Role of Fundus Fluorescein Angiography in Early Diabetic Maculopathy: A Cross-sectional Study

Ghulam Hyder Sahito a≡, Mahtab Alam Khanzada a≡, Azfar Ahmed Mirza a#,
Mona Liza Mahesar a†, Imtiaz Ahmed Gilal a‡ and Urooj Bhatti b¥*

a Institute of Ophthalmology, LUMHS, Jamshoro, Pakistan.
LUMHS, Jamshoro, Pakistan.

Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/JPRI/2022/v34i11A35532

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/81743

ABSTRACT

Aim: To assess the role of fundus fluorescein angiography (FFA) for early detection of diabetic maculopathy.

Study Design: Prospective Cross-sectional study.

Place and Duration: Department of Ophthalmology, unit II Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Hyderabad between March 2020 to March 2021.

Methodology: Diabetic patients above the age of 20 years were screened by visual acuity recording, fundus, slit-lamp examination, and Fundus fluorescein angiography. Complete ophthalmic detail was obtained from each participant using pre-designed Proforma. Outcomes of the study were recorded.

Results: A total of 100 subjects having 200 eyes were observed in the study. There were 53(53%) males and 47(47%) females with a mean age of 54±21.22 years. FFA was done in 124(62%) eyes. Diabetic maculopathy with diabetic retinopathy was higher in moderate nonproliferative diabetic retinopathy (NPDR) 53(42.7%) followed by proliferative diabetic retinopathy (PDR) 22(17.7%).
severe NPDR 20(16.1%), and mild NPDR 08(6.5%). Most of the subjects 79(63.7%) had the diffuse type of leakage followed by focal 33(26.6%) and mixed type of leakage. Best-corrected visual acuity (BCVA), intraocular pressure (IOP), and Central Macular Thickness (CMT) were improved at the 3rd and 6th-month follow-up visit as compared to baseline visit.

Conclusion: Fundus fluorescein angiography (FFA), a diagnostic method of diabetic retinopathy is reliable, more accurate, and precise. Our study recommends that diabetic patients should be regularly screened through FFA to save the precious vision of the diabetic population.

Keywords: Fundus fluorescence angiography; diabetic retinopathy; diagnosis; macular degeneration.

1. INTRODUCTION

Diabetes is a serious health issue in developed as well as in developing countries like Pakistan [1]. Pakistan, at present, stands in the top ten countries in diabetes with a prevalence of 26.3% as reported in the recent second National Diabetes Survey of Pakistan (2016 – 2017) [2]. People with diabetes have a higher chance to become blind than non-diabetics, mainly due to diabetes-induced maculopathy and retinopathy [3]. Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) described that diabetic retinopathy (DR) was present in more than 50% of cases of diabetes. United Kingdom Prospective Diabetes Study (UKPDS) also gave the same results [4,5,6]. In Pakistan, scarce data was found on DR and maculopathy representing between 10.6% and 91.34% for DR [7].

Macula measures 5.5 mm in diameter and it is a round area at the posterior pole. In the center of the fovea, there is a dipped area of 1.5 mm in diameter, called macula [8]. During Fundoscopy macula gives rise to an oval light reflex, while the foveola is the thinnest area of the retina measuring about 0.35 mm in diameter. Outside the foveola, there is a foveal avascular zone [9]. In Diabetic maculopathy there is the involvement of fovea along with edema, hard exudates, or ischemia. Techniques used for screening of DR are slit-lamp biomicroscopy, Fundoscopy, fundus pictures, fundus fluorescein angiography, and optical coherence tomography [10]. FFA detects ischemia, microaneurysms, and intraretinal microvascular abnormalities (IRMA) that are further confirmed on angiogram [11].

There is a marked reduction of visual loss if DR is early detected by FFA [12]. The reduction in glycosylated hemoglobin A1C declines proliferative DR. One percent decline in HbA1c reduces by nineteen percent the eye problems [13]. Proper glycemic control delays dangerous problems of DR. In literature, scarce data was found for search terms of FAZ, aneurysm, and leakage. Very few studies presented FFA findings in diabetic retinopathy. Therefore, this study aimed to present the role of FFA in the early detection of subclinical diabetic maculopathy.

2. METHODOLOGY

This prospective cross-sectional study was designed at the Department of Ophthalmology, unit II Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro/Hyderabad. The duration of the study was one year between March 2020 to March 2021. A convenience sampling technique was used during the study. Diabetic patients above the age of 20 years coming in Eye-OPD were screened by visual acuity recording, slit lamp, and fundus examination and then further evaluated by FFA. A total of 100 diabetic subjects were selected aged 20 years or above with no history of allergic reaction to fluorescein and having a normal renal profile. Participants with opaque ocular media, allergic to Fluorescein, impaired renal function, hypertension, retinal diseases other than diabetes and those participants who were treated with photoocoagulation (macular or Panretinal), intravitreal injections, plana pars vitrectomy, media opacity, venous occlusion, epiretinal membrane, vitreomacular traction were excluded from the study.

Complete ophthalmic detail was obtained from each participant using pre-designed Proforma. It includes a history of eye, ocular examination by Snellen visual acuity was converted to logmar units and assessment of intraocular pressure. One drop of Irop Plus eye (Cipla Ltd. India - Tropicamide-0.8% and Phenylephrine Hcl-5%) was used to dilate pupils of the eye. Fundus examination was done by the anterior segment of the eye. Fundus Fluorescin Angiography (FFA) of affected eye was done using Topcon Retinal camera –GRC 50DX Germany. Before FFA, for half an hour, each subject was given an intradermal test dose of the 20% Sodium
Fluorescein. Radiography was done for 10 to 15 minutes to the accuracy of the examination. The aneurysm size ≤30µm and >30µm was assessed by calibring artery at the superotemporal disc margin (considered as 60µm). The foveal avascular zone (FAZ) size was studied during the arteriovenous phase as compared to optic disc diameter and margin regularity. The presence of focal, diffuse, and mixed leakage was noted. If the leakage occurs from a single aneurysm it is called focal leakage, leakage from dilated capillaries is called diffuse leakage, and from petaloid appearance, leakage is called mixed leakage. Diabetic retinopathy (mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and PDR) and maculopathy (mild, moderate, and severe diabetic macular edema (DME)) were clinically classified and graded based on the National Academic Conference of Fundus Diseases and international classification [14,15]. Best-corrected visual acuity (BCVA) and intraocular pressure (IOP) were measured by using the Snellen visual acuity chart and Goldman applanation tonometry. Central macular thickness (CMT) was analyzed by optical coherence tomography [16].

All these features were analyzed by using a statistical package for social sciences (SPSS) version 20. Chi-square test and paired t-test were used. P-value < 0.05 was called as significant.

3. RESULTS

A total of 100 subjects having 200 eyes was observed in the study. Of 200 eyes, 124(62%) eyes (left eye 73(58.9%) and right eye 51(41.1%)) were selected with diabetic retinopathy for further observations. There were 53(53%) males and 47(47%) females. The mean age of the participants was 54±21.22 years. Only one (1%) subject was between 20–30 years, seven (7%) between 31-40 years, 19(19%) between 41-50 years, 39(39%) between 51-60 years, 23(23%) between 61-70 years and 11(11%) subjects were having more than 70 years. Thirty-nine (39%) subjects were having <5years duration of diabetes and 61(61%) subjects had 5 years or more duration of diabetes. Most of the subjects were having hypertension and dyslipidemia (as shown in Table 1).

Characteristics of the eye is shown in Table 2. Of 124(62%) eyes, 37(29.8%) had phakia and 87(70.2%) had pseudophakia. FFA was done in 124(62%) eyes. Most of the eyes were observed with diffuse maculopathy 79(63.7%) followed by focal maculopathy 33(26.3%) and mixed maculopathy 12(9.7%). Most of the eyes 59(47.6%) had BCVA 6/18 - 6/24 and 41(33.1%) had 6/36 – 6/60. Aneurysm size ≤30µm maculopathy was present in 64(51.6%) eyes, while >30µm aneurysm size was present in 23(18.5%) eyes.

Table 3 presents the frequency of patients with diabetic retinopathy and diabetic maculopathy. Most of the eyes had moderate NPDR 61(49.2%) followed by PDR 26(21%), severe NPDR 22(17.7%), and mild NPDR 15(12.1%). Similarly, diabetic maculopathy in subjects with diabetic retinopathy was also higher in moderate NPDR 53(42.7%) followed by PDR 22(17.7%), severe NPDR 20(16.1%), and mild NPDR 08(6.5%).

Table 4 shows the frequency of margin of FAZ to grades of maculopathy. Of 124 eyes, 93(75%) presented with regular margin of FAZ [mild 11(11.8%), moderate 57(61.3%), severe 25(26.9%)] and 31(25%) with distorted margin of FAZ [mild 07(22.6%), moderate 21(67.7%), severe 03(9.7%)].

Table 5 presented the frequency of leakage to grades of maculopathy. Most of the subjects 79(63.7%) had diffuse type of leakage [mild 13(16.5%), moderate 47(59.5%), severe 19(24.1%)] followed by focal 33(26.6%) [Mild 07(21.2%), moderate 17(51.5%), severe 09(27.3%)] and mixed type of leakage 12(9.7%) [Mild 02(16.7%), moderate 09(75%), severe 01(8.3%)].

Outcomes of changes in BCVA, IOP, and CMT are shown in Table 6. BCVA was significantly improved at 6 months follow up 0.59±0.19 as compared to baseline visit 0.21±0.038. IOP was non-significantly improved at the 3rd and 6th months visit, while CMT was significantly improved at the 3rd and 6th months follow up visit as compared to baseline visit.

4. DISCUSSION

In our study, most of the eyes were observed with diffuse maculopathy followed by focal maculopathy and mixed maculopathy. Diabetic maculopathy in subjects with diabetic retinopathy was higher in moderate NPDR followed by PDR, severe NPDR, and mild NPDR. The frequency of the focal type of leakage was found higher.
compared with diffuse and mixed types of leakage. Collectively, BCVA, IOP, and CMT were improved at the 6-month follow-up as compared to the baseline visit.

Table 1. Baseline characteristics of studied participants

| Parameters                        | N (%), Mean ±SD |
|-----------------------------------|-----------------|
| Number of participants            | 100             |
| Total number of eyes              | 200             |
| Number of eyes affected           | 124             |
| Gender                            |                 |
| Males                             | 53(53%)         |
| Females                           | 47(47%)         |
| Age (years)                       |                 |
| 20-30                             | 01(1%)          |
| 31-40                             | 07(7%)          |
| 41-50                             | 19(19%)         |
| 51-60                             | 39(39%)         |
| 61-70                             | 23(23%)         |
| >70                               | 11(11%)         |
| Duration of diabetes              |                 |
| <5 years                          | 39(39%)         |
| ≥5 years                          | 61(61%)         |
| Laterality                        |                 |
| OD: Right eye                     | 51(41.1%)       |
| OS: Left eye                      | 73(58.9%)       |
| Risk factors                      |                 |
| Hypertension                      | 79(79%)         |
| Dyslipidemia                      | 74(74%)         |
| Smoking                           | 11(11%)         |
| Nephropathy                       | 08(8%)          |

Data presented as n (%); mean±SD

Table 2. Characteristics of the eye of study participants

| Characteristics of eye                   | No. of eyes |
|-----------------------------------------|-------------|
| Total no. of eyes affected              | 124         |
| Lens status N (%)                       |             |
| Phakia                                  | 37(29.8%)   |
| Pseudophakia                            | 87(70.2%)   |
| Maculopathy                             |             |
| Focal                                   | 33(26.6%)   |
| Diffuse                                 | 79(63.7%)   |
| Mixed (Ischemic + exudates)             | 12(9.7%)    |
| Fundus Fluorescein Angiography          |             |
| No                                      | 76(38%)     |
| Yes                                     | 124(62%)    |
| Best-corrected visual acuity (BCVA)     |             |
| 6/6 – 6/12                              | 18(14.5%)   |
| 6/18 – 6/24                             | 59(47.6%)   |
| 6/36 – 6/60                             | 41(33.1%)   |
| >6/60                                   | 06(4.8%)    |
| Size of an aneurysm to maculopathy     |             |
| ≤30µm non-maculopathy                  | 28(22.6%)   |
| >30µm non- maculopathy                 | 09(7.3%)    |
| ≤30µm maculopathy present              | 64(51.6%)   |
| >30µm maculopathy present              | 23(18.5%)   |

Data presented as n (%)
**Table 3. Grades of diabetic retinopathy and diabetic maculopathy**

| Grades of dr | Diabetic retinopathy | Diabetic maculopathy |
|--------------|----------------------|----------------------|
| Mild NPDR    | 15(12.1%)            | 08(6.5%)*            |
| Moderate NPDR| 61(49.2%)            | 53(42.7%)*           |
| Severe NPDR  | 22(17.7%)            | 20(16.1%)            |
| PDR          | 026(21%)             | 22(17.7%)            |

Data presented as n (%); *indicate p-value <0.05 statistically significant.

**Table 4. Presence of maculopathy and the foveal avascular zone (FAZ) grades of maculopathy**

| Margins          | Characteristics | Regular | Distorted | Total |
|------------------|-----------------|---------|-----------|-------|
| Maculopathy      | Absent          | 59(77.6%)* | 17(22.4%) | 76(38%) |
|                  | Present         | 93(75%)*  | 31(25%)   | 124(62%) |
| **FAZ to grades of maculopathy** | Mild | 11(11.8%) | 07(22.6%) | 18(14.5%) |
|                  | Moderate        | 57(61.3%)* | 21(67.7%) | 78(62.9%) |
|                  | Severe          | 25(26.9%)* | 03(9.7%)  | 28(22.6%) |

Data presented as n (%); *indicate p-value <0.05 statistically significant.

**Table 5. Presence of maculopathy and leakage to grades of maculopathy**

| Leakage Type | Characteristics | Diffuse | Focal | Mixed (Ischemic + exudates) | Total |
|--------------|-----------------|---------|-------|-----------------------------|-------|
| Maculopathy  | Absent          | 16(21.1%) | 57(75%) | 03(3.9%) | 76(38%) |
|              | Present         | 79(63.7%) | 33(26.6%)* | 12(9.7%) | 124(62%) |
| **Leakage type to grades of maculopathy** | Mild | 13(16.5%) | 07(21.2%) | 02(16.7%) | 22(17.7%) |
|              | Moderate        | 47(59.5%) | 17(51.5%) | 09(75%) | 73(58.9%) |
|              | Severe          | 19(24.1%) | 09(27.3%)* | 01(8.3%) | 29(23.4%) |

Data presented as n (%); *indicate p-value <0.05 statistically significant.

**Table 6. Outcomes of changes in BCVA, IOP, and CMT**

| Characteristics | Baseline     | 3" Month    | 6" Month |
|-----------------|--------------|-------------|----------|
| BCVA            | 0.21±0.038   | 0.37±0.14   | 0.59±0.19* |
| IOP (µm)        | 13.7±0.8     | 14.6±1.7    | 16.5±2.4  |
| CMT (mmHg)      | 583.06±43.3  | 276.12±32.16| 201.15±61.24* |

Best-corrected visual acuity (BCVA), Intraocular pressure (IOP), Central macular thickness (CMT). Data presented as mean ± SD; *indicate p-value <0.05 statistically significant.

In our study diabetic maculopathy was assessed by FFA. This method is used for many decades for the evaluation of retinal vasculature. Although currently OCT is also used for detecting diabetic maculopathy FFA remains the gold standard for the evaluation of retinal vascular abnormalities [17]. Our study is consistent with Rajappa A.S et al who also used fluorescein angiography to diagnose macular disorders and further categorize diabetic maculopathy. He further confirmed that FFA plays an important role in the clinical diagnosis and management of maculopathy [18]. However, a previous study by Wykes et al reported that only 40% of diabetic maculopathy cases can be confirmed by using FFA [19].
Our study is unique to present FFA in diabetic maculopathy in this part of the world thus highlighting the strength of our research. In our study, diffuse leakage was higher similar to Mehoob et al study observed diffuse leakage as a common finding [20]. Syed SH et al also found an increased prevalence of diffuse leakage of maculopathy in people with diabetic retinopathy followed by facial and ischemic types of leakage [21]. However, a recent study by Rasquinha et al found a high frequency of the focal type of leakage unlike our study and other previous ones [15]. We also observed functional improvement in BCVA, IOP, and CMT at six months follow up which is a good achievement in our resource constraint society similar to recent study findings on diabetic macular edema [16]. Most of the participants had diabetes-associated risk factors such as hypertension and dyslipidemia which are major causes of developing eye complications and should be treated earlier. We did not find the association of FFA with age, gender, and duration of diabetes as previous studies reported no significant association with these kinds of parameters. However, most of our study subjects were males, had average age between 51-60 years, and had five years or more duration of diabetes similar to previous studies [17].

For FAZ visualization, the disruption spectrum involving the FAZ includes FAZ area or diameter enlargement, disruption, and widening of terminal vessels [12]. Screening program should be developed for the early detection of diabetic maculopathy, as a vision of diabetic patients can be saved. With the advancement of technology, digital photography with telemedicine should also be promoted [12]. A study limitation was consistent with the small sample size in the large population, resulting in no correlation between FFA with OCT, which is mostly used to quantify macular edema.

5. CONCLUSIONS

FFA, a diagnostic method of diabetic retinopathy is reliable, more accurate, and precise. Our study highly recommends the screening of diabetic patients in the early stages through FFA to save the precious vision of the diabetic population.

CONSENT

Each selected participant was pre-informed and written informed consent was taken.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the ethics committee of LUMHS.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Akhtar S, Nasir JA, Abbas T, Sarwar A. Diabetes in Pakistan: a systematic review and meta-analysis. Pakistan journal of medical sciences. 2019;35(4):1173.
2. Riaz Z, Ali MN, Qureshi Z, Moin M. In vitro investigation and evaluation of novel drug based on polyherbal extract against type 2 diabetes. Journal of Diabetes Research. 2020 Mar 19; 2020.
3. Pandova MG. Diabetic retinopathy and blindness: An epidemiological overview. Visual Impairment and Blindness-What We Know and What We Have to Know; 2019 Aug 19.
4. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology. 2009;116(3):497-503.
5. Tah V, Mall S, Myerson C, Saha K, Emsley E, Swampillai A, Ramsamy G, Hanumunthadu D, Bindra M. Diabetic retinopathy—an update on pathophysiology, classification, investigation, and treatment. Ophthalmo Curr Clin Res Updates; 2014 Sep 3.
6. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye and vision. 2015;2(1):1-25.
7. Mumtaz SN, Fahim MF, Arslan M, Shaikh SA, Kazi U, Memon MS. Prevalence of diabetic retinopathy in Pakistan. A systematic review. Pakistan Journal of Medical Sciences. 2018;34(2):493.
8. Kolb H, Nelson R, Fernandez E, Jones B. The organization of the retina and visual system. Anatomy and Physiology of the retina. University of Utah Health Science Center: Webvision; 2013.
9. Chui TY, Zhong Z, Song H, Burns SA. Foveal avascular zone and its relationship to foveal pit shape. Optometry and Vision Science. 2012;89(5):602.
10. Salz DA, Witkin AJ. Imaging in diabetic retinopathy. Middle East African Journal of Ophthalmology. 2015;22(2):145.
11. Amato A, Nadir F, Borghesan F, Cicinelli MV, Chatziralli I, Sadik S, Mirza R, Bandello F. Widefield Optical Coherence Tomography Angiography in Diabetic Retinopathy. Journal of Diabetes Research. 2020 Nov 24.2020.
12. Hautala N, Aikkila R, Korpelainen J, Keskitalo A, Kurikka A, Falck A, Bloigu R, Alanko H. Marked reductions in visual impairment due to diabetic retinopathy achieved by efficient screening and timely treatment. Acta ophthalmologica. 2014;92(6):582-7.
13. Zhang B, Zhang B, Zhou Z, Guo Y, Wang D. The value of glycosylated hemoglobin in the diagnosis of diabetic retinopathy: a systematic review and Meta-analysis. BMC Endocrine Disorders. 2021;21(1):1-1.
14. Wang S, Zuo Y, Wang N, Tong B. Fundus fluorescein angiography in diagnosing diabetic retinopathy. Pakistan Journal of Medical Sciences. 2017;33(6):1328.
15. Rasquinha DA, Bappal DA, Arunachalam DC. Fundus fluorescein angiography in diabetic retinopathy: correlation of angiographic findings to the clinical maculopathy. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). 2016;15(2):80-88.
16. Sultan S, Shakeel A, Waris N, Bano S. Early visual recovery in patients with diabetic macular edema after giving intravitreal injection avastin and posterior subtenon triamcinolone. Annals of King Edward Medical University. 2021 Jul 8;27(2).
17. Eldaly Z, Soliman W, Sharaf M, Reyad AN. Morphological characteristics of normal foveal avascular zone by optical coherence tomography angiography. Journal of Ophthalmology. 2020 Aug 19.2020.
18. Rajappa S, Molleti DCN, Donepudi G, Kudache J. Role of fundus fluorescein angiography in macular disorders. International Journal of Biomedical Research. 2014;5:636-71.
19. Wykes WN, Livesey SJ. Review of fluorescein angiograms performed in one year. Br J Ophthalmol. 1991;75:398-400.
20. Mehboob Q, Hussain Z, Arif M. Diagnosis of diabetic macular edema (DME) based on fundus fluorescein angiography (FFA) findings. Journal of University Medical & Dental College. 2015;6(1):28-32.
21. Syed SH, Arif M, Saleem F. Incidence of angiographic patterns of diabetic maculopathy. A.P.M.C. 2009;3:148-151.