Study on clinical evaluation of diabetic retinopathy by fundus fluorescein angiography

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Abstract

Background: Diabetic retinopathy was responsible for 11.1% of new cases of legal blindness in all the age group and 19.1% of those in 20-64 years age group. The detection of pre-proliferative and proliferative diabetic retinopathy can prevent the complications if these patients are appropriately treated by photocoagulation of the ischemic retina. This study is meant to determine the role of F.F.A. in detection of diabetic retinopathy changes in diabetic patients.

Methods: The present study was conducted for a period of two years. A hospital based cross sectional study of 100 eyes of 50 patients with diabetic retinopathy consisted of detailed anterior segment, and fundus examination clinically with FFA. Each angiogram was studied for the number, size and location of aneurysms, size and shape of foveal avascular zone and type of leakage.

Result: The mean age of the patients was 55.65 years, the youngest was 21 years old and the eldest was 80 years old. 30% of total eyes were found to have micro aneurysms only, 20% of eyes were found to have moderate NPDR changes, IRMAS were found in 6% of eyes, 4% of eyes with ischemic maculopathy which was identified only through FFA. 30% of eyes with very severe NPDR turned out to PDR changes by FFA.

Conclusion: In this study, we were able to identify the role of FFA in differentiating the lesions and assessing severity of characteristics like capillary loss. The procedure was useful in identifying subtle changes, which are otherwise difficult to appreciate by ophthalmoscopy, like, the number of micro aneurysms and their localization in different areas of fundus, and their size.

Keywords: Diabetic retinopathy, Fundus fluorescein angiography, NPDR, PDR.

Introduction

Diabetic retinopathy is one of the leading causes of blindness. According to "Statistics on blindness in the Model Reporting Area 1969-70", Diabetic retinopathy was responsible for 11.1% of new cases of legal blindness in all the age group and 19.1% of those in 20-64 years age group.(1) The prevalence of diabetes among the population is varied and different in different parts of the world. In India it has been reported form 4-28%.(2) There is prevalence of 6.7% of retinopathy in patients of NIDDM at the initial diagnosis of diabetes.

Both longitudinal and cross sectional studies show that the best predictor of diabetes retinopathy is the duration of diabetes. For insulin dependent diabetes mellitus virtually there is no clinically apparent retinopathy for 4-5 years after the initial diagnosis of retinopathy. PDR is rare before 10 years and is unknown before 5 years duration of diabetes. In NIDDM Yanko & others have reported NPDR prevalence of 23% for 10-13 years after the diagnosis of diabetes & 60% for 16 years after the diagnosis.(3)

In India retinopathy was detected in 52% of patients with NIDDM of over 25 years duration.(4) Among this NPDR was seen in 41% & PDR in 10.3% patients.

Predisposing factors: Duration of diabetes appears to be the most important factor in the precipitation of retinopathy, while diabetic retinopathy is also correlated with it's severity, proteinuria, renal disease, insulin usage and decreased uric acid level. There is less evidence on the influence of age at onset, gender, associated hypertension, cardiovascular disease, serum cholesterol, serum triglycerides and high density lipoprotein. Adequate control of diabetes has been found to delay the retinopathy in many studies but not all.

AGGRAVATING FACTORS**:** Humoral factors like onset of puberty and pregnancy can result in Progression of diabetic retinopathy.(5)

Roll of Fluorescein Angiography in Diabetic patient: F.F.A can be used for:

i. As a screening means for detection of diabetic retinopathy
ii. Detection of presence and extent of retinal edema
iii. To differentiate between aneurysm and hemorrhage.
iv. To detect maculopathies-Focal, diffuse, ischemic.
v. To assess the retinal blood flow (Arm retinal circulation and arteriovenous passage, retinal circulation time.
vi. To detect area of capillary non-perfusion.
vii. To detect presence of new vessels (NVD, NVE.) and their extent.
viii. To assess the progression of diabetic retinopathy in a patient.
ix. To assess the effect of treatment on the patient. E.g., Laser photocoagulation.

The detection of pre proliferative and proliferative diabetic retinopathy can prevent the complications if these patients are appropriately treated by photocoagulation of the ischemic retina.

This study is meant to determine the role of F.F.A. in detection of diabetic retinopathy changes in diabetic patients especially when these changes are not appreciated ophthalmoscopically or in doubtful causes, with emphasis on detection of early proliferative diabetic

retinopathy cases, their extent, follow up and response to treatment.

Objectives: The present study was carried out for clinical evaluation and efficacy of diabetic retinopathy by fundus fluorescein angiography

Materials and Methods

This analytical study was conducted in Narayana Medical College Hospital, Nellore for a period of two years (2008 to 2010). The cases included in the study were diabetic patients of both sexes and various age groups. Those included were selected from the patients attending the department of medicine, Narayana Medical College Hospital, Nellore for the treatment of diabetes mellitus, and referred to department of ophthalmology for evaluation, known diabetic patients who attended the ophthalmology outpatient department directly for the ophthalmic evaluation were also included in the study. Accordingly, total number of patients included in the study is fifty. All these patients were examined and data were recorded in standardized proforma. An institutional ethical clearance was obtained prior to start the study and informed consent was taken after explaining the purpose of study.

The selection criteria for the inclusion of patients for the study are based on as following:

Inclusion criteria:

All the patients with the history of diabetes confirmed by investigations (RBS Values > 180mg/dl) and among those who have ophthalmoscopically detectable diabetic retinopathy changes.

Exclusion criteria:

i. Patients of diabetic retinopathy who have media opacities or hazy media due to cataract or other causes.
ii. Patients of diabetic retinopathy who have undergone treatment for Diabetic retinopathy by photo – coagulation or other surgeries.
iii. Allergic to drugs
iv. Porphyrias
v. End stage kidney disease

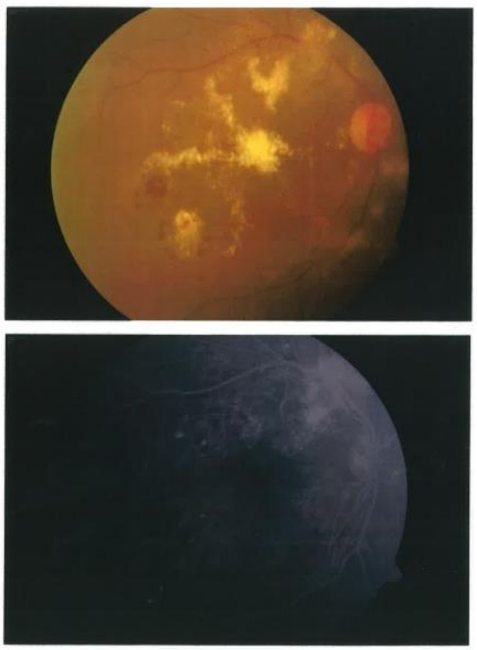

Fig. 1: PDR changes with NVD and Hyperfluoresent leaks in late phases

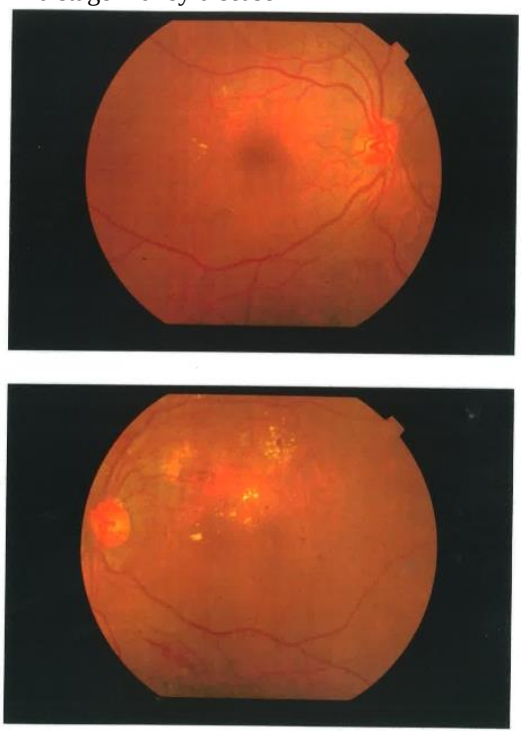

Fig. 2: Moderate NPDR with CSME

Visual acuity was recorded and retinoscopy was done in all the cases. Blood glucose and blood urea & serum creatinine were done in all cases and recorded.

The initial examination was started with fundus examination with direct opthalmoscope after papillary dilation with a combination of phenylephrine and tropicamide eye drops. Due care was taken to rule out hypertension in the patient before administration of this eye drops to avoid cardiovascular complications.

The study of diabetic changes in the fundus was performed by non- invasive techniques like direct

ophthalmoscopy, slit lamp biomicroscopy using +78D lens, and indirect opthalmoscope with +20D Volk lens. After getting the opinion from the physician regarding the fitness for the fundus fluorescein angiography, the patient was taken up for the procedure.

The patient was informed in vernacular about the procedure in detail. He was explained about the purpose, procedure, and possible adverse reactions, which are likely to occur during or immediately after the procedure and management of the likely adverse effect also. All the emergency drugs were kept to treat the adverse reactions, which may occur during the procedure.

On the day of appointment, the patient was examined and his pupils were dilated with eye drops of a combination of tropicamide and phenylephrine. The procedure was carried out during the outpatient department during working hours. Zeiss FF 450 plus fundus camera was used throughout the study.

The patient was seated comfortably in front of the fundus camera. The antecubital vein was secured and scalp vein set was fixed. His chin was placed on the chin rest and the forehead on the head bar. Patient was asked not to move his head, which would lead of loss of focus eventfully leading to poor quality photographic frames. On aiming and focusing the camera on the area of primary interest the patient was asked to fix the gaze by looking at the target.

Color fundus picture and then red free photographs were taken using green filter. Then pre injection photographs were taken with exciter and barrier filters, if it was found necessary in the fundoscopic examination through fundus camera unit.

3ml of 20% fluorescein dye was injected into the antecubital vein and serial pictures were taken after 7 – 10 sec of post injection for every 10 sec. late films were taken 10 min after injection. After the procedure the patient was made to lie down and relax for 15to 30 minutes. He was also explained about the change in the color of urine and skin.

The findings were recorded in the case sheet of the patient The features, which were observed, were presence of microaneurysms, retinal edema, capillary dropouts, IRMA, new vessels, maculopathies – focal, diffuse or/ and exudative.

Statistical Analysis

Descriptive statistics such as mean, SD and percentage was used to present the data. Chi-square test was used to assess the relationship between variables. A p-value less than 0.05 were considered as significant.

Results

Age and sex distribution: The mean age of the study subjects was 55.65 years with standard deviation (SD) of 11.3 years. The youngest was 21 years old and the oldest, 80 years old. The 51-60 years age group contained the majority of patients (48%) followed by the 61- 70 (22%). There were 37 male and 13 female patients. The sex ratio is 2.9:1. There were almost three times as many males as female patients.

Natural history of diabetes

Duration: At the time enrolment into the study, the patients had a mean duration of illness of 9.32 years with a SD of 4.63 years. The shortest duration was 2 years and the longest, 20 years.

The distribution of the patients according to the length of diabetic illness is shown in Table 1.

Table 1: Duration of diabetic illness

Duration (years)	Number of patients	Percent
1-5 yrs.	10	20%
6-10 yrs.	24	48%
11-15 yrs.	9	18%
16-20 yrs.	7	14%

The majority of patients (48%) were suffering from diabetes for between 6 to 10 years.

Table 2: Age and duration of illness in diabetic patients

Age group (years)	Duration of diabetes (years)				Total
	1-5 yrs.	6-10 yrs.	11-15 yrs.	16-20 yrs.	
21-30	2	-	-	-	2
31-40	2	1	-	-	3
41-50	3	5	-	-	8
51-60	3	5	5	3	16
61-70	-	7	4	2	13
71and above	-	6	-	2	8
Total	10	24	9	7	50

With increasing age of the patients, the duration of illness too increases. Under 50 yrs, all the patients have diabetes for less than 10yrs. After 50 yrs, 16 out of 37 (43.24%) have illness of 10 yrs or more (Table 2).

Treatment modality: 45 patients (90%) were on oral hypoglycaemic agents. 4 patients (8%) were on insulin therapy. A 72 year old male diabetic was on both Insulin and oral hypoglycaemic therapy.

Treatment regularity: Treatment in as many as 41 patients (82%) was regular. Therapy in the case of the rest 18% was irregular.

Visual acuity:

Right eye: In the right eye of 16 diabetic patients (32%) the vision was 6/6 – 6/9. In 4 patients the right eye was economically blind (3/60 or worse). The remaining right eyes had loss of vision of various Intermediary degrees.

Left eye: Vision in left eye was normal (6/6) in 16 patients. In 4patients the left eye was economically blind (3/60 or worse). The remaining left eyes had loss of vision of various intermediary degrees.

Ophthalmoscopic Findings:

Table 3: Ophthalmoscopic findings of right and left eye

Diagnosis	Right eye		Left eye	
	Number of cases	Percent	Number of cases	Percent
Mild NPDR	14	28	14	28
Moderate NPDR	10	20	11	22
Severe NPDR	6	12	4	8
NPDR with CSME	11	22	12	24
PDR	9	18	9	18
Total	50	100	50	100

Right eye: 30 right eyes (60%) showed no – proliferative diabetic retinopathy (NPDR). Of these mild and moderate cases were 14 (28%) and 11 (22%) respectively, 6 (12%) were severe NPDR. In 11 patients (22%), ophthalmoscopy revealed NPDR associated with clinically significant macular edema (CSME). Whereas in 9 cases (18%) proliferative diabetic retinopathy (PDR) was detected.

Left eye: The Table depicts, 29 eyes (58%) showed NPDR. Of these 14 (28%) were mild, 11 (22%) were moderate and 4 (8%) were severe NPDR. Ophthalmoscopy revealed NPDR with CSME in 12 patients (24%) whereas, in 9 patients (18%) PDR was detected.

Role of Age & Duration of Illness on Ophthalmoscopic Findings:

To elucidate the role of the above factors on the retinal complications of diabetes, ophthalmoscopic changes of both eyes are totaled (100 eyes), and grouped into two tentative categories:

(a) Mild NPDR category

(b) Other severe categories.

The latter is made up of moderate NPDR, severe NPDR, NPDR+CSME and PDR

Role of Age:

Table 4: Age & extent of retinopathies in diabetic patients (100 eyes)

Age group (years)	NPDR mild category		Other severe categories		Total	
	Number (eyes)	Percent	Number (Eyes)	Percent	Number (eyes)	Percent
21-30	2	50.00	2	50.00	4	100
31-40	4	66.67	2	33.33	6	100
41-50	9	56.25	3	43.75	16	100
51-60	10	20.25	33	78.75	48	100
61-70	3	22.73	17	77.27	22	100
71 & above	0	100.00	4	100.00	4	100

With the increase in age of the patient upto 50 yrs, the proportion of severe categories is low. After 50 yrs this proportion goes on increasing. This relationship is statistically significant. ($\chi^2 = 20.3$, p=0.0011).

Roll of Duration of Illness:

Table 5: Duration of illness in diabetic patients

Duration (years)	NPDR mild		Other severer categories		Total	
	Number	Percent	Number	Percent	Number	Percent
1-5	15	75.00	5	25.00	20	100
6-10	12	25.00	36	75.00	48	100
11-15	2	11.11	16	88.88	18	100
>16 years	0	0.00	14	100.00	14	100

The severity of retinopathy as revealed by ophthalmoscopic examination rises with the increase in the duration of illness. The changes noted in the above are statistically significant ($\chi^2 = 29.44$, p=<0.001).

Table 6: Comparison of ophthalmoscopy with FFA findings

Category	Detected by Ophthalmoscopy	True cases by FFA
Mild NPDR	14	15
Moderate NPDR	10	10
Severe NPDR	5	3 (remaining cases were diagnosed as PDR)
NPDR with Exudative Maculopathy	10	10
NPDR with Ischemic Maculopathy	0	2
Neovascularization	9	11

Discussion

The present study consists of 50 diabetic patients who attended the outpatient department or who were admitted to Narayana medical College Hospital, Nellore during the study period.

The mean age of the subjects was 55.65 years with SD of 11.13 years. In a similar study conducted by Ramsevak V. et al[6] who have studied 775 cases, the mean age was 72.1 years.

Another study conducted by Gonzalez Villalpando C. et al[7] where 231 patients were examined, mean age was 62.4 years.

The mean age in the first study is more when compared to the remaining three studies due to the reason that the patients selected for the study are only of type 2 diabetes mellitus when compared to the patients of the other three studies where in the patients are of both type I and type 2diabetes mellitus.

Male: Female Ratio: Male: Female ratio in our study is 37.13 i.e. 2.9:1 when compared to the study conducted by Gonzalez Villalpando V et al[7] where to female ratio is 0.91:1.

This may be due to lack of proper health care of women in India when compared to the access to proper health care of the women in the west.

Duration of the Disease: The mean duration of diabetics in the present study is 9.32 years whereas is the study conducted by Ramsevak V. et al[6] the mean duration of the disease was 13 years.

Another study conducted by Gonzalez Villalpando C. et al,[7] mean duration of diabetes was 11 years.

Comparison of Ophthalmoscopic and Fluorescein angiography Findings: Detailed study of dilated ophthalmoscopy, biomicroscopy wherever needed, was followed by fluorescein angiography. The different grades of retinopathy observed in our study are compared with the following studies.

In our study we found more case of mild/moderate NPDR than other studies. This may be due to the fact that we had exclusion criteria of not including the patients having hazy media and the patients who had already undergone photocoagulation.

In the study conducted by Bertram et al,[8] 48 patients (9.8%) had already undergone laser photocoagulation, 13 panretinal scatter, 18 with focal photocoagulation and 17 with both.

The NPDR category in the study conducted by Ramsevak V. et al[6] is 21.4% which is also less when compared to the present study. This is because they have screened the patients of diabetes mellitus patients who attended the ophthalmlic clinic for the first time for the evaluation.

The microaneurysms were appreciated better both in the number, position and in relation to vasculature.

This was is consensus with the study conducted by Friberg TR and other[9] who studied 101 patients, about twice as many microaneurysms were detected on the FFA as on the colour photography. Also FFA showed

microaneurysms in 57% of the eyes that had no detectable microaneurysms on colour photography.

However the study conducted by Niesel P. et al[10] states that the described method of quantitative evaluation of diabetic retinopathy quantifies the progression of retinopathy. Accurate quantitative analysis of the comparison between the ophthalmoscopic quantification and angiographic quantification was difficult because of the cumbersome nature of counting especially by ophthalmoscopy, lack of accuracy and interpretation problems.

In a study conducted by Hellstedt, et al[11] it is concluded that although microaneurysms in fluorescein angiography and red spots in color or red free photographs all reflect the degree of retinopathy, about half of the red dots in photography don't represent open micro aneurysms in fluorescein angiography.

Ischaemic maculopathy was better appreciated by fluorescein angiography than by ophthalmoscopy. Widening of FAZ was also better delineated with fluorescein angiography than by ophthalmoscopy.

In a study conducted by Smith RT et al,[12] they studied 34 diabetic patients with clinically significant macular edema (CSME) by fundus photography, fluorescein angiography and vitreous fluorophotometry observed that all the three investigations together best predicted visual acuity.

They also concluded that by performing fluorescein angiography it is possible to quantitative macular ischaemia.

Clinically significant macular edema was observed better by fluorescein angiography than by ophthalmoscopy. The study conducted by Kylstra JA et al[13] where 100 patients were studied by six retina specialists also concluded that the use of FA improves the accuracy of treatment planning of CSME.

Fluorescein angiography was also more accurate is exact localization and extent of neovascularization. This finding was in concurrence with the one observed by Jain BA, et al[14] who studied 25 patients of diabetic retinopathy by ophthalmoscopy and fundus fluorescein angiography.

Conclusion

Our study proves the role of fluorescein angiography in clinical evaluation of diabetic retinopathy as, FFA is useful in differentiating the lesions and assessing severity of characteristics like capillary loss, useful in classifying the diabetic retinopathy and FFA is mandatory for the treatment of diabetic maculopathy and helps in guiding the treatment of PDR.

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