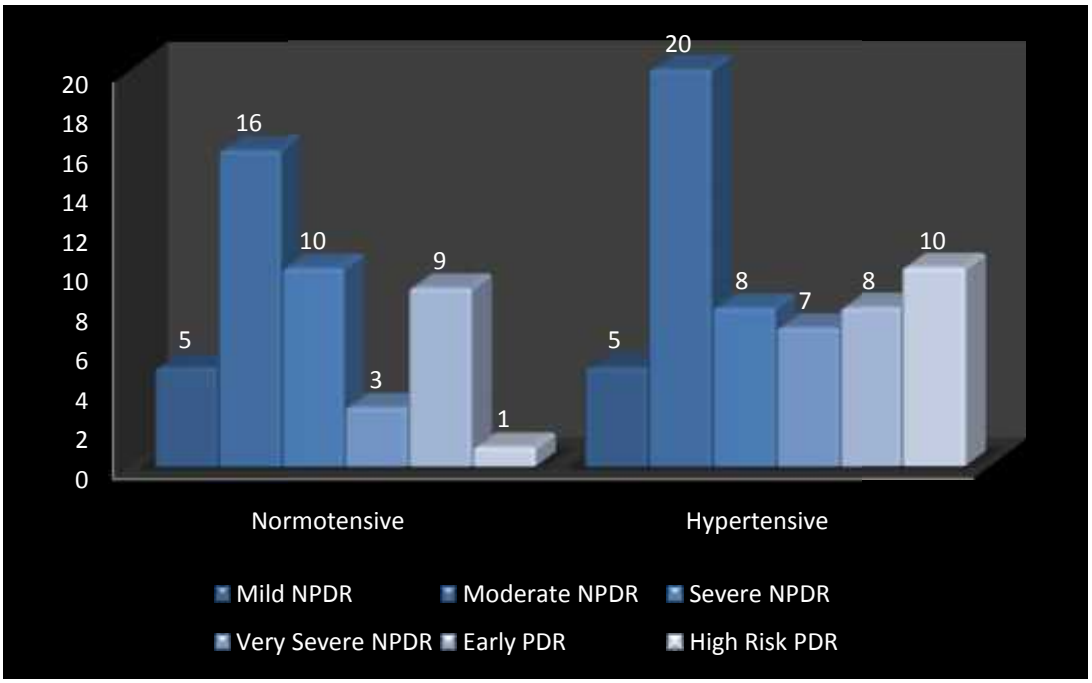


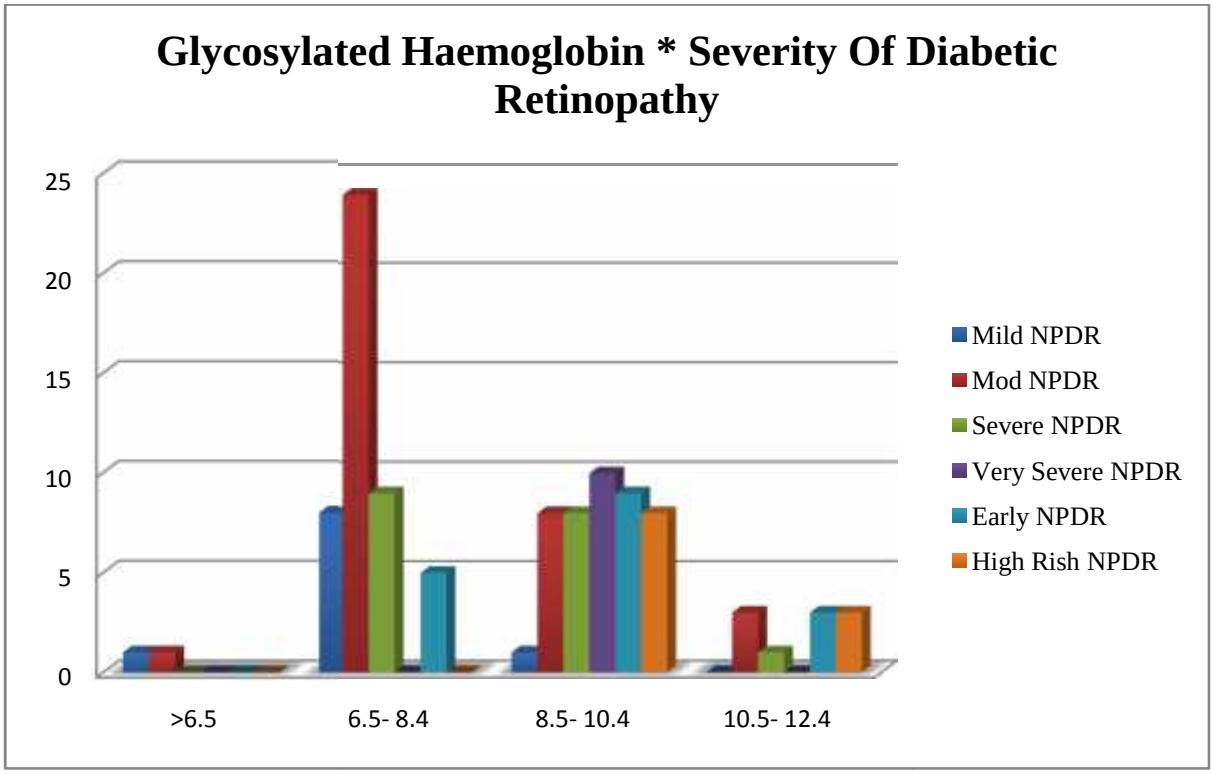
Table 9: Correlation of Severity of Retinopathy (by FFA) with HbA_{1c}

Glycosylated Haemoglobin * DiabeticRetinopathy Crosstabulation

		DiabeticRetinopathy						
		Mild NPDR	Mod NPDR	Severe NPDR	Very Severe NPDR	Early PDR	High Risk PDR	Total
Glycosylated Haemoglobin (%)	<6.5	1	1	0	0	0	0	2
	6.5 -8.4	8	24	9	0	5	0	46
	8.5- 10.4	1	8	8	10	9	8	44
	10.5- 12.4	0	3	1	0	3	3	9
Total		10	36	18	10	17	11	102

Mean HbA_{1c} - 8.73
Std. dev- 1.50
p <0.001 (HS)

Graph 11.Correlation of Severity of Retinopathy (by FFA) with HbA_{1c}



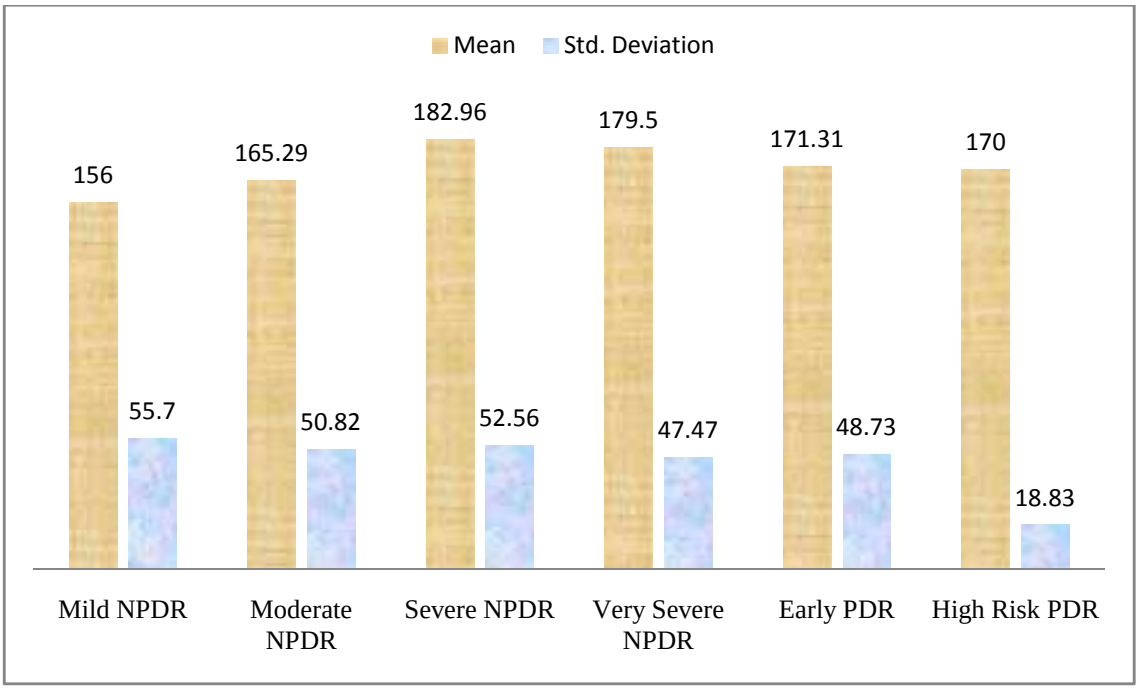
90% cases with mild NPDR had HbA_{1c} less than 8.5%, 69% of cases with moderate NPDR had HbA_{1c} less than 8.5%, 50% of cases with severe NPDR and 100% of cases with very severe NPDR had HbA_{1c} more than 8.5%. 82% cases of PDR had HbA_{1c} more than 8.5%.

Table 10:Means and S.D. of Fasting blood sugars and severity of Retinopathy

	Mean blood sugar	Std. Deviation
Mild NPDR	156.00	55.70

Moderate NPDR	165.29	50.82
Severe NPDR	182.96	52.56
Very SevereNPDR	179.50	47.47
Early PDR	171.31	48.73
High Risk PDR	170.00	18.83

Graph 12. Means and S.D. of Fasting blood sugars and severity of Retinopathy



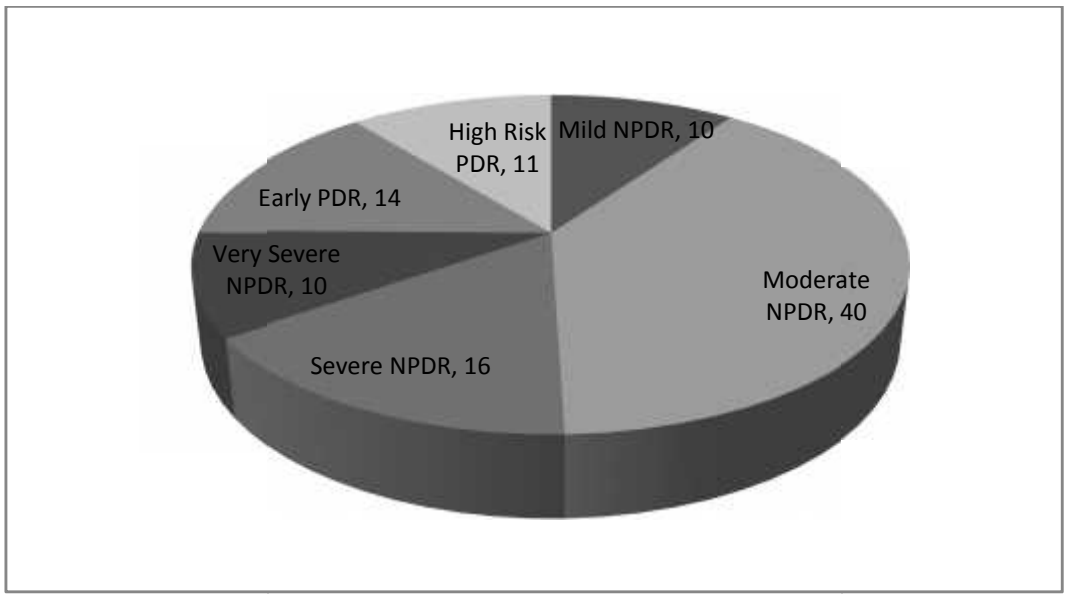
The table shows the means of FBS in each level of severity of diabeticretinopathy. The mean of FBS in mild NPDR was 156.00 ± 55.70, in moderate NPDR was 165.29 ±50.82, in severe NPDR was 181.96 ± 52.56, in very severe NPDR it was 179.5 ±47.7, in Early PDR was 171.31± 48.73 and in High risk PDR was 170 ± 18.83. Therefore, as the severity of retinopathy increased, the mean FBS for that level of severity also increased

Table 11A: Grading of Diabetic Retinopathy by Slit Lamp Ophthalmoscopy

	Number of eyes	Percent (%)
Mild NPDR	10	9.8

Moderate NPDR	40	39.2
Severe NPDR	16	15.7
Very Severe NPDR	10	9.8
Early PDR	14	13.7
High Risk PDR	12	11.8
Total	102	100

Graph 13: Grading of Diabetic Retinopathy by Slit Lamp Ophthalmoscopy



On slit lamp biomicroscopy 102 eyes with diabetic retinopathy were graded as 9.8% mild NPDR, 39.2% moderate NPDR, 15.7% severe NPDR, 9.8% very severe NPDR, 13.7% early PDR, 11.8% high risk PDR.

Table 11B:Detection of Diabetic Maculopathy by Slit Lamp Ophthalmoscopy

	Number	**Percentage**
CSME present	29	28.43
CSME absent	73	71.67
Total	102	100

Graph 14: Detection of CSME by Slit Lamp Ophthalmoscopy

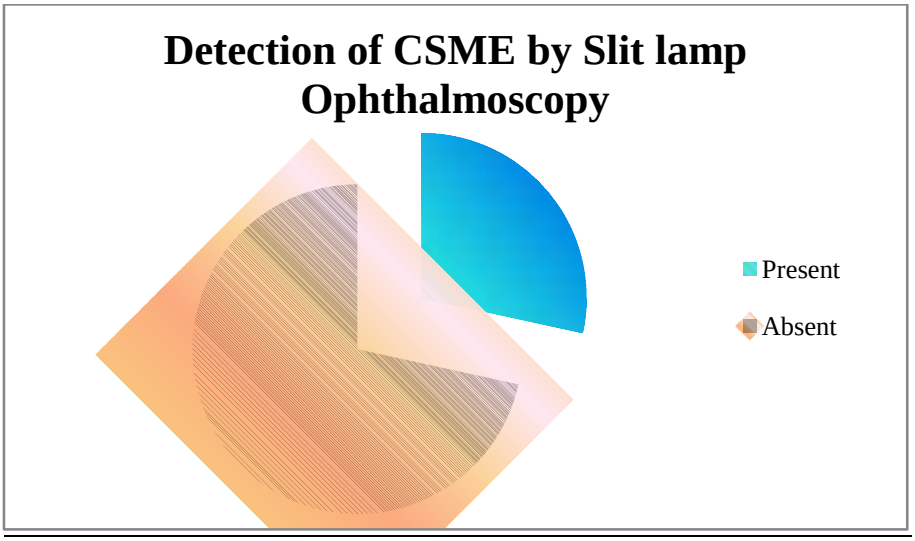
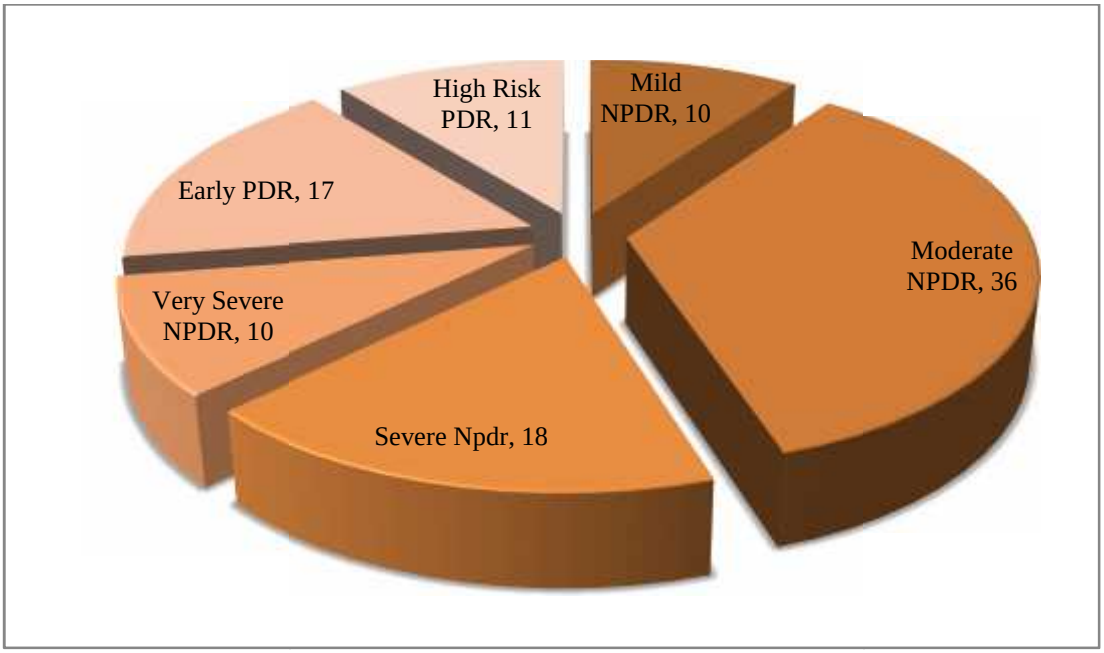


Table 12A: Grading of Diabetic Retinopathy by Fundus Flourescein Angiography

	Number of eyes	Percent (%)
Mild NPDR	10	9.8
Moderate NPDR	36	35.3
Severe NPDR	18	17.6
Very Severe NPDR	10	9.7
Early PDR	17	16.7
High Risk PDR	11	10.8
Total	102	100.0

Graph 15: Grading of Diabetic Retinopathy by Fundus Flourescein Angiography



On fundus flourescein angiograohy 102 eyes with diabetic retinopathy were found to include a9.8% mild NPDR, 39.2% moderate NPDR, 15.7% severe NPDR, 9.8% very severe NPDR, 13.7% early PDR, 11.8% high risk PDR.

Table 12B: Detection of Diabetic Maculopathy by by Fundus Flourescein Angiography

	Number	Percentage
CSME present	29	28.43
CSME absent	73	71.67
Total	102	100

Graph 16: Detection of CSME by Fundus Flourescein Angiography

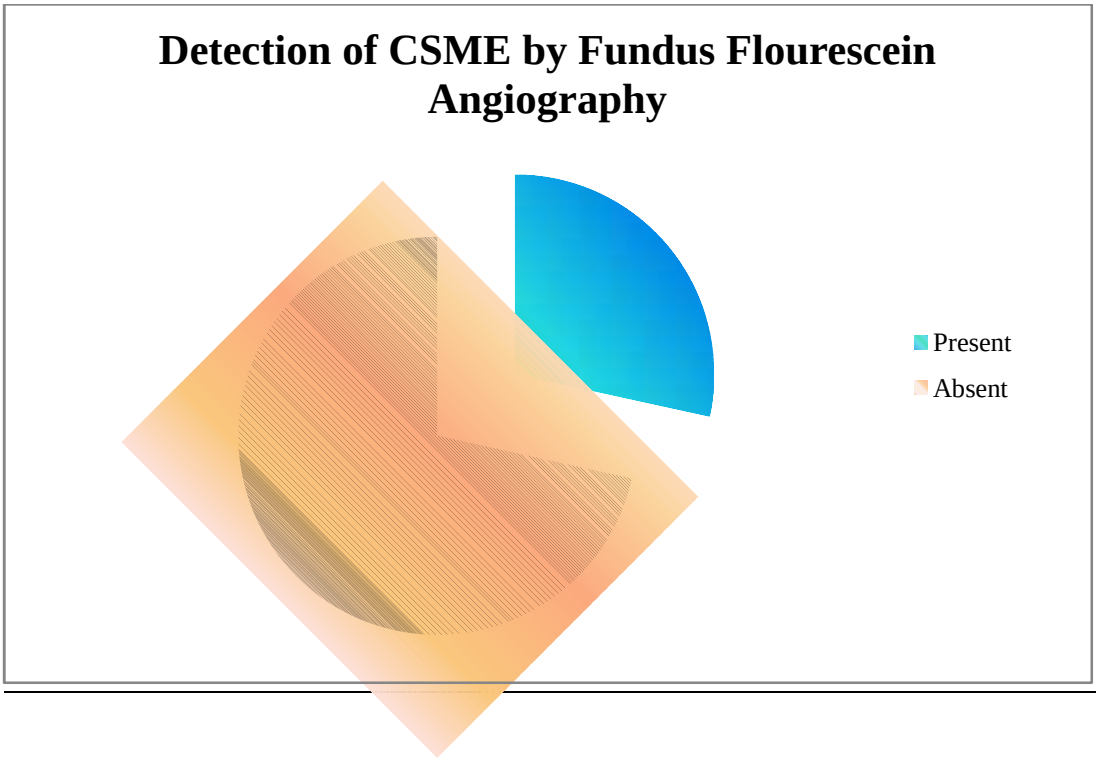


Table 13A: Correlation Between Slit Lamp Ophthalmoscopy And Fundus Flourescein Angiography for Grading of Diabetic Retinopathy

Slit Lamp Ophthalmoscopy * Fundus Flourescein Angiography Crosstabulation

		Fundus Flourescein Angiography						Total
		Mild NPDR	Mod NPDR	Severe NPDR	Very Severe NPDR	Early PDR	High Risk PDR	
Slit Lamp Ophathmoscopy	Mild NPDR	10	0	0	0	0	0	10
	%	100%						
	Moderate NPDR	0	35	5	0	0	0	40
	%		97.2%	27.8%				
	Severe NPDR	0	0	13	0	3	0	16
	%			72.2%		17.6%		

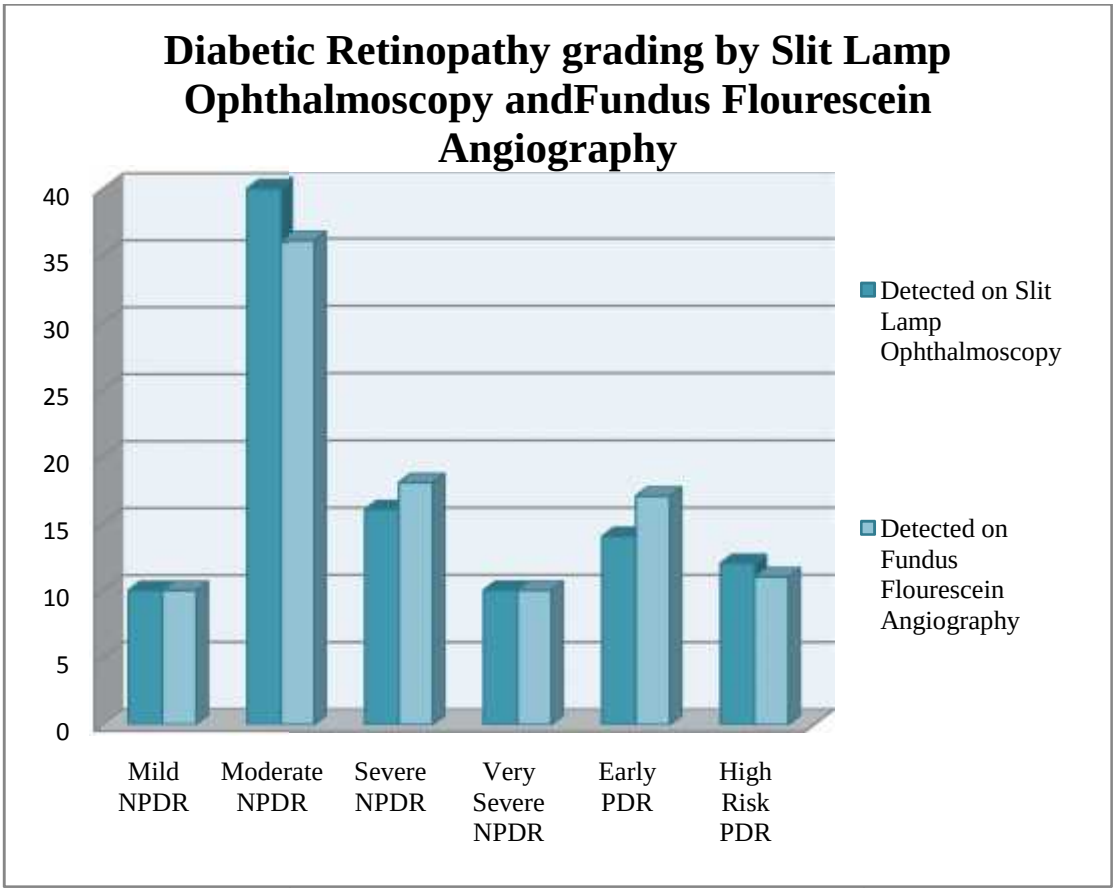
	V.Severe NPDR	0	0	0	8	2	0	10
	%				80%	11.7%		
	Early PDR	0	0	0	2	12	0	14
	%					70.6%		
	High Risk PDR	0	1	0	0	0	11	12
	%		2.8%				100%	
Total		10	36	18	10	17	11	102

p= 0.000 (HS)

chi^2 of 383.731 (df= 25 and p<0.001). Kappa statisitcs = 0.836 with p<0.001 which states that there is excellentcorrelation between Slit Lamp Biomicroscopy and Fundus Flourescein Angiography.

Slit lamp ophthalmoscopy agree dwith FFA grading in 88 (86.2%) cases. 10 cases were underdiagnosed and 4 cases were overdiagnosed by slit lamp ophthalmoscopy.

Graph 17: Comparison of Diabetic Retinopathy grading by Slit Lamp Biomicroscopy and FFA



13B: Comparison of Diabetic Retinopathy grading by Slit Lamp Biomicroscopy and FFA

Slit lamp Ophthalmoscopy	FFA	
	Correctly Graded	Incorrectly Graded
Correctly Graded	88	04
Incorrectly Graded	10	--

Sensitivity: True Positive/ (True Positive + False Negative)
= 88/ (88+10) = 89.7 %

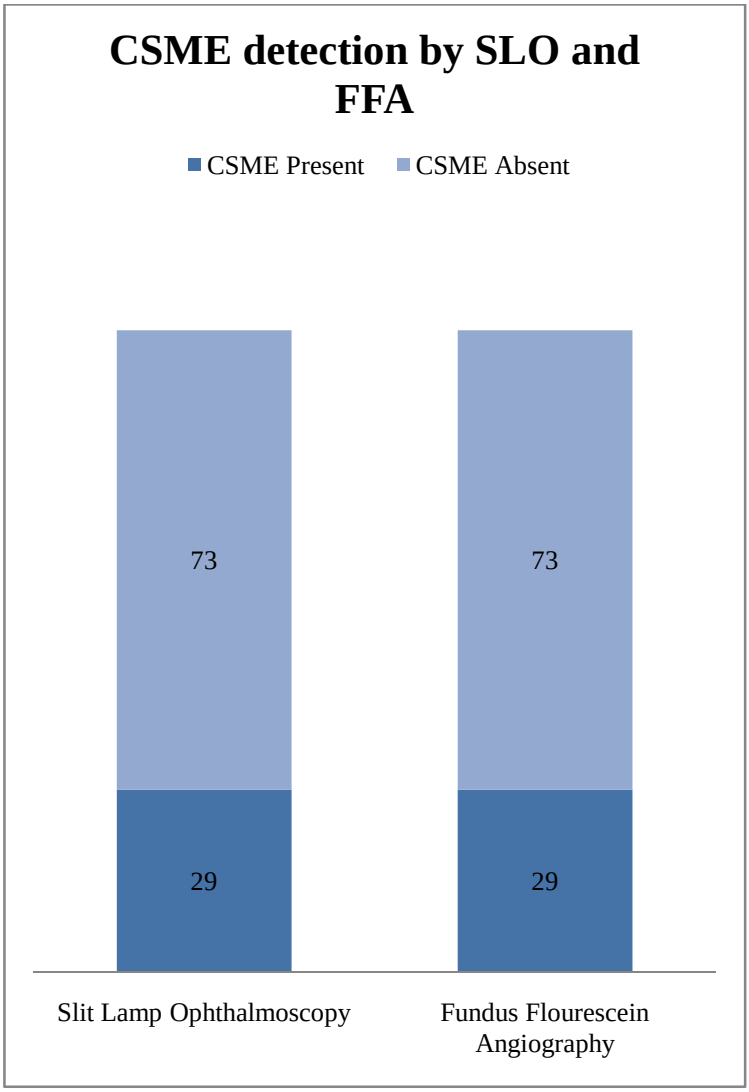
Positive Predictive Value: True Postive/ (True Positive+ False Positive)
= 88/ (88+4) = 95.6%

Specificity and Negative Predictive Value could not be calculated as there were no true negatives in this study. FFA, being an invasive procedure was not performed on patients who did not have DR on ophthalmoscopy; hence such patients were not included in the study.

Table 13 C: Correlation Between Slit Lamp Ophthalmoscopy and Fundus Flourescein Angiography For Detection Of CSME

Slit lamp Ophthalmoscopy	FFA	
	CSME Present	CSME Absent
CSME Present	29	0
CSME Absent	0	73

Graph 18: Comparison of CSME detection by Slit lamp ophthalmoscopy and flourescein angiography



Sensitivity: True Positive/ (True Positive + False Negative)
= 29/ (29+0) = 100%

Specifictiy: True Negative/ (True Negative+ False Positive)
= 73/ (73+0) = 100%

DISCUSSION

The present study was conducted as a descriptive observational study to determine the correlation of clinical and angiographical grading of diabetic retinopathy.DR was graded clinically using a Volk Superfield Non Contact lens with slit lamp biomicroscopy and angiographical grading was done by fundus flourescein angiography.

The 52 patients included in this study were known diabetics who either exhibited lesions of diabetic retinopathy on direct or indirect retinopathy during routine examination.Five of these patients were cases of T_1DM, while the rest, i.e. Forty-seven patients were cases of T_2DM**.**

Both eyes of 50 patients were included in the study while only one eye each of 2 patients was included. These two patient's other eye was excluded due to severe media haze from lenticular opacity and a history of laser photocoagulation respectively. Hence, a total of one hundred and two eyes were included in this study.

Age Distribution:

The mean age of participants in this studywas 55.88± 12.27years. In a metanalysis of 28 studies that included 27,120 diabetic patients assessed for diabetic retinopathy at the 4-, 5-, and 10-year time points, the mean patient age was 49 years.[142]This difference in mean age of participants between the two studies may be attributed to a higher maximum diabetic age in our study.

Gender Distribution:

There were 29 males and 23 females in our study group, with a male female ratio of 1.3:1. Similar results of DR prevalence being more in males were depicted

inWESDR study.[64] Contrary to this, Bajpai*et al* revealed higher femalepreponderance, the analysis showed that there was no significant variation in the

stages of retinopathy based on sex of the patient.[143]

Severity of Retinopathy:

The present study included 102 eyes which constituted 9.8% mild NPDR, 35.3%moderate NPDR, 17.6 %severe NPDR, 9.8% very severe NPDR, 16.7% early PDR and 10.8% high risk PDR. Out of 102 eyes studied, moderate NPDR was the highestand PDR accounted for 25% of the cases. In the Andhra Pradesh Eye Disease Study (APDES)Krishnaiah*et al*[144]reported 51.3% mild NPDR35.9% moderate NPDR and 2.6% PDR .The Chennai Urban Rural Epidemiology Study (CURES) Eye Study revealed the prevalence of DR was 34.1%. The prevalence included 30.8% with NPDR, 3.4% with PDR.[145]A hospital based Epidemiological study for DR in China reported an incidence of 39.71% mild NPDR, 20.29% moderate NPDR, 18.86% severe NPDR, 21.14% proliferative diabetic retinopathy. [146]The differences in the findings of each off these studies to ours could be attributed to variable population characteristics as age of onset, diabetic duration, treatment and its adherence.

The prevalence of diabetic macular oedema has been reported to vary between 3-28% in patients with type 2 diabetes (Rema el al. 2005, Varma*et al*. 2014, Ding *et al*. 2012, Yau*et al*. 2012, Klein *et al* 1984)WESDR .[145,146-149,91]The prevalence of macular edema was 28.4 % in our study. .

None of the type 1 diabetics in our study had macular edema. In the WisconsinEpidemiologicStudy of Diabetic Retinopathy (WESDR), the 10-year rate of developing DME was 20.1% in patients with type 1 diabetes and, in patients with type

2 diabetes, it was 25.4% for those treated with insulin, and 13.9% for those not treated with insulin.[91]

Age of Onset of Diabetes

In our study the mean age of onset of diabetes was 16.8± 6.8 years for Type 1 diabetics. Of the 5 patients belonging to this category, the age of onset for 1 patient was 6 years who had non proliferative diabetic retinopathy, the rest of the cases had either PDR (13.5%) or very severe NPDR (7.7%), this correlates with the findings of the WESDR, wherein Klein *et al*stated that children with the onset of DM before the age of ten do not usually have DRP and definitely nottreatment needing lesions. [64]

The average age of onset for Type 2 diabetics was 48.6± 10.2 years. Maximum number of patients i.e. 34.6% were diagnosed at the age ranging between 46 to 55 years, this correlates with the findings of an earlier Indian in study had shown the mean age at diagnosis or onset to be 46.5± 10.25 years (Ramachandran*et al.* 1988.[150]

According to previous studies there exists an increased inherent susceptibility to diabetic retinopathy with earlier-onset type 2 diabetes (Henricsson*et al*. 1996, Wong *et al.*2008)[80, 151]We were not able to establish a significant correlation between age of onset of diabetes and severity of diabetic retinopathy.This may be due to a recall bias by the patients since the earliest documents in our sub population are seldom available and patients recall history of their disease from from memory. Also, many diabetic patients go undetected for years and may often be first investigated for diabetes or hypertension after the onset of complications.

Duration of Diabetes:

Duration of diabetes is an important risk factor for the development of retinopathy. The average duration in our study was 10.37 ± 5.94 years, was much shorter than the 17.3 years reported by Lee *et al* (1993).[134]

The mean duration of T_1DM was 13.4 ± 1.8 years. According to Sultan *et al* who studied risk factors for paediatric diabetic retinopathy, The earliest signs of background DR rarely occur before the fifth year of disease with the prevalence reaching 50% by year 10. [152]

In our study of T_2DM participants, 27 eyes (26.5%) with DR had a diabetic age less than5 years.This was in agreement with UKPDS findings in which 13% to 39% of patients with Type 2 DM had some DRP at baseline ophthalmologic examination (two to five years from diagnosis of DM),they further stated these patients are at risk to develop STDR in the follow-up period of ten years.[83]

It can be gathered from our study that 60% of mild NPDR were seen upto 10 years of diabetic duration, almost 86% moderate NPDR were less than 20 years of diabetic duration, 56% severe and very severe NPDR were seen in over 15 years duration and almost 72% PDR were seen in diabetic duration of more than 10 years. It is evident from these findings that there was worsening of the retinopathy with the increasing duration of diabetes in these individuals.In India, virtually all studies have shown an increased prevalence of DR as the duration ofdiabetes increased (Dandona*et al*. 1999, Rema*et al*.2000, 2005)[153,154,145]

In the study conducted byDandona*et al*[153] in type 2 diabetes, it is reported that87.5 per cent of those with >15 yr duration of diabeteshad DR compared with 18.9 per cent of those whohad <15 yr duration. In the CURES Eye study[145],41.8 per cent had DR after 15 yr of diabetes andseverity of DR proportionally increased with longerduration of diabetes. In addition, it has beendemonstrated that for every five year increase induration of diabetes, the risk for DR increased by1.89 times.

WESDR study revealed that the prevalence of diabetic retinopathy varied from 17%to

97.5% in persons with diabetes for less than five years and 15 or more years respectively. Proliferative retinopathy varied from 1.2% to 67% in persons withdiabetes for less than ten years and 35 or more years, respectively concluding a directcorrelation between the frequency and severity of DR and the duration of DM.[64]

Association of Diabetes Treatment and Severity of Diabetic Retinopathy: In our study, 3.8% participants were not on any treatment, 65.8% were on oral hyperglycaemic agents only, 18% were on insulin alone and 13% were taking both insulin and OHA. There was a clinically significant correlation between insulin use and increased severity of retinopathy. Almost 50% on patients with PDR were either being treated with insulin or insulin and OHA combination.The SR- DREAMS II studyfound insulin us to be a risk factor for diabetic retinopathy.[156]A recent study found that in type 2 diabetic patients treated with insulin there a reduction in HbA_{1c} values but an increase in IGF-1 (insulin like growth factor),they found a positive relationship between progression of retinopathy and a higher IGF-1 value at 3 years of insulin useHenricsson*et al.* 2002.)[155]

Association with hypertension

Twenty-nine (56%) patients in our study had concomitant hypertension along with diabetes. Hypertension has been known to accentuate diabetic retinopathy. Inour study, of the 28 eyes afflicted with PDR only 10 eyes (35.7%) belonged to normotensive patients, the rest 18 eyes (64.3%) afflicted with PDR belonged to hypertensive patients suggesting a 2 fold higher chance of patients with high blood pressure to develop proliferative diabetic retinopathy. There was statistically significant correlation between hypertension and severity of retinopathy in our study.

According to the SankaraNethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study III patients with systolic blood pressure of >140 mm Hg (19.8% vs 8.6%; p<0.0001), and diastolic blood pressure of >90 mm Hg (15.5% vs 8.8%; p=0.002) had a higher risk of developing diabetic retinopathy.[156]

The UKPDS has proved that patients on intensive therapy for blood pressure control had a reduction in progression of DR.[157] Contrary to this, theAppropriateBlood Pressure Control in Diabetes (ABCD) trial did not find any significant difference in progression of DR in the moderate and intensive blood pressure control groups.[158]

Relation to Glycosylated Haemoglobin (HbA_{1c}):

HbA_{1c} levels have been found to be closely associated with the prevalence and incidence of diabetic retinopathy. This test is a method for estimating the degree of hyperglycaemia over the preceding 2 to 3 months. The mean value of glycosylated haemoglobin in our study was was 8.73± 1.50. The UKPDS revealed a mean HbA1c of 8.6%, the values ranging from 5.3% to 15.6%.[14]These findings are close to the findings of our study. Moreover, in our study none of the patients with HbA_{1c} less than 8% had PDR whereas patients HbA_{1c} more than 10% only had moderate NPDR or above, none of them had mild NPDR. This strongly suggests that higher HbA_{1c} levels are associated with greater retinopathy (p value <0.001).

The protective effect of glycaemic control on the development and progression of DR has been investigated in both type 1 (WESDR and Diabetes Control and Complications Trial- DCCT) and type 2diabetic patients (UKPDS)[13,14]. In the 14 yr progression of retinopathy study (WESDR), the prevalence of retinopathy in type 1 diabetic subjects was 12 per cent when glycated haemoglobin (HbA1c) was <7 per cent as compared to 40.7 per cent when HbA1c levels were >10 per cent and an

increasedrisk of PDR was associated with more severe baseline retinopathy and higher HbA1c levels. The DCCT Research Group36 demonstrated that intensive therapy reduced the mean risk of retinopathy by 76 per cent

as compared with conventional therapy in the primary-prevention cohort. While in the secondaryintervention cohort, intensive therapy reduced the risk of eye complications by 54 per cent for the development of DR, decreased progression of NPDR to PDR or severe NPDR by 47 per cent and the need for laser therapy by 56 per cent. Rema*et al*[145]have also shown that the visual outcome of laser photocoagulation for eyes with PDR was also dependent on the degree of glycaemic control.

Blood Sugars and Diabetic Retinopathy

Fasting and post prandial blood sugars are known to predict occurrence and severity of diabetic retinopathy. We found a clinically significant correlation in higher fasting blood sugars and increased severity of diabetic retinopathy**.** In our study, as the mean FBS at each level of DR was higher than the previous one which shows that as the blood sugar control becomes poorer, retinopathy tends to progress. Several researchers however, are of the opinion that blood sugar levels at the time of diagnosis of diabetes are a greater indicator of how the progression of diabetic retinopathy years later maybe, and even patients with good diabetic control later in life may progress to severe diabetic retinopathy if initial blood sugars at the time of onset of diabetes were grossly deranged (Kowluru. 2010, Zang*et al.* 2012, Jayaraman. 2012). [159-161]

Correlation of Diabetic Retinopathy Grading by Slit Lamp Ophthalmoscopy and Fundus Flourescein Angiography.

Of the 102 eyes included in our study Slit lamp biomicroscopy detected non proliferative diabetic retinopathy in 77 eyes, and proliferative diabetic retinopathy in 25 eyes. Flourescein Angiography detected non proliferative diabetic retinopathy is 74 eyes and proliferative retinopathy in 28 eyes.

In our study Biomicroscopy agreed in 88 (86.4%) eyes and disagreed with angiography in 14 (13.7%) eyes. Of the latter 4 cases were overdiagnosed and 10 underdiagnosed in biomicroscopy.4 cases were graded as PDR in biomicroscopy, but angiography showed moderate to very severe NPDR in those cases. In 3 of these cases it was due intraretinal microvascular abnormalities being wrongly diagnosed as new vessels by biomicroscopy, in 1 case biomicroscopy diagnosed neovascularization of the disc which proved to be only disc collaterals on flourescein angiography. 10 cases were underdiagnosed on biomicroscopy, in these cases new vessels were wrongly diagnosed as intraretinal microvascular abnormalities on biomicroscopy and 5 cases of severe NPDR were graded as moderate NPDR on slit lamp biomicroscopy. There was no significant correlation between decreased visual acuity due to cataract and missing some diabetic retinopathy changes on ophthalmoscopy in comparison to flourescein angiography.

Our study had a kappa statistics of 0.836 with $p<0.001$ (significant) which states that there is almost perfect correlation between Slit Lamp Biomicroscopy and Fundus Flourescein Angiography. Here we considered Flourescein Angiography as the gold standard and sensitivity of slit lamp biomicroscopy for grading of diabetic retinopathy was 89.7% with a chi^2 of 383.731 (df= 25 and $p<0.001$). These findings were similar to those of Khalaf *et al*[137] who studied 376 eyes of 189 patients and had a kappa statistics of 0.870 with a sensitivity of 91.2% with a chi^2 of 543 (df= 4; $p=0.000$) .

These findings are also comparable with study done by Prasad *et al*.[8]They studied the effectiveness of optometrists as screeners for diabetic retinopathy using slit-lamp binocular indirect ophthalmoscopy through dilate pupils . The sensitivity for identification of sight threatening diabetic retinopathy was 76%. So slit-lamp biomicroscopy is highly sensitive for screening diabetic retinopathy grading in diabetic patients.

Our findings also correlate to the findings of a study between slit-lamp biomicroscopy and fluorescein angiography in diagnosing of diabetic retinopathy undertaken at a medical college in Raipur, Madhya Pradesh which concluded concludesthat slit-lamp biomicroscopy is highly sensitive with a sensitivity of 89.14% for screening diabetic retinopathy and grading in diabetic patients and a degree of agreement kappa was 0.832 when compared to FFA.[162]

In our study, all 29 cases of CSME by flourescein angiography were detected on slit lamp ophthalmoscopy, slit lamp ophthalmoscopy was found to have to have 100% sensitivity in detection of clinically significant macular edema, In a study for detection of diabetic foveal edema with biomicroscopy, fluorescein angiography and optical coherence tomography. Hannouche*et al*found Excellent correlation was observed between OCT and slit-lamp Biomicroscopy and s a significant correlation between OCT and fluorescein angiography features in diabetic macular edema.[163]

CONCLUSION

"Diabetic retinopathy is, by and large a treatable condition so that blindness can be prevented by treatment. Indeed, of all the complications of diabetes, diabetic retinopathy is the most amenable to therapy."- R.K. Blach, 1985

The above statement illustrates that even though blindness is the most feared complication of diabetic retinopathy, it is largely preventableif treated on time. It is for this reason, that screening for diabetic retinopathy is extremely important.

The findings of our study demonstrate that slit lamp ophthalmoscopy by an ophthalmologist, experienced in retinal examination, can compare favourably with fundus flourescein angiography in grading of diabetic retinopathy.

Fundus Flourescein Angiography is expensive, time consuming and not readily available. In developing countries like India very small numbers of eye centres are well equipped with flourescein angiography. It is also an invasive procedure. Although the adverse reactions are seen in only a minority of patients, but there is risk of hypersensitivity reaction.

Our results also suggest that diabetic age, hypertension and high HbA_{1c} are clinically and statistically significant risk factors for diabetic retinopathy.

We recommend that diabetic patients with a diabetic age of over 10 years, and diabetics with concomitant hypertension should be more rigorous in controlling their blood sugars. Patients with higher diabetic age, hypertensives and those with poor glycaemic control should be screened more regularly.

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SUMMARY

Diabetes mellitus is a public health problem which has reached epidemicproportions. Diabetic retinopathy remains a serious vision threatening complication of diabetes mellitus.

The study titled "A Clinico-Angiographical Correlation in Grading of Diabetic Retinopathy- A one year hospital based cross sectional study" was conducted in KLES Hospital and MRC, Belagavi in J.N. Medical College during the period of 01st January 2014 to 31st December 2014.

The summary of the results obtained is as follows:

- The mean age of participants in this study was 55.88± 12.27 years.
- There was a male preponderance, male:female ratio being 1.3:1
- The mean age at diagnosis for Type 1 diabetes was 16.8 ± 6.8 years, and for Type 2 diabetes it 48.6± 10.2 years. Age of onset of diabetes was not significantly associated with severity of diabetic retinopathy
- The mean diabetic age of participants was 10.37 ± 5.94 years. Severity of diabetic retinopathy had a strong correlation with duration of diabetes, with a higher diabetic age severity of diabetic retinopathy was found to be more.
- The study group consisted of 52 diabetic patients consisting of 9.8% mild NPDR, 35.3% moderate NPDR, 17.6% severe NPDR, 9.8% very severe NPDR, 16.7% early PDR and 10.8% high risk PDR. 28.5% of the patients also had CSME.
- Patients on insulin treatment were found to have more severe diabetic retinopathy
- Diabetic patients with concomitant hypertension had a clinically significant correlation with increasing severity of diabetic retinopathy

- The study revealed strong association between HbA_{1c} and severity of retinopathy. Better glycaemic control was associated with less severe retinopathy and worsening of glycaemic control (HbA_{1c}) was associated with worsening of diabetic retinopathy.
- Patients with more severe diabetic retinopathy had higher mean fasting blood sugars.
- Slit lamp ophthalmoscopy had excellent agreement (k=0.836) with flourescein angiography in grading of diabetic retinopathy and hence can be reliably used for screening of diabetic retinopathy.
- The sensitivity of slit lamp ophthalmoscopy in accurate grading of diabetic retinopathy was 89.7%
- Slit lamp ophthalmoscopy had a 100% sensitivity and 100% specificity in detection of clinically significant macular hence CSME detected by slit lamp ophthalmoscopy need not be confirmed by flourescein angiography.

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ANNEXURE I - INFORMED CONSENT

CONSENT FOR PARTICIPATING IN A RESEARCH STUDY

J.N. Medical College

K.L.E. University

Belagavi- 590010

Mr/ Mrs/ Ms _____

You are invited to participate in our research study titled "**A Clinico-Angiographical Correlation in Grading of Diabetic Retinopathy- A one year hospital based cross sectionalstudy**." Conducted by**Dr.** _____ Postgraduate student in the department of Ophthalmology, J.N. Medical College, Belgaum under the guidance of **Dr.** _____ Professor& Head in the Department of Ophthalmology, J.N. Medical College, Belgaum

Respected Sir/Madam we request you to enrol yourself to participate in our study as you are eligible to participate in the study. Your participation in research is voluntary. If you decide to participate, you are free to withdraw anytime.

Need for the Study: Diabetic mellitus is the systemic disease that most often leads to blindness. There is a latent period before the development of symptomatic disease and outcomes may be substantially improved if latent disease is detected. This study needs to be undertaken to establish an accurate, time effective and cost effective method for early detection of diabetic retinopathy changes in the visually asymptomatic diabetic patients so measures may be taken in time to save their vision.

Purpose of the Study: The purpose of this study is to compare the non invasive method of ocular fundus examination using slit lamp biomicroscopy with the invasive technique of fundus fluorescein angiography in grading of diabetic retinopathy and to establish a co-relation between the findings of the two methods.

Procedure of the Study: If you agree to enrol in the study, you will be asked about your present, past and family history. You will be clinically examined and data of relevant investigations (blood sugar, glycosylated haemoglobin, serum creatinine and blood urea) will be accessed. Then you will be subjected to indirect ophthalmoscopy, slit lamp biomicrsocopy, fundus photography, and fundus flourescein angiography. The hence obtained data will be monitored and documented.

Risks and Benefits: Of the above mentioned procedures, fundus fluorescein angiography carries the risk of anaphylaxis, it may also cause transient nausea, vomiting, urticaria or it may cause syncope. In case of any such adverse adequate medical care will be provided immediately. The other mentioned procedures carry no risk of any adverse reactions.

Your participation may benefit you and others suffering from the same ailment in the future by helping us achieve the purpose of this study. Also, the findings of this study will help us determine the best course of management for prevention of potential future visual loss for you.

Alternatives: If you are not willing to participate, you will be treated according to the existing protocol and it will not affect your relationship with this hospital.

Costs for participating in this research: The participant will have to pay for the investigations which are the part of the existing management protocol for this ailment.

Privacy and Confidentiality: No information about you or information provided by you during the research will be disclosed to others without your written permission

Authorization to publish results: when the results if the research are publishes or discussed, in a conference, no information would be divulged that would disclose your identity.

Compensation:

In the event of any injury related to the study, treatment will be made available through KLES Prabhakar Kore Hospital and MRC, Belgaum. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide adequate facilities and medical attention to you.

Questions:

If you have any questions about the research you may please contact

1) **Dr.** _____ - Chief Investigator P.G., Department of Ophthalmology, JNMC, Belgaum. Contact number: _____

2) **Dr.** _____ GuideProfessor& Head, Department of Ophthalmology, JNMC, Belgaum, Contact number: _____

3) **Dr.** Chairperson of Institutional Ethics Committee, Contact number: _____

4) **Dr.** _____ - Principal J.N. Medical college, Belgaum, Contact number: _____

Statement for Participation in Research Trial

I, Mr./Mrs./Ms. _____ voluntarily agree for the participation as a subject of this study. By signing this consent form I am not giving any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me, in my own vernacular language, including the risks and benefits and after having all my questions answered.

Subject's name: _____

Signature or the Left thumb Print of the Subject: _____

Witness' name: _____

Signature of the witness: _____

Investigator's Name: _____

Investigator's Signature: _____

Date:

Place: Belagavi

Name of guide:**Dr.** _____

Signature of guide:

ANNEXURE II – PROFORMA

KLE UNIVERSITY'S
J.N. MEDICAL COLLEGE, BELAGAVI
Department of Ophthalmology

TITLE OF THE STUDY: **A Clinico-Angiographical Correlation in Grading of Diabetic Retinopathy- A one year hospital based cross sectional study**

Data collection Instrument

I.D. No.

Name

Age
(in years)

Sex 1) Male 2)Female

Address

O.P. No.

I.P. No.

Diagnosis: ________________

1) Type I Diabetes Mellitus

2) Type II Diabetes Mellitus

3) Maturity Onset Diabetes of the Young

Informed Consent:
1) Taken 2)Not taken

Chief Complaints:
1= YES 2=NO

RELE

1) Diminution of Vision ☐ ☐

2) Pain ☐ ☐

3) Flashes ☐ ☐

4) Floaters ☐ ☐

5) Metamorphopsia ☐ ☐

6) Polyuria ☐

7) Polydypsia ☐

8) Polyphagia ☐

9) Any Other Complaints

If Yes: _____

PAST HISTORY:

1- Yes 2- No

10) Duration of Diabetes Mellitus _____

11) History of Hypertension ☐ If Yes, duration _____

12) History of Wearing Glasses ☐ If Yes, duration _____

13) History of any Ocular surgery ☐ If Yes, specify _____

14) Any Other ☐ If Yes, specify _____

15) **FAMILY HISTORY**:

1- Significant 2- Not Significant ☐

16)**Life Style**:

1- Yes 2- No

Active ☐

Sedentary ☐

Personal History:

1- Yes 2-No

17) Alcohol ☐ If Yes, duration _____

18) Smoking ☐ If Yes, duration _____

19) Diet: Veg/Mixed ☐ (1- Veg 2-Mixed)

Diabetic History:

20) Age of Onset of Diabetes _____ years

21) Duration of Diabetes _____ years

22) Any significant events _____

Treatment History:
1- Yes 2-No

23) Oral Hypoglycaemic Pill: Single ☐ If Yes, duration _____

Multiple ☐ If Yes, duration _____

Group of drug used: a. 1st generation sulfonylureas

b. Biguanides.

c. Miglitinideanologues.

d. Thiazolidinediones.

e. Glucosidase inhibitor.

f. Others, Specify: _____

24) Insulin Injections: ☐ If Yes, duration _____

25) Laser: RE ☐ If Yes, duration _____

LE ☐ If Yes, duration _____

General Physical Examination:

26) Pulse Rate/min ☐☐

27) Blood Pressure (in mm Hg)

Systolic ☐☐☐

Diastolic ☐☐☐

28) Temperature (in deg F) ☐☐☐

Systemic Examination:
1- Normal 2-Abnormal

29) CVS: ☐ If abnormal _____

30) R/S: ☐ If abnormal _____

31) P/A: ☐ If abnormal _____

32) CNS: ☐ If abnormal _____

33) Renal: ☐ If abnormal _____

34) Skin: ☐ If abnormal _____

35) Foot: ☐ If abnormal _____

Ocular Examination:

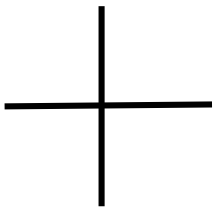
36) Head Posture: ☐ 1- Erect 2- Tilted

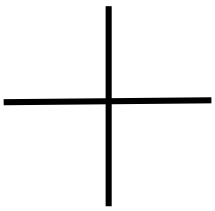
37) Facial Symmetry: ☐ 1- Symmetrical 2- Deviated

38) Visual Axis: ☐ 1- Parallel 2-Deviated

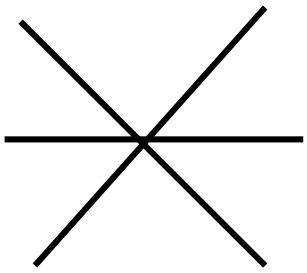
39) Extraocular Movements: ☐ 1- Normal 2- Restricted

Uniocular: RE ☐ LE ☐





Binocular: ☐



RE LE

IOP

Ocular Examination:	**Right Eye**	**Left Eye**
40) **Visual Acuity** 1)6/6-6/12 2)6/18-6/36 3) <6/60 Unaided Vision: With Pinhole: With spectacles: 2) **Near Vision** 1) N6 2)N8- N12 3) N18- N36 4)<N36	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
41) **Adnexa** 1- Normal 2- Abnormal If 2, Specify _____	☐	☐
42) **Lids** 1- Normal 2- Abnormal If 2, Specify _____	☐	☐
43) **Conjunctiva** 1- Normal 2- Congested 3- Other If 3, Specify _____	☐	☐
44) **Cornea** 1- Clear 2- Hazy 3- Other If 3, Specify _____	☐	☐
45) **Anterior Chamber**: depth 1- Normal 2- Shallow 3- Deep	☐	☐
46) **Iris**: color and pattern 1- Normal 2-Atrophic Patches	☐	☐
47) **Pupil**: A) Size 1- Normal 2-Constricted 3- Dilated B) Reaction Direct Indirect 1- Present 2- Absent 3- Sluggish C) PupillaryMargin 1- Normal 2- Abnormal If 2, Specify _____ D) Accomodation 1- Present 2- Absent 48) Lens: 1- Clear 2- Cataractous 3- Pseudophakia 4- Aphakia	☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐

Investigations:

49) Rbs: _____ mg/dl

50) HbA_1C: _____ %

51) Serum Creatinine: _____ mg/dl

52) Blood Urea: _____ mg/gl

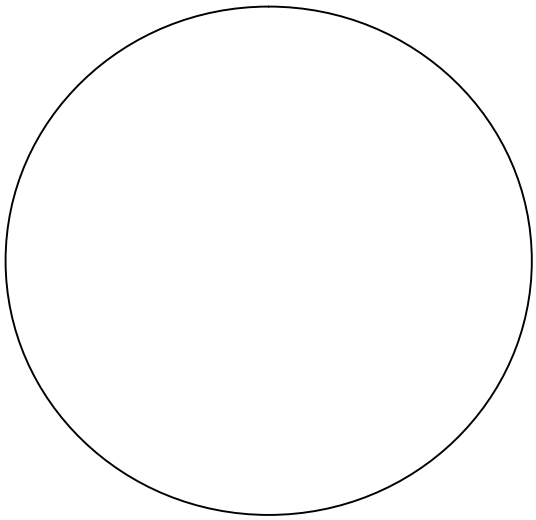
Fundus Examination:	Right Eye	Left Eye
53) Glow 1- Present 2- Faint 3- Absent	☐	☐
54) Media 1- Clear 2- Hazy If 2, a) Corneal b) Lenticular c) Vitreous	☐ ☐	☐ ☐
55) Disc 1- Normal 2- Pallor 3-Neovascularization in Diabetes (NVD) If 3, Specify NVD in disc area _____	☐	☐
56) Cup: Disc Ration 1- Normal (0.3) 2- Abnormal If 2, Specify _____	☐	☐
57) Venous abnormalities 1- None 2- Venous Beading 3- Venous Dilatation 4- Venous Looping 5- Venous Tortousity	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
58) Intraretinal Mirovascular Abnormalities (IRMAs) 1- Present 2- Absent If 2- specify quadrant a) superonasal quadrant b) superotemporal quadrant	☐ ☐ ☐	☐ ☐ ☐

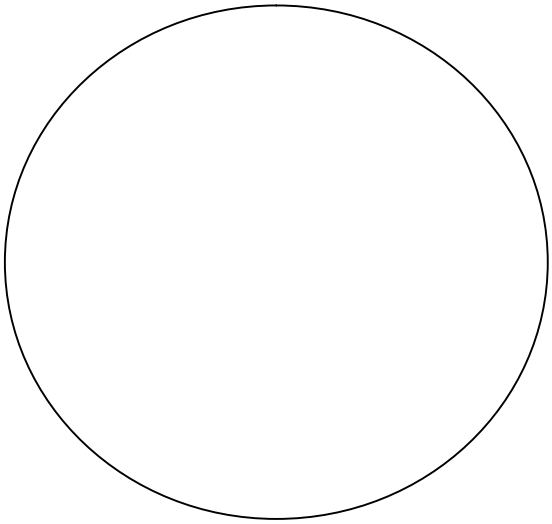
c) inferonasal quadrant d) inferotemporal quadrant	☐ ☐	☐ ☐
59) Background 1- Normal 2- Abnormal	☐	☐
A) Microaneurysms 1-Present 2-Absent If 1- specify quadrant a) superonasal quadrant b) superotemporal quadrant c) inferonasal quadrant d) inferotemporal quadrant	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐
B) Haemmorhages Types of Haemmorhage 1- Dot Blot Haemmorhages 2- Flame shaped Haemmorhage 3- Dark Blot Haemmorahage 4- Pre-retinal/ VitreousHaemmorhage	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐
60) Soft Exudates 1- Present 2- Absent	☐	☐
61) Hard Exudates 1- Present 2-Absent	☐	☐
62) New Vessels Elsewhere (NVE) 1- Present 2-Absent If 1, Specify NVE in disc area _____	☐	☐
63) Fibrovascular Proliferation 1- Present 2- Absent	☐	☐
64) Others _____	_____	_____
65) Macula 1- Normal 2- Abnormal If 2- A- Present B- Absent a. Microaneurysms b- Haemmorhage c-Hard Exudates d-thickening in 500µm or less from center of	☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐

macula e- Hard exudates in 500 µm or less from thecenter of macula. f- Thickening >/= 1 disc area, any portion of which is </= 1 disc diameter from center of macula Others, Specify _____	☐ ☐	☐ ☐

Fundus Drawings:

1. Slit lamp Biomicroscopy





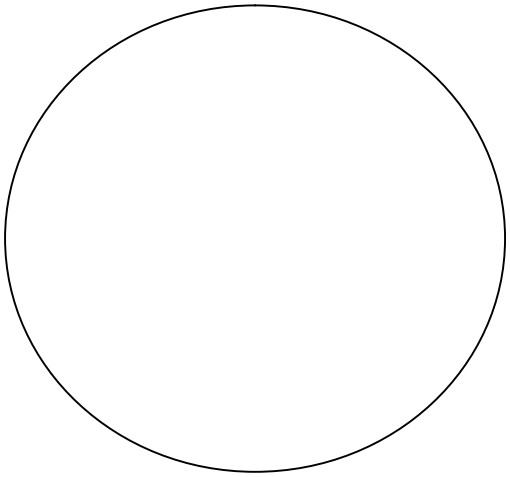
Diagnosis: **RIGHT EYE** **LEFT EYE**

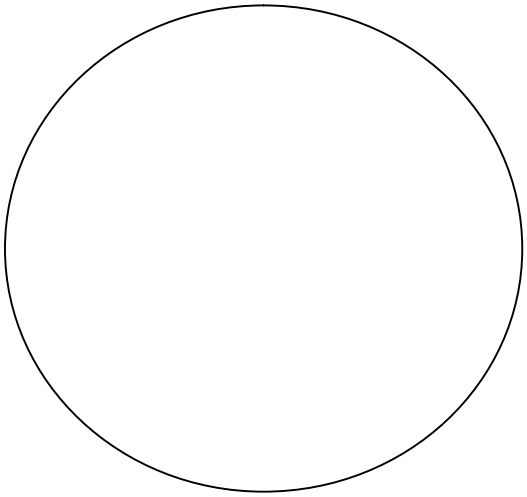
Background Diagnosis _____ Background Diagnosis _____

Macular Diagnosis _____ Macular Diagnosis _____

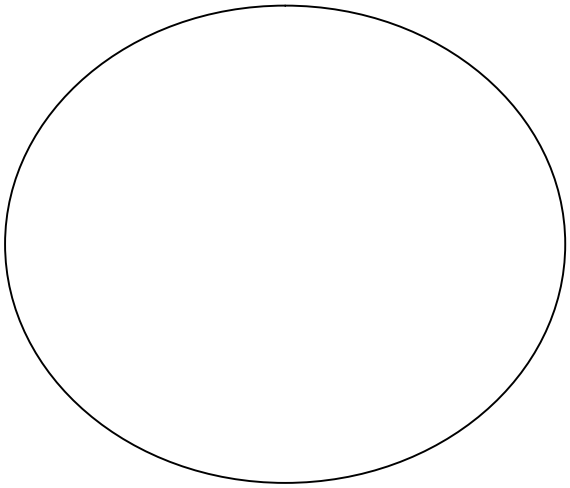
2. Fundus Flourescein Angiogrpahy

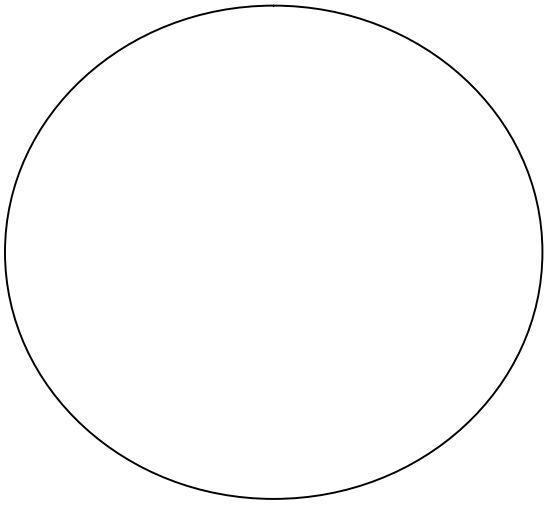
A) Pre-arterial Phase



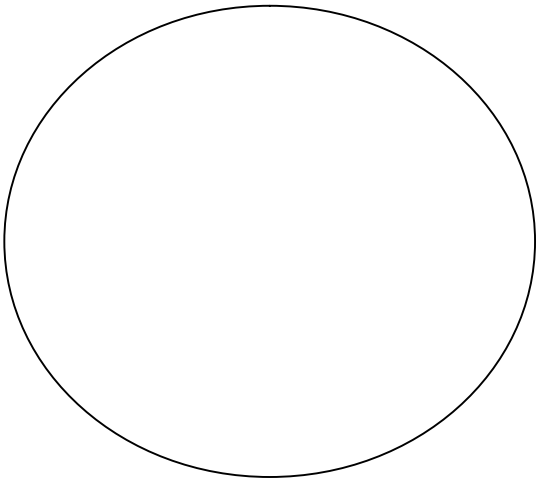


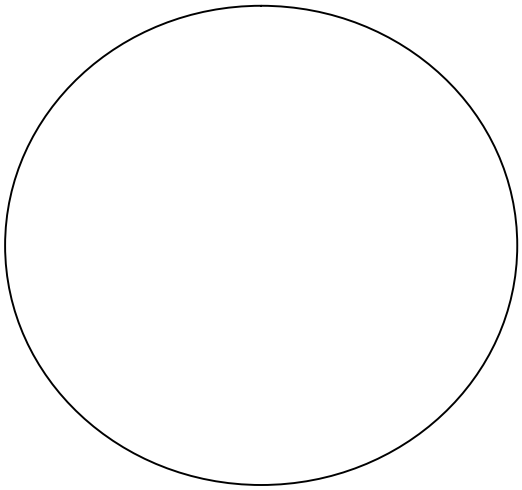
B) Arterial Phase



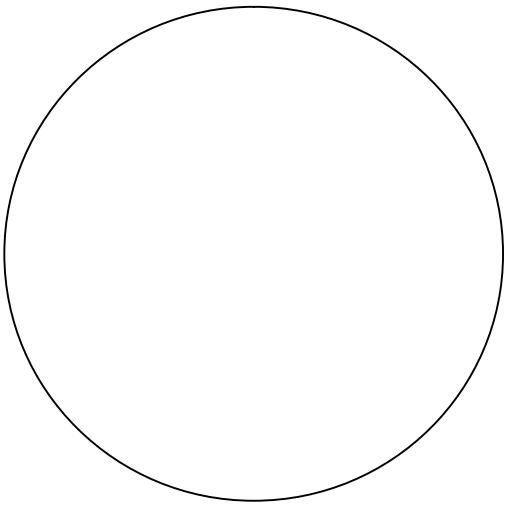


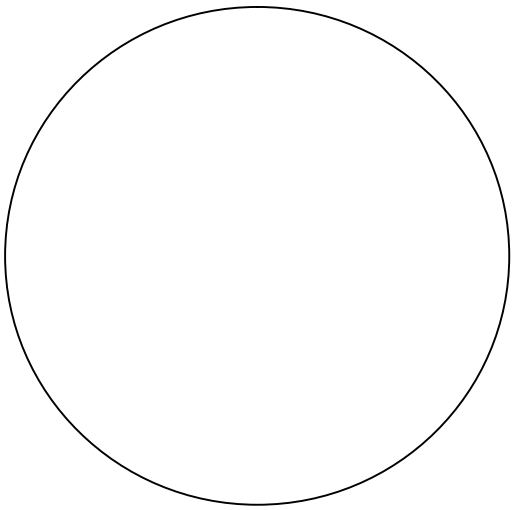
C) Arterio- Venous Phase





D) Venous Phase





Diagnosis: **RIGHT EYE** **LEFT EYE**

Background Diagnosis _____ Background Diagnosis _____

Macular Diagnosis _____ Macular Diagnosis _____

Photo1. Examination of fundus by slit lamp biomicroscopy using VolkSuperfield Non Contact lens

Photo 2.Volk SuperField NC lens

Photo 3. Fundus Photography Unit

Photo 4. Emergency Drug KIt

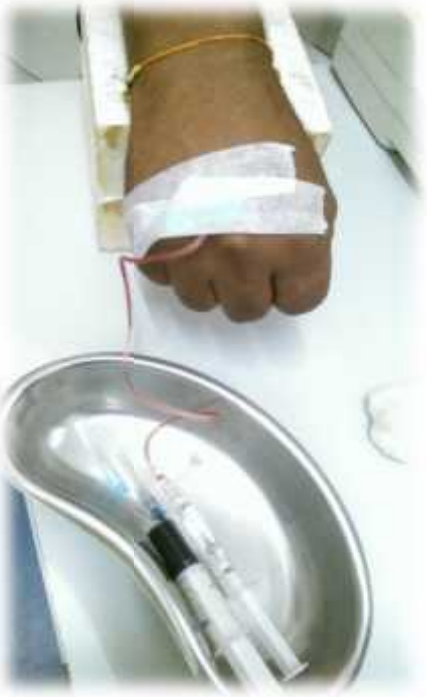


Photo 5.Scalp vein set in situ for flourescein injection.

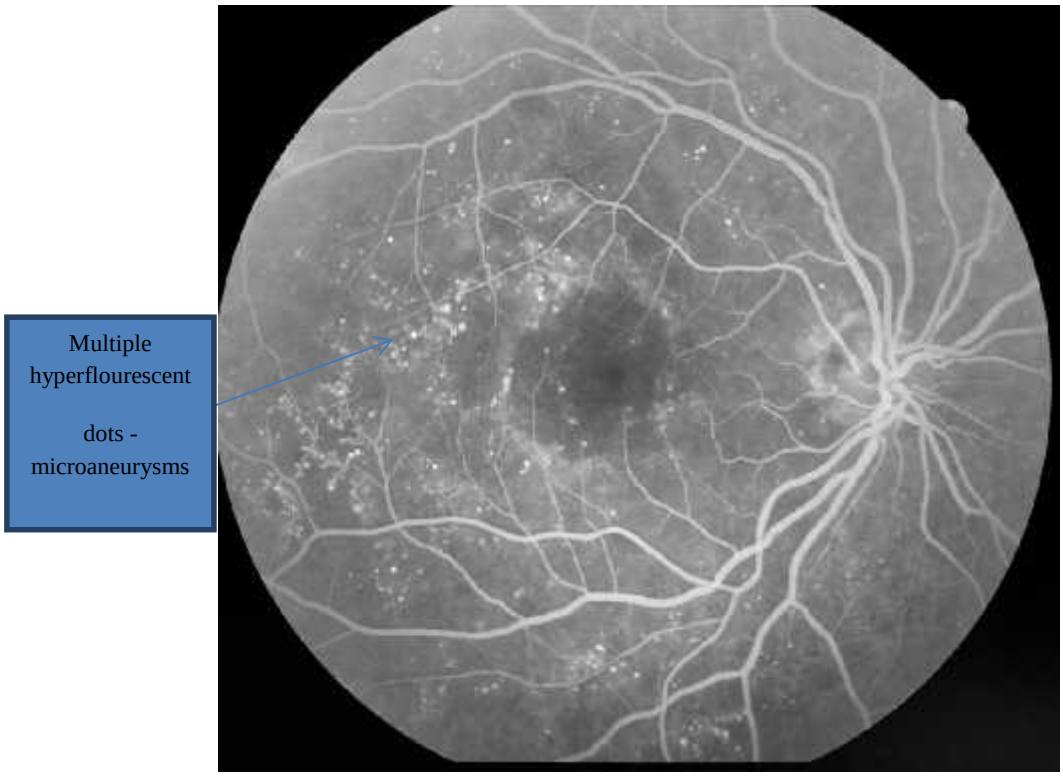


Photo 6. Fundus Flourescein Angiography picture 1

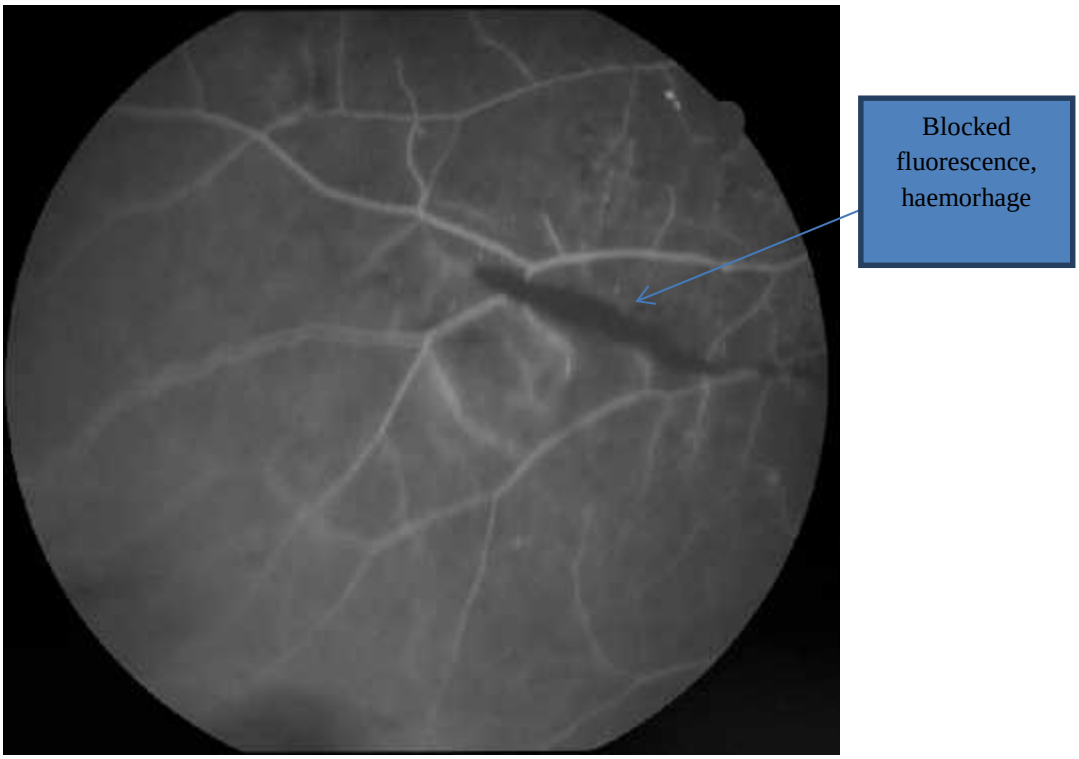


Photo 7. Fundus Flourescein Angiography picture 2

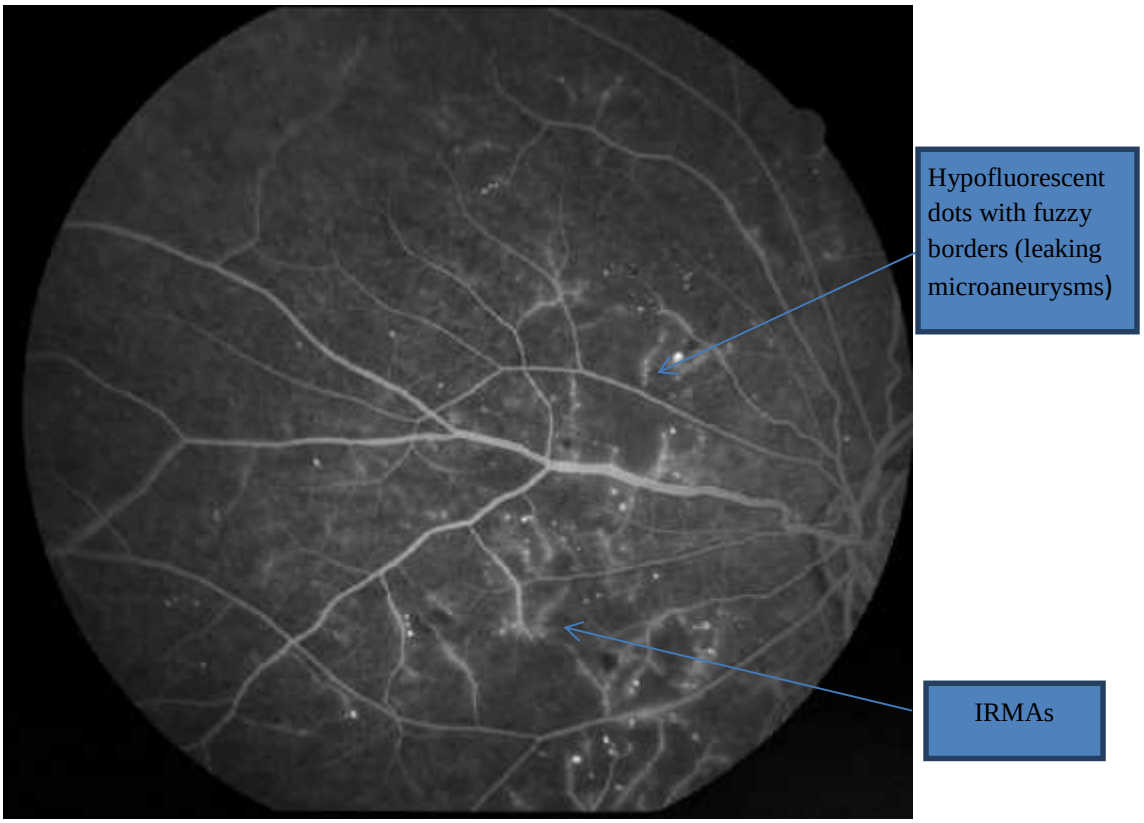


Photo 8. Fundus Flourescein Angiography picture 3

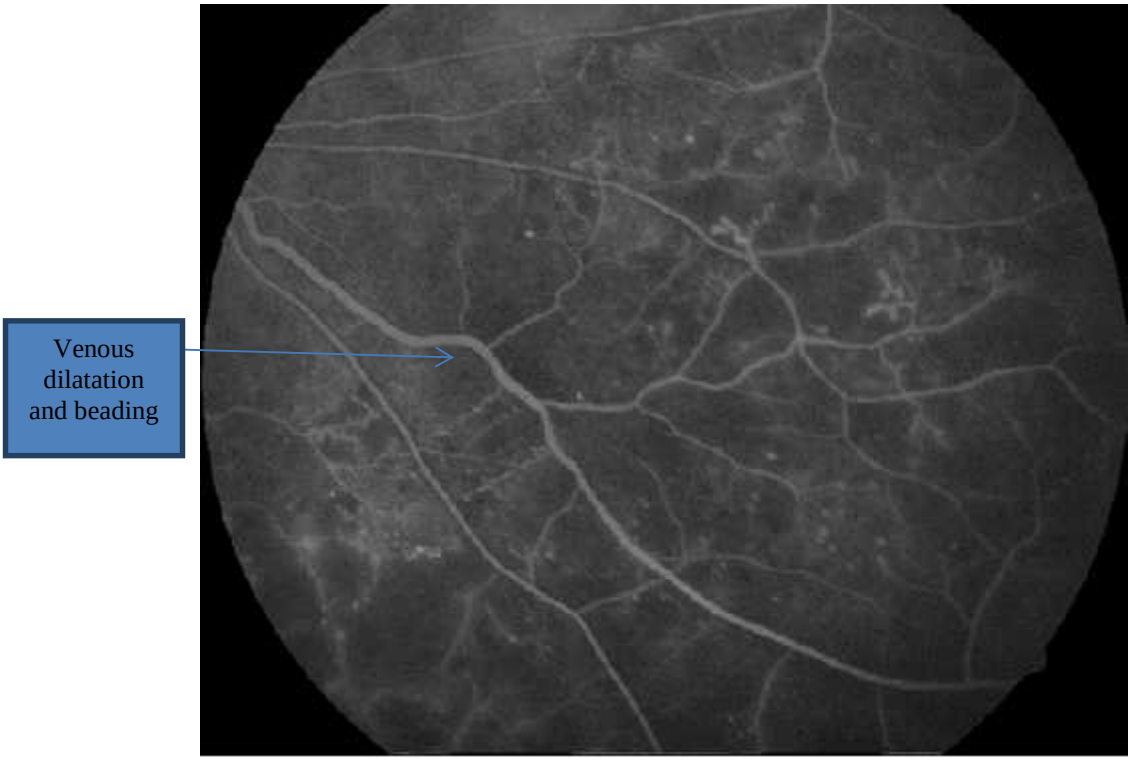


Photo 9. Fundus Flourescein Angiography- picture 4

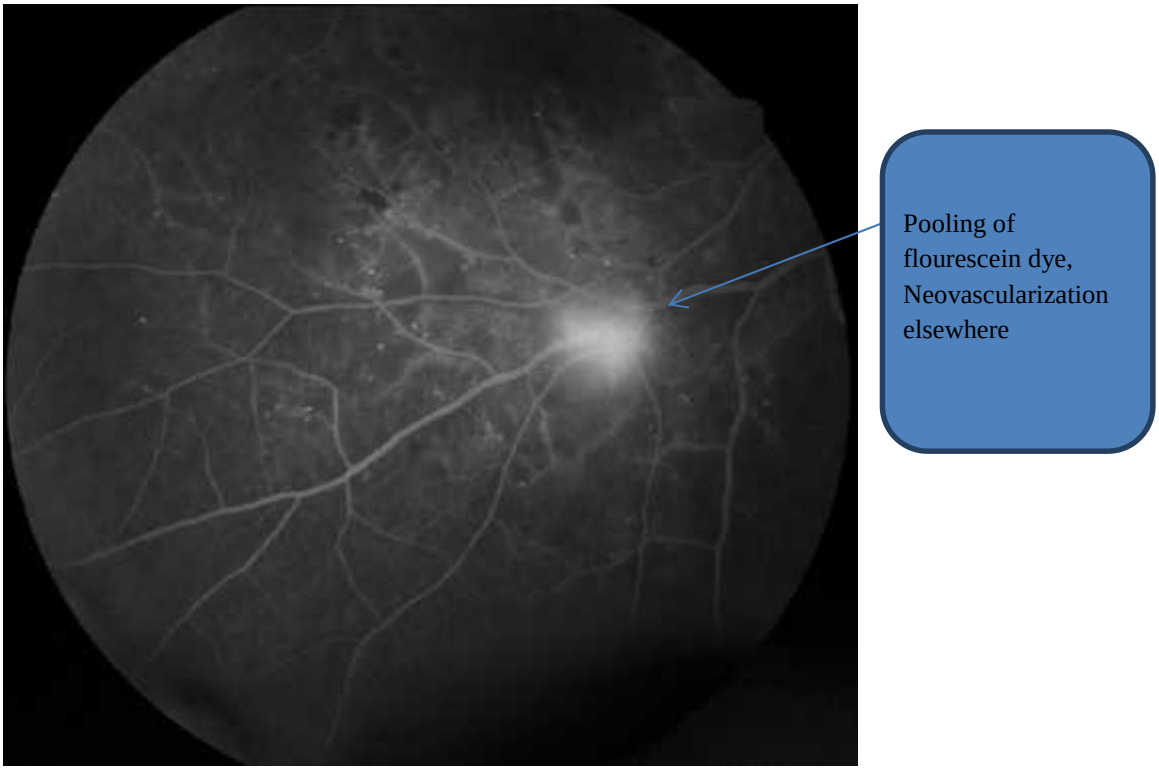


Photo 10. Fundus Flourescein Angiography picture 5

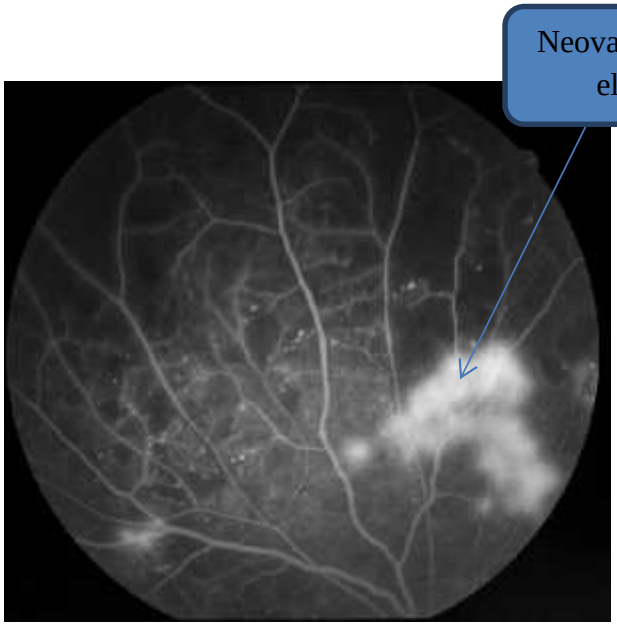


Photo 11. Fundus Flourescein Angiography picture 6

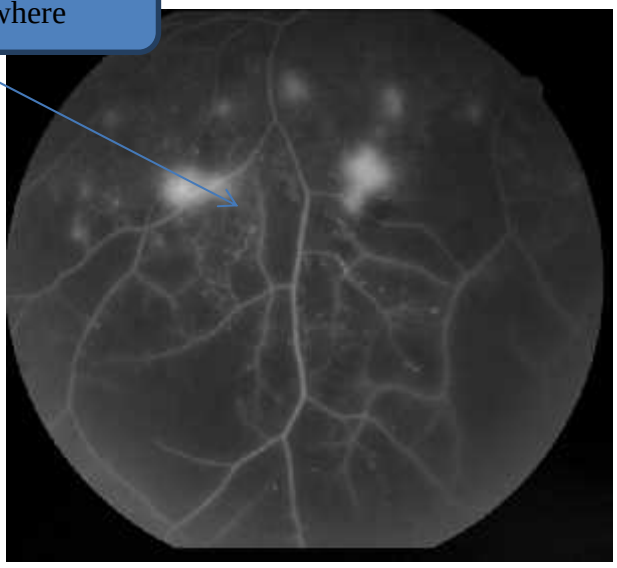


Photo 12. Fundus Flourescein Angiography picture 7

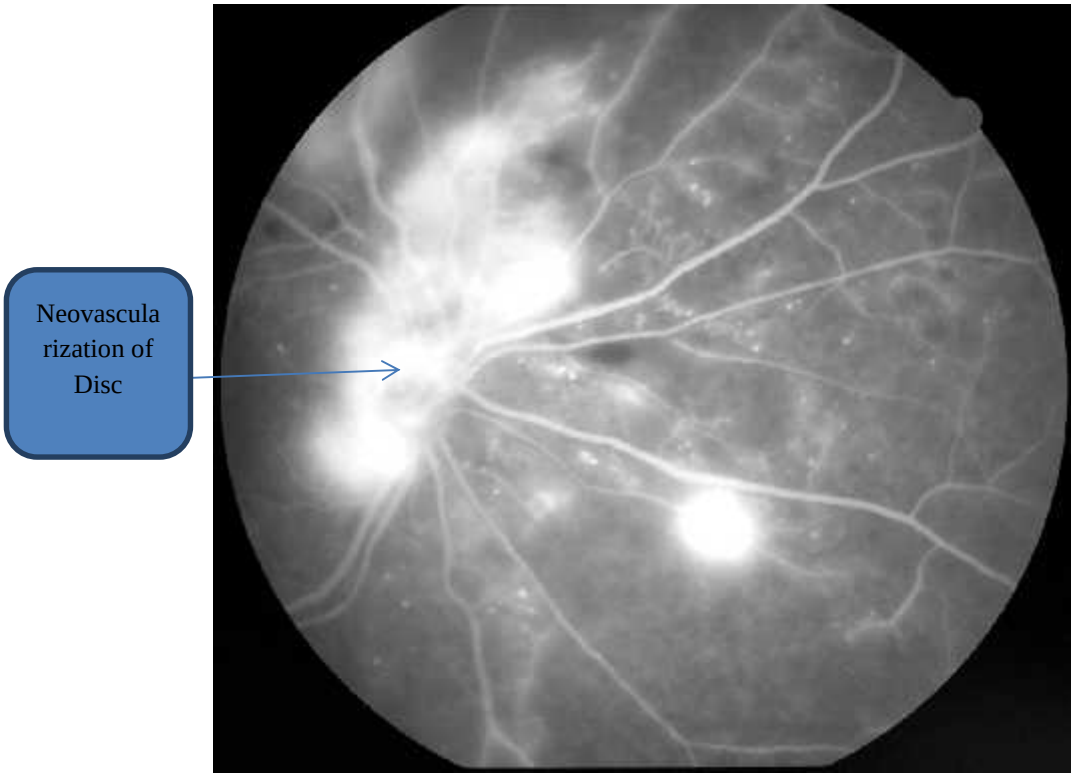


Photo 13. Fundus Flourescein Angiographypicture 8

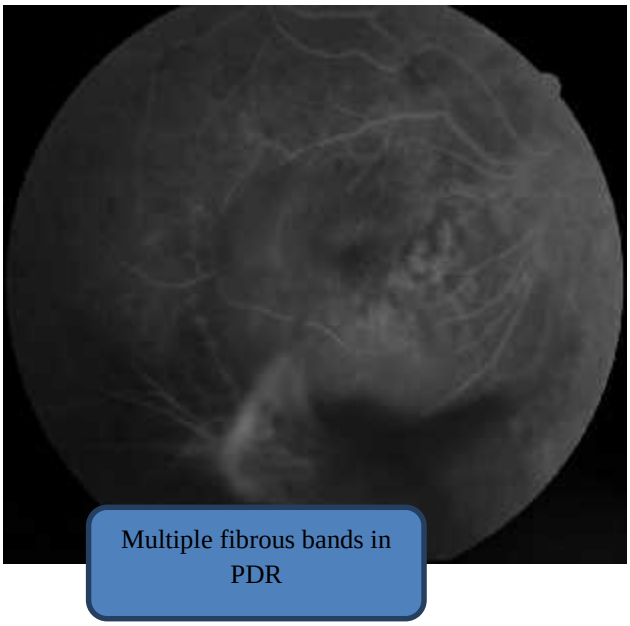


Photo 14.Fundus Flourescein Angiographypicture 9

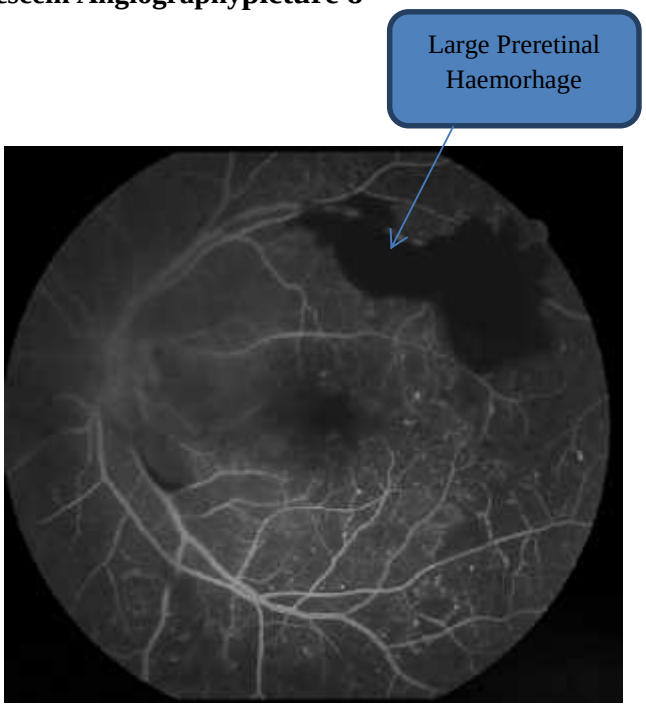


Photo 15. Fundus Flourescein Angiography picture 10

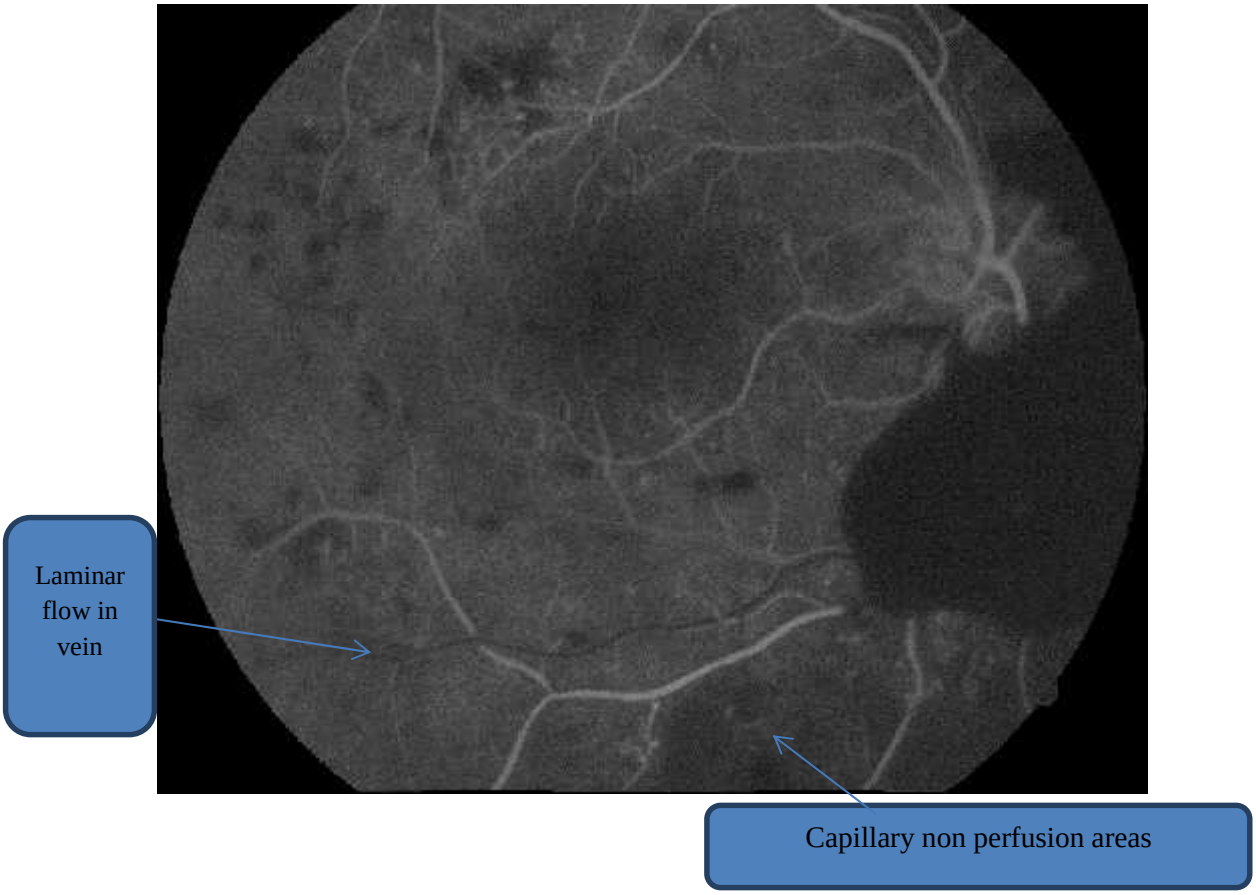


Photo 16. Fundus Flourescein Angiography picture 11

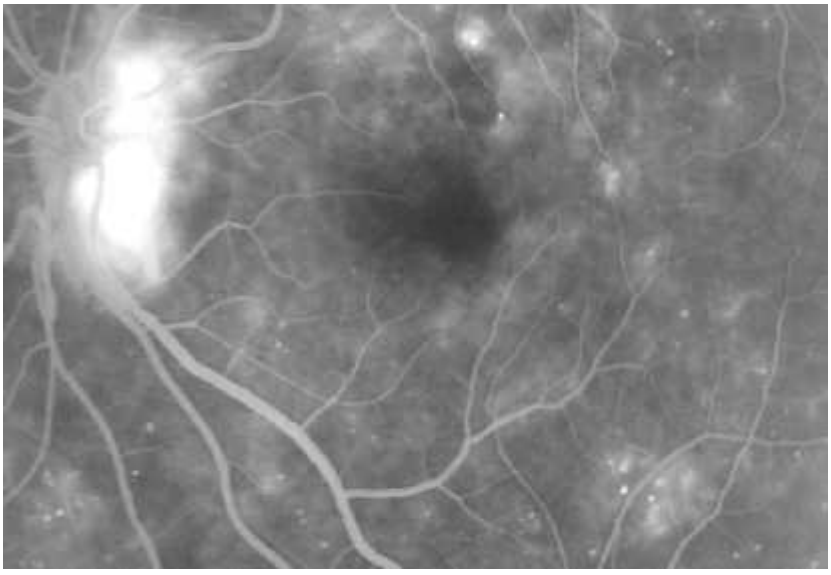


Photo 17. Fundus Flourescein Angiography picture 12