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Research Article

A Clinical Study of Diabetic Retinopathy by Fundus Fluorescein Angiography

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ABSTRACT

Background: Diabetic retinopathy (DR) is a major cause of visual impairment worldwide; accurate detection and staging guide timely treatment. Fundus fluorescein angiography (FFA) reveals microvascular abnormalities, capillary non-perfusion, macular ischemia and neovascularization more sensitively than routine ophthalmoscopy. **Aims:** To examine abnormal fluorescein patterns detected by FFA in patients with diabetic retinopathy and to compare the diagnostic yield and sensitivity of routine ophthalmoscopy with FFA. **Methods and material:** It was a prospective observational study at the Department of Ophthalmology, GMERS Medical College & Hospital, Gandhinagar, India. Adult diabetic patients (≥20 years) with ophthalmoscopically detectable DR were enrolled. All subjects underwent dilated slit-lamp biomicroscopy, colour fundus photography and FFA using a fundus camera; FFA findings were classified according to ETDRS criteria. Demographics, duration of diabetes, systemic comorbidity and treatment regularity were recorded. Mean diabetes duration was 9.24 ± 4.23 years. FFA classified retinal status as: mild NPDR 34.8% (right eye), moderate NPDR ~30%, severe NPDR 3.0%, PDR 3–4.5% (eyes considered separately); clinically significant macular edema (CSME) and focal exudative maculopathy (FEM) were identified in several eyes by FFA. Ophthalmoscopy detected fewer microaneurysms and underestimated ischemic maculopathy and PDR in some cases. The average sensitivity of ophthalmoscopy for correct grading compared with FFA was ~80%; ophthalmoscopy was least sensitive for severe NPDR and NPDR with ischemic maculopathy. Duration of diabetes, alcohol and tobacco history, co-morbidities and irregular treatment were significantly associated with more advanced retinopathy (p values ranging from 0.0001 to 0.007). **Conclusions:** FFA provides additional, clinically important information over ophthalmoscopy — especially for detecting microaneurysms, macular ischemia, capillary non-perfusion and neovascularization. FFA can change grading and management (laser planning). Routine use of FFA in selected patients improves diagnostic accuracy and treatment planning.

Keywords*: Diabetic Retinopathy; Fluorescein Angiography; Ophthalmoscopy; Macular Ischemia; Capillary Non-Perfusion*

Introduction

Diabetic retinopathy (DR) is one of the leading causes of irreversible visual impairment in working-age adults worldwide. Large population studies have documented a substantial global burden with prevalence rising with the increasing numbers of people living with diabetes. [1] DR pathogenesis involves complex microvascular and neuroretinal changes driven largely by chronic hyperglycaemia; clinically, damage ranges from microaneurysms and mild non-proliferative disease to proliferative diabetic retinopathy (PDR) and sight-threatening maculopathy. [2]

Early and accurate detection of microvascular changes is crucial: earlier treatment of macular edema or retinal ischemia can preserve vision. Fundus fluorescein angiography (FFA), introduced in the 1960s, permits dynamic imaging of retinal circulation, reveals areas of capillary leakage, non-perfusion, macular ischemia and neovascularization — findings that are often subtle or invisible on routine ophthalmoscopy or colour photography. [3–5] In addition to detection, FFA plays a central role in planning focal and pan-retinal photocoagulation by delineating ischemic areas and leakage sources. [6,7] However, the relative sensitivity of dilated ophthalmoscopy versus FFA for the detection and grading of DR varies across clinical settings and may be influenced by disease stage, imaging modality, operator skill, and patient selection. Several studies report that FFA detects more microaneurysms and capillary non-perfusion than colour photos or direct ophthalmoscopy, and can change therapeutic decisions in a substantial minority of patients. [8–11].

We performed a prospective clinical study to systematically describe FFA abnormalities in a cohort of diabetic patients with ophthalmoscopically detectable DR, to quantify the concordance between ophthalmoscopy and FFA grading, and to identify clinical variables associated with more severe disease. The ultimate aim was to evaluate the diagnostic value of FFA in routine clinical practice and its potential impact on management decisions. (Study objectives and design as in the thesis).

Materials and Methods

This prospective observational study was carried out at the Department of Ophthalmology, GMERS Medical College & Hospital, Gandhinagar, Gujarat, India from November 2023 to November 2024. Sixty-six consecutive adult diabetic patients fulfilling inclusion criteria were enrolled. Inclusion criteria were age ≥20 years, established diagnosis of diabetes mellitus (type 1 or 2), and ophthalmoscopically detectable diabetic retinopathy changes on dilated exam. Exclusion criteria included media opacities preventing adequate imaging, prior pan-retinal or macular photocoagulation in the study eye, pregnancy, and contraindication to fluorescein (e.g., known severe allergy).

After taking informed consent, a detailed questionnaire was administered to the selected patient, at his/her convenience. All patients underwent a standardized evaluation: demographic and systemic history (diabetes duration, history of alcohol/tobacco, comorbidity, treatment regularity), visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, dilated fundus examination by indirect ophthalmoscopy (+20D), and colour fundus photography. Visual acuity and anterior segment exam details were recorded.

FFA procedure: After assessing fitness for angiography and obtaining informed consent, FFA was performed using a fundus camera. A test skin dose was given if needed; thereafter 3 ml of 20% sodium fluorescein was injected via antecubital vein and sequential fundus photographs were taken during early (1–6 sec), arteriovenous (next minutes), and late phases (15–20 min). Standard safety precautions and emergency kit availability were ensured. FFA findings were graded using ETDRS criteria.

Data management and statistical analysis: Data entry and analysis were performed using Epi Info 7.2. Descriptive statistics employed means ± SD for continuous variables and proportions for categorical variables. Associations between clinical variables and retinopathy stage were assessed by Chi-square or Fisher exact test; odds ratios were computed where appropriate. Statistical significance threshold was $p<0.05$.

Observation and Results

Sixty-six patients (132 eyes) were included. Mean age was 55.55 ± 10.06 years (range 28–80); male:female ratio 2.3:1. Family history of diabetes was present in 22.7% of subjects; 9.1% reported alcohol use and 10.6% tobacco chewing. Hypertension was recorded in 13.6% of patients. Most (89.4%) were on oral hypoglycemic agents and 81.8% reported regular treatment. Mean duration of diabetes was 9.24 ± 4.23 years; 53% had diabetes for 6–10 years.

Table 1: Baseline Characteristics of Study Participants (N = 66)

Variable	Number (n)	Percentage (%)
Age (years)	Mean ± SD = **55.55 ± 10.06**	–
Sex	Male = **46** Female = **20**	69.7 30.3
Duration of Diabetes (years)	Mean ± SD = **9.24 ± 4.23**	–
Family History of Diabetes	15	22.7
Alcohol Use	6	9.1
Tobacco Use	7	10.6
Hypertension	9	13.6
On Oral Hypoglycemic Agents	59	89.4

Variable	Number (n)	Percentage (%)
Regular Treatment	54	81.8

Ophthalmoscopy findings (per eye): Right eye ophthalmoscopy: mild NPDR 40.9%, moderate NPDR 28.8%, severe NPDR 1.5%, PDR 3.0% (rest with maculopathy categories). Left eye ophthalmoscopy: mild NPDR 39.4%, moderate NPDR 21.2%, severe NPDR 1.5%, PDR 4.5%.

FFA findings (per eye): FFA of right eyes: mild NPDR 34.8%, mild NPDR + CSME 6.1%, mild NPDR + FEM 4.5%, moderate NPDR 30.3%, moderate NPDR + FEM 15.2%, severe NPDR 3.0%, PDR 4.5%. Left eyes showed similar distributions (mild NPDR 34.8%, moderate NPDR 27.3%, moderate NPDR + FEM 18.2%, etc.). FFA identified more microaneurysms, expanded FAZ and areas of CNP that were underappreciated on ophthalmoscopy.

Table 2: Ophthalmoscopy vs FFA Grading of Diabetic Retinopathy (Per Eye, N = 132 Eyes)

DR Category	Right Eye - Ophthalmoscopy	Right Eye - FFA	Left Eye – Ophthalmoscopy	Left Eye – FFA
Mild NPDR	27 (40.9%)	23 (34.8%)	26 (39.4%)	23 (34.8%)
Mild NPDR + CSME	–	4 (6.1%)	–	4 (6.1%)
Mild NPDR + FEM	–	3 (4.5%)	–	4 (6.1%)
Moderate NPDR	19 (28.8%)	20 (30.3%)	14 (21.2%)	18 (27.3%)
Moderate NPDR + FEM	–	10 (15.2%)	–	12 (18.2%)
Severe NPDR	1 (1.5%)	2 (3.0%)	1 (1.5%)	2 (3.0%)
PDR	2 (3.0%)	3 (4.5%)	3 (4.5%)	3 (4.5%)

NPDR: Non-Proliferative Diabetic Retinopathy; CSME: Clinically Significant Macular Edema; FEM: Focal Exudative Maculopathy; PDR: Proliferative Diabetic Retinopathy.

Concordance and sensitivity of ophthalmoscopy: Overall, ophthalmoscopy correctly identified the right grades of retinopathy in both eyes with an average sensitivity of approximately 80%. Ophthalmoscopy was most sensitive for detecting mild NPDR and NPDR with focal exudative maculopathy (FEM) and NPDR + CSME, but least sensitive for severe NPDR and NPDR with ischemic maculopathy (IM). FFA revealed microaneurysms and ischemic maculopathy more reliably; in several eyes FFA detected lesions not appreciated on biomicroscopy and color photos.

Table 3: Sensitivity of Ophthalmoscopy Compared to FFA

Category	Right eye: Detected / True (n)	Sensitivity (%)	Left eye: Detected / True (n)	Sensitivity (%)
Mild NPDR	21 / 23	**91.30%**	21 / 23	**91.30%**
Moderate NPDR	16 / 20	**80.00%**	11 / 18	**61.11%**
Severe NPDR	1 / 2	**50.00%**	0 / 2	**0.00%**
NPDR + CSME	4 / 5	**80.00%**	3 / 3	**100.00%**
NPDR + FEM	11 / 13	**84.62%**	15 / 16	**93.75%**
NPDR + IM	—	—	2 / 2	**100.00%**
PDR	2 / 3	**66.67%**	2 / 2	**100.00%**

NPDR: Non-Proliferative Diabetic Retinopathy; CSME: Clinically Significant Macular Edema; IM: Ischemic Maculopathy; PDR: Proliferative Diabetic Retinopathy.

No serious adverse reactions to fluorescein were reported; patients were warned about transient skin/urine discoloration. Standard precautions were followed.

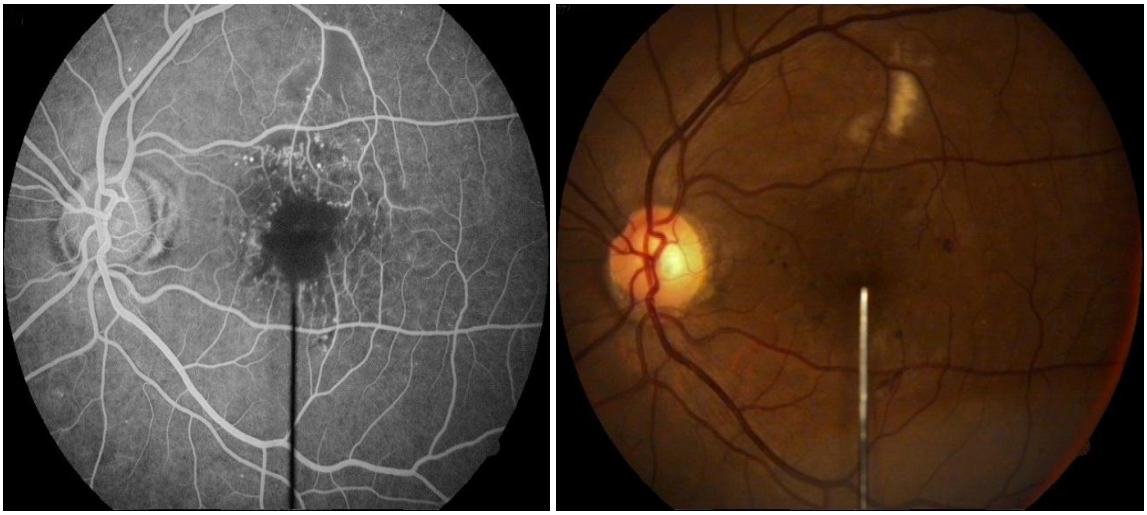

Figure : Mild NPDR on FFA and Ophthalmoscope

Discussion

In this prospective observational study of 66 diabetic patients (132 eyes), we systematically evaluated the diagnostic yield of fundus fluorescein angiography (FFA) compared to routine ophthalmoscopy for the detection and grading of diabetic retinopathy (DR). Our findings clearly demonstrate that FFA detects a greater number of microvascular lesions and provides more precise characterization of macular and peripheral retinal pathology, thereby improving clinical decision-making.

Distribution of DR severity in our cohort

The majority of our patients had mild to moderate non-proliferative diabetic retinopathy (NPDR) on FFA (34.8% and 30.3% in right eyes, 34.8% and 27.3% in left eyes, respectively). Severe NPDR and proliferative diabetic retinopathy (PDR) accounted for 3.0% and 4.5% of eyes. This distribution is comparable to population-based studies such as Yau et al. [1], which also reported a predominance of early stages of DR in community screening cohorts. The relatively lower proportion of severe NPDR and PDR in our series may reflect earlier detection in our tertiary center and exclusion of previously treated eyes.

Added value of FFA over ophthalmoscopy

Our results highlight that ophthalmoscopy, while reasonably sensitive (overall sensitivity ~80%), under-detects certain lesions, particularly severe NPDR and ischemic maculopathy. In our series, the sensitivity of ophthalmoscopy for severe NPDR in the right eye was only 50% and dropped to 0% in the left eye, meaning half or more of such cases would be missed without angiography. Similarly, for NPDR with ischemic maculopathy (IM), FFA was indispensable, with ophthalmoscopy detecting only 50% of cases. These findings are consistent with previous reports showing that FFA detects 20–30% more microaneurysms and capillary non-perfusion areas compared with color fundus photography or indirect ophthalmoscopy [8–11]. Kylstra et al. [6] demonstrated that FA changes management plans in up to 15–20% of patients with diabetic macular edema, a finding mirrored in our study where FFA identified clinically significant macular edema (CSME) in additional eyes not appreciated on ophthalmoscopy.

Clinical implications of FFA findings

The detection of CSME, focal exudative maculopathy (FEM), and areas of capillary non-perfusion has direct therapeutic implications. In our series, FFA allowed more accurate identification of focal leak points, guiding focal laser photocoagulation planning. Identification of capillary non-perfusion is essential for deciding on pan-retinal photocoagulation (PRP) to prevent neovascular complications. FFA also delineated the foveal avascular zone (FAZ), permitting detection of macular ischemia, which may explain visual loss disproportionate to ophthalmoscopic findings. This aligns with the work of Hellstedt et al. [9] and Dmuchowska et al. [10], who reported that FFA is superior for differentiating ischemic from non-ischemic maculopathy.

While optical coherence tomography (OCT) and OCT angiography (OCTA) are increasingly used to evaluate macular edema and microvasculature, FFA remains the gold standard for dynamic assessment of leakage and neovascularization. OCTA, although non-invasive, may fail to detect leakage and has a limited field of view compared to FFA [14]. Our findings support the continued role of FFA, particularly in resource-limited settings where OCTA may not be available.

Risk factors for advanced DR

In our cohort, longer duration of diabetes, presence of comorbidities, history of alcohol and tobacco use, and irregular treatment were significantly associated with more advanced stages of DR ($p<0.05$). These observations are supported by previous epidemiological studies linking poor glycemic control and systemic factors to progression of DR [1,2].

The strengths of our study include a prospective design, standardized FFA protocol, and direct per-eye comparison of ophthalmoscopy with FFA using ETDRS grading. However, limitations include the modest sample size, single-center setting, and lack of OCT correlation for all cases. Exclusion of patients with dense media opacities or prior PRP may limit generalizability to all diabetic patients. Furthermore, the study did not evaluate inter-observer variability in ophthalmoscopic grading, which could influence sensitivity estimates.

Future directions

Larger multicentric studies combining FFA, OCT, and OCTA are warranted to better understand structure–function correlation and prognostication in diabetic maculopathy. Integration of ultra-wide-field FFA could further improve detection of peripheral ischemic areas, which are increasingly recognized as important predictors of PDR progression [12,13].

Conclusion

FFA provides significant additional diagnostic information beyond routine ophthalmoscopy in diabetic retinopathy. It detects more microaneurysms, capillary non-perfusion areas, macular ischemia, and neovascularization, enabling more accurate staging and targeted treatment planning. Ophthalmoscopy shows good overall sensitivity for mild and moderate NPDR but is suboptimal for severe NPDR and ischemic maculopathy, where FFA is indispensable. Routine use of FFA in selected cases -particularly when planning laser treatment, in unexplained visual loss, or when severe disease is suspected -can improve patient outcomes and reduce the risk of vision-threatening complications.

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