Original Research Article

The role of fundus fluorescence angiography in diabetic retinopathy

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Abstract

Objective: To study the role of fundus fluorescence angiography in patients having Diabetic Retinopathy. **Method:** 30 patients(60 eyes) who were having Diabetes mellitus having high clinical suspicion of diabetic retinopathy were selected and underwent direct ophthalmoscopy and FFA. present study was conducted for period of two years between September 2019 to August 2021 at Shri Chatrapati Shivaji Maharaj Sarvopchar Rugnalay, Solapur in a Tertiary Care Hospital. The manifestation characteristics of FFA in diagnosis of diabetic retinopathy were summarized. **Result:** In Diagnosis with Direct ophthalmoscopy out of 60 eyes, 8 eyes showed Normal fundus, 14 eyes showed Mild NPDR, 17 eyes showed Moderate NPDR, 10 eyes showed Severe NPDR, 11 eyes showed PDR. While In Diagnosis with FFA, 22 eyes showed mild NPDR, 17 eyes showed moderate NPDR, 6 eyes showed severe NPDR and 15 eyes showed PDR. 8 eyes(13.33% eyes)which were normal on ophthalmoscopy turned out to mild NPDR changes on FFA and 4 eyes (7% eyes) with severe NPDR turned out to PDR changes by FFA. ischemic maculopathy and capillary dropout area was identified only through FFA. Detection rate of Diabetic retinopathy using FFA was significantly higher than that of ophthalmoscopy. **Conclusion:** In our study FFA proved to be important for early detection of microaneurysm, accurate identification, localisation and extension of neovascularisation and capillary dropout area (ischemia). FFA is also helpful in early diagnosis and accurate staging of diabetic retinopathy.

Keywords: Diabetic retinopathy, FFA, NPDR, PDR.

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INTRODUCTION

Diabetes mellitus is a complex metabolic disorder, characterised by deficiency and resistance to insulin by receptors that lead to persistent hyperglycaemia which in turn lead to microangiopathy and organ damage. Diabetes mellitus is a leading cause of morbidity in the Indian subcontinent. It comes with an array of microvascular complications, i.e. retinopathy, nephropathy, neuropathy not just in India, but throughout the world.[1] Diabetic retinopathy is one of the leading cause of blindness and visual impairment in both developing and developed countries.[2] Diabetic retinopathy is a microangiopathy primarily affecting the precapillary arterioles, capillaries and post capillary venules.[3] Fluorescein angiography has been extremely valuable for expanding our knowledge to visualize the chorioretinal circulation and in evaluating retinal vascular disorders. In diabetic retinopathy the angiogram is useful in identifying the extent of ischemia, location of micro aneurysms, presence of intraretinal microvascular abnormalities (IRMA) that can only be confirmed on angiogram; neovascularization and the extent of macular edema.[4] FFA is not only useful for diagnosis but also to gauge the progression and management of diabetic retinopathy (DR). FFA is a therapeutic guide to laser photocoagulation treatment for several retinal vascular diseases.[5] This study is meant to identify the role of FFA in early Diagnosis and accurate

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staging of Diabetic Retinopathy and its role to gauge the progression and management of diabetic retinopathy.

MATERIALS AND METHODS

Study period: From September 2019 to August 2021
Sample size: 60 eyes of 30 patients
Inclusion criteria: Patients older than 12 years of age suffering from Diabetes Mellitus having high clinical suspicion of diabetic retinopathy.
Exclusion criteria: Patients younger than 12 years of age. Patients with hazy media. Pregnant women. Patients with hypersensitivity to fluorescein dye. Renal insufficiency. Patients who have already received anti VEGF's. Patients who have undergone laser photocoagulation therapy. Patients having hypertension.
Instruments and drugs: Direct ophthalmoscope. Indirect ophthalmoscope. Tropicamide 0.8% + phenylephrine 5% eyedrop. 3ml 20% Inj.Sodium fluorescein. Emergency tray with instrument and drugs. Fundus camera (Canon CF1).

METHOD

Patients detailed clinical history with information regarding age of onset, duration of disease, association of any other systemic Morbidity and treatment taken, were noted.
Detailed examination was done and noted as per proforma prepared.
Fundus fluorescein angiography procedure

1. Procedure explained to patient.
2. Written informed consent taken.
3. Emergency tray was kept ready during procedure with Anesthesist standby
4. After achieving mydriasis first fundus photograph was taken before injecting the dye.
5. After injecting the dye in a single bolus intravenously sequential photographs were taken with filter in place
6. Patient observed for next 30min

Staging criteria of diabetic retinopathy

In the international AAO (American Academy of Ophthalmology) classification,
1) Non proliferative diabetic retinopathy NPDR is graded as: (i) Mild, (ii) Moderate, (iii) Severe
2) Proliferative diabetic retinopathy (PDR)
(i) New vessels on the disc (NVD) or within 1 disc diameter (DD) of the margin of the disc, (ii) New vessels elsewhere in the retina (NVE) (more than 1DD from the disc).

RESULT

Table 1: Distribution of patients according to age, sex and type of Diabetes

Age in years	Type 1 diabetes		Type 2 diabetes	
	Male	Female	Male	Female
12-20	0	0	0	0
21-40	2	1	1	0
41-60	0	0	11	6
>60	0	0	7	2
Total	**2**	**1**	**19**	**8**

There was higher incidence in male patients. Male: Female ratio is 2.33:1 The age incidence was maximum with 17 patients (56.6%) between 41 to 60 year

Table 2: Distribution of patient in relation to status of Glycemic control and severity of Retinopathy

Glycemic control	Mild NPDR	Mod NPDR	Severe NPDR	PDR	Total	Percentage
Controlled	5	6	0	2	13	**43**
Uncontrolled	6	2	3	6	17	**57**
Total	**11**	**8**	**3**	**8**	**30**	**100**

(Considering fasting and post prandial BSL, urine sugar) 57% patient had uncontrolled blood sugar levels

Table 3: Distribution of number of patients eyes in relation to severity of Retinopathy with duration of disease

Duration in year	No of eyes Mild NPDR	No of eyes Mod NPDR	No of eyes Severe NPDR	No of eyes PDR	Total
0-5	14	4	0	0	18
6-10	4	4	2	2	12
11-15	4	8	2	8	22
16-20	0	1	2	3	6
>20	0	0	0	2	2
Total	**22**	**17**	**6**	**15**	**60**

Maximum no of patients eye had duration of diabetes 11-15yr (22 eyes) followed by 0-5yr (18 eyes)

Table 4: Distribution of finding on ophthalmoscope and on FFA

	Eyes on ophthalmoscopy		Eyes on FFA	
	No of Eyes	Percentage	No of Eyes	Percentage
Microaneurysm	34	57%	60	100%
Neovascularisation	11	18%	15	25%
Macular edema	23	38%	26	43%
Ischemic maculopathy	0	0%	2	3%
Capillary dropout	0	0%	20	33%

In our study it was found that All 60 patients had MA when subjected to FFA testing.Whereas only 34 patients had Microaneurysm in Ophthalmoscope. This indicates that FFA can accurately find out Microaneurysm. FFA detected Neovascularisation in 15 eyes whereas Ophthalmoscopy detected neovascularisation in 11 eyes (X^2 value- 40.41, p-value <0.001) and this difference is found to be statistically significant. Maculopathy was seen in 26 eyes on doing FFA whereas only 23 eyes showed Maculopathy on ophthalmoscope (X^2 value- 48.77 p-value <0.001.) and this difference is found to be statistically significant.

Table 5: Comparison of the diagnosis made based on Ophthalmoscope vs FFA

		Diagnosis on FFA					Total
Diagnosis on Ophthalmoscope		Mild NPDR	Mod NPDR	Sever NPDR	PDR	WNL	
	Mild NPDR	14	0	0	0	0	14
	Mod NPDR	0	17	0	0	0	17
	Sever NPDR	0	0	6	4	0	10
	PDR	0	0	0	11	0	11
	WNL	**8**	0	0	0	0	8
Total		**22**	**17**	**6**	**15**	**0**	**60**

X^2 value- 146.66; p-value <0.001.

On Ophthalmoscope 8 eyes showed no abnormal changes (Normal), Mild NPDR was seen in 14 eyes, Moderate NPDR in 17 eyes, Sever NPDR in 10 eyes and PDR in 11 eyes. FFA diagnosed Mild NPDR in 22 eyes, Moderate NPDR in 17 eyes, Sever NPDR in 6 eyes and PDR in 15 eyes. The major difference in diagnosis was seen in mild NPDR, PDR.

DISCUSSION

The material for the present study consist of 60 eyes of 30 Diabetic patients who attended the outpatient department or who were admitted to Our tertiary Care Hospital during the period of September 2019 to August 2021.

Age and sex distribution: In our study out of 30 patient with Diabetic retinopathy 21 were males (70%) and 9(30%) were females.

Male: Female Ratio is 2.33:1. Udaysridhar Mulgund, Rakhesh Chandran in 2017 studied 50 patients of diabetes, out of which 37 were males and 13 were females and where male to female ratio was 2.9:1[6] The mean age of present study subject was 53.9 year. In our study the 41-60 years age group contained the majority of the patients (56.6%). In another study conducted by Sumi S. *et al.* who studied 242 patients, the mean age of patients was 52.9 year.[7]

Distribution according to age ,sex and type of diabetes. In our study out of 30 patients ,27 patients (90%)had type 2 diabetes and 3 patients(10%) had type 1 diabetes.

In type 1 diabetes 2 patients(6.6%)were male and 1 (3.4%) was female. In type 2 diabetes 19 patients (63%) were male and 8 patients (27%) were female. Most of the patients with type 2 diabetes comes under age group of 41-60 year. As per data published in Diabetes care in 2010 by the American diabetes association, Type 2 diabetes is more common type with 90% of patients having diabetes belonging to type 2 diabetes group.[8] In 1999 Vijay Vishwanathan, did a study in which most diabetic patients belongs to age group of 45 to 65 year.[9]

Glycemic control and severity: In our study, glycemic control was defined on the basis of fasting and postprandial sugar levels and urine sugar levels. In our study, out of 30 patients, 13 patients (43%) had controlled blood sugar levels and 17 (57%) had uncontrolled blood sugar level. Out of these 17 patients 6 had mild NPDR, 2 had moderate NPDR, 3 had severe NPDR and 6 had PDR. All patients of severe NPDR(3 patients) and 75% (6 patients) of PDR had an uncontrolled status of diabetes. In 1986, a study by Krolewski *et al.* showed that risk for development of proliferative diabetic retinopathy was greater with poor glycemic control.[10]

Distribution of patients in relation to duration and severity of diabetes: The mean duration of diabetes in the present study is 9.63 years whereas in the study conducted by Pallamreddy shri Laxmi and others in 2017 the mean duration of disease was 9.32 years.[11] 18 eyes comes under duration of 0-5 years of the disease, out of it most of the eyes i.e. 14 eyes (77.77%) were having mild NPDR. 12 eyes comes under duration of 6-10 years of the disease, majority eyes were having mild NPDR (34%) and moderate NPDR (34%). 22 eyes comes under duration of 11-15 years of the disease, out of it majority of the eyes i.e., 8 eyes out of 20 eyes (40%) were having PDR. 6 eyes comes under duration of 16-20 years, majority of the eyes i.e., 3 eyes (50%) having PDR. 2 eyes comes under duration above 20 year and both of eyes having PDR Above data shows that, as the duration of diabetes increases, the severity of diabetic retinopathy increases. A study conducted by Gonzalez Villalpando C. *et al.* shows that severity of diabetic retinopathy increases with the duration of diabetes.[12]

Comparison of ophthalmoscopic and Fluorescein Angiography findings: In our study, it was found that all the 60 (100%) eyes had microaneurysms when subjected to FFA testing whereas, only 34 (57%) eyes showed microaneurysms on ophthalmoscopic examination.On FFA the microaneurysms were appreciated better both in the number, position and in relation to vasculature . DJ Scott and his coworkers (1963) on studying the fundus of Diabetic retinopathy found many more fluorescent spots in FFA than microaneurysms in the colour fundus photograph and concluded that additional fluorescent spots were microaneurysms undetectable by routine of Ophthalmoscopy or colour photography.[13] In our study, the percentage of Microaneurysms was 100% percent on FFA and 8 eyes with mild diabetic retinopathy, only manifested as retinal microaneurysms suggesting that microaneurysm is the earliest sign of diabetic retinopathy which was similar to research achievement of LV Peilin.[14] It indicates that, FFA could identify fundus lesions which were not discovered by direct ophthalmoscope and had a higher accuracy in the early diagnosis of diabetic retinopathy. In our study, it was found that 15 eyes had neovascularisation when subjected to FFA. whereas only 11 eyes had showed neovascularisation on ophthalmoscopic examination. Fluorescein angiography was also more accurate in exact localization and extent of neovascularization. This finding was in occurrence with the one observed by Jain BA *et al.* who studied 25 patients of diabetic retinopathy by ophthalmoscopy and funders fluorescein angiography.[15] In our study, it was found that 26 eyes (43%) had macular edema when subjected to FFA testing whereas, only 23 eyes (38%) showed macular edema on ophthalmoscopic examination. 33% eyes (20 eyes) showed capillary dropout, 3% eyes (2 eyes) showed ischemic maculopathy were diagnosed only by FFA. In our study, it was found that 22 eyes (36.6%) had mild NPDR when subjected to FFA testing whereas, only 14 eyes (23%) showed mild NPDR on ophthalmoscopic examination. 8 eyes (13%) which were considered as normal based on their ophthalmoscopic examination showed mild NPDR when subjected to FFA. Thus, patient with Diabetes who is not diagnosed as retinopathy by ophthalmoscopy can be accurately diagnosed on FFA as retinopathy. 10 eyes when subjected to Ophthalmoscopic examination were diagnosed as severe NPDR. While, 4 eyes out of these 10 eyes were diagnosed as Proliferative Retinopathy (PDR) when subjected to FFA. In our study, it was found that all the 15 eyes (25%) had PDR when subjected to FFA testing whereas, only 11 eyes (18%) showed PDR on ophthalmoscopic examination. 4 eyes (6.5%) which were underdiagnosed as severe NPDR based on their ophthalmoscopic examination are turned out to PDR on FFA. Thus, Fundus Fluorescein Angiography can be used as an effective tool for the accurate staging of severity of diabetic retinopathy. Robert N.F. (1982), in his study on juvenile onset diabetes mellitus of short duration, found that the number of fundoscopy positive retinopathy patients were 19 and after FFA the number was increased up to 29.[16] Samar Banerjee *et al.* (2007) in their comparative evaluation of ophthalmoscopy and FFA for the assessment of DR found that appropriate grading of retinopathy is better with FFA and concluded that FFA should be strongly advised, at least in the high risk group for appropriate grading.[17] Thus from above discussion it can be concluded that microanueurysm, macular edema, neovascularisation, capillary dropout area, ischemic maculopathy are better identified and located on FFA .FFA is very additive and useful tool for early detection and accurate grading of Diabetic Retinopathy .

CONCLUSION

Thus from our study it can be concluded that all the ophthalmoscopic clinical finding correlate well with Fundus fluorescein angiography finding in diabetic retinopathy. In addition Fundus fluorescein angiography is a very useful ancillary diagnostic procedure. FFA could identify Microaneurysms I.e.early lesions of diabetic retinopathy which were not discovered by direct ophthalmoscope and had a higher accuracy in the early diagnosis of diabetic retinopathy. It is helpful in diabetic retinopathy in characterisation and quantification of Microaneurysms. Fluorescein angiography was also more accurate in quantification, exact localization and extent of neovascularization. It is also useful in assessing the severity of characteristics like the extent of capillary loss i.e. capillary dropout area(Ischaemia).Fundus fluorescein

angiography is Very useful in accurate grading of diabetic retinopathy thus useful in classification of diabetic retinopathy(ETDRS Report No.11). Fundus fluorescein angiography helpful in diagnosis of diabetic maculopathy and classifying it into focal, diffuse and ischaemic maculopathy. FFA is mandatory for treatment of diabetic maculopathy and useful in guiding the treatment of diabetic retinopathy.

Normal fundus finding (fig 1.a) on ophthalmoscopy, diagnosed as Mild NPDR (fig 1.b) on FFA

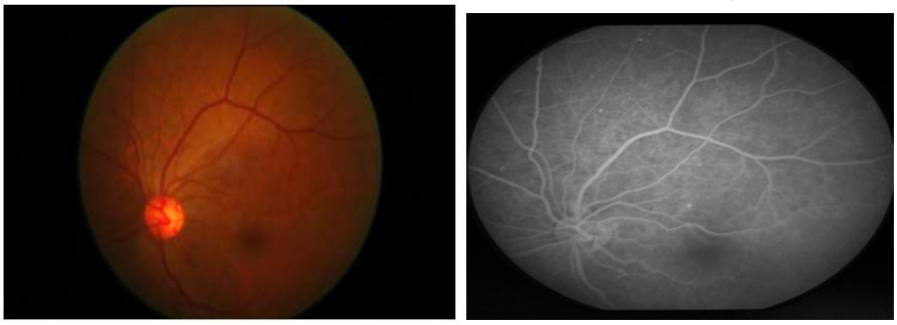

Figure 1a **Figure 1b**

Figure 1a: Normal fundus on Ophthalmoscopy; **Figure 1.b:** Same image shows Mild NPDR on FFA and Shows few microanueurysm (earliest sign of DR) on FFA"

Serve NPDR

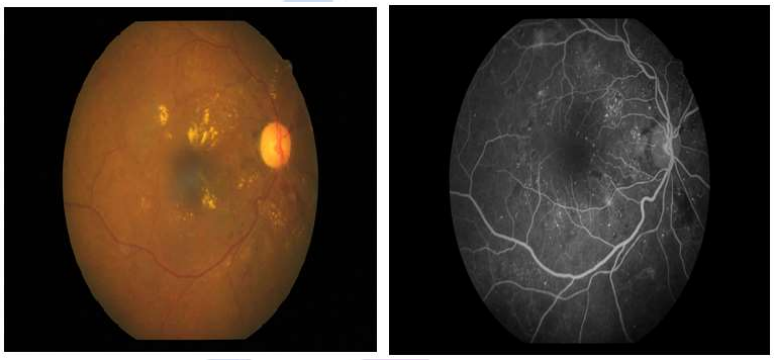

Figure 2.a: Severe NPDR on ophthalmoscopy; **Figure 2.b:** Severe NPDR on FFA

Proliferative diabetic retinopathy

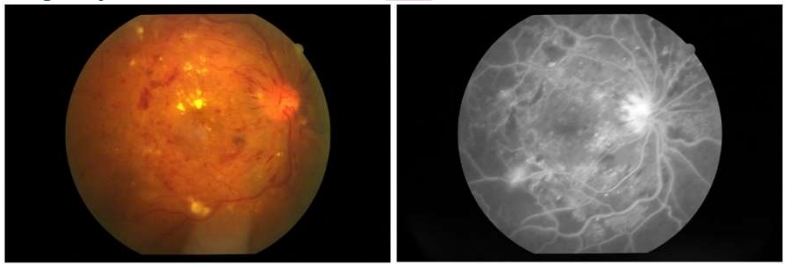

Figure 3.a **Figure 3.a**

Figure 3.a: Proliferative Retinopathy on ophthalmoscopy showing NVD and NVE

Figure 3.b: PDR show profuse leakage at disc and in periphery indicates NVD and NVE.

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