Original Research Article

Role of fundus fluorescein angiography in early diabetic maculopathy: A cross sectional study

Abstract

AIM: To assess the role of fundus fluorescein angiography (FFA) for early detention 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 Performa. Outcomes of the study were recorded.

Results: Total of 100 subjects having 200 eyes were 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 with mean age of 54±21.22 years. FFA was done in 124(62%) eyes. Diabetic maculopathy in subjects 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 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 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 in order to save precious vision of diabetic population.

Keywords: Fundus fluorescein angiography, diabetic maculopathy, retinopathy, intraocular pressure, Central Macular Thickness

Introduction

Diabetes is a serious health issue in developed as well as in developing countries like Pakistan.(1) Pakistan, at present, stands at top ten countries in diabetes with a prevalence of 26.3% as reported in recent second National Diabetes Survey of Pakistan (2016 – 2017).(2) People with diabetes have 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% cases of diabetes. United Kingdom Prospective Diabetes Study (UKPDS) also gave the same results.(4,5,6) In Pakistan, scarce of data was found on DR and maculopathy, representing between 10.6% and 91.34% for DR.(7)

~~In Diabetic maculopathy there is involvement of fovea along with oedema, hard exudates or ischemia.~~ Macula measures 5.5 mm in diameter, and it is a round area at the posterior pole. In the center of 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 foveola is the thinnest area of

retina measuring about 0.35 mm in diameter. Outside the foveola there is a foveal avascular zone.(9) In Diabetic maculopathy there is involvement of fovea along with edema, hard exudates or ischemia. Techniques used for screening of DR are slit lamp bio microscopy, Fundoscopy, fundus pictures, fundus fluorescein angiography and optical coherence tomography.(10) FFA detects ischemia, micro aneurysms, and intraretinal microvascular abnormalities (IRMA) that is further confirmed on angiogram.(11)

There is 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 problem of DR. ~~Although,~~ In literature, scarce of 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 for early detection of sub clinical diabetic maculopathy.

Methodology:

This prospective cross-sectional study was designed at 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. Each selected participant was pre-informed and written informed consent was taken. Ethical approval for the study was obtained from the ethics committee of LUMHS. 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 normal renal profile. Participants

with opaque ocular media, allergic to Fluorescein, ~~deranged~~ impaired renal function, hypertension, retinal diseases other than diabetes, and those participants who were treated with photocoagulation (macular or Panretinal), intravitreal injections, plana pars vitrectomy, media opacity, venous occlusion, epiretinal membrane, and vitreomacular traction were excluded from the study.

Complete ophthalmic detail was obtained from each participant using pre-designed Performa. It includes history of eye, ocular examination by Snellen visual acuity ~~was~~ converted to logmar units, and assessment of intraocular pressure. One drop of Itrop Plus eye (Cipla Ltd. India - Tropicamide-0.8% and Phenylephrine H~~c~~Cl-5%) was used to dilate pupils of eye. Fundus examination was done by the anterior segment of eye. Fundus Fluorescein Angiography (FFA) of affected eye was done using Topcon Retinal camera –GRC 50DX Germany. Prior to 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 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. Presence of focal, diffuse, and mixed leakage was noted. If the leakage occurs from a single aneurysm, it is called focal leakage; a leakage from dilated capillaries is called diffuse leakage, and ~~from~~ a petalloid 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 National Academic Conference of Fundus Diseases and international classification.(14,15) Best corrected visual acuity (BCVA), and ~~interocular~~ intraocular pressure (IOP) were measured by using Snellen visual acuity chart,

and Goldman applanation tonometry. Central macular thickness (CMT) was analyzed by optical coherence tomography.(16)

All these features were analyzed ~~for~~ by using 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.

Results

Total of 100 subjects having 200 eyes were 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. Mean age of the participants was 54±21.22 years. Only ~~01~~ one (1%) subject was between 20-30years, ~~07~~ seven (7%) between 31-40years, 19(19%) between 41-50years, 39(39%) between 51-60years, 23(23%) between 61-70years, and 11(11%) subjects were having more than 70years. Thirty-nine (39%) subjects were having <5years duration of diabetes and 61(61%) subjects have 5years or more duration of diabetes. Most of the subjects were having hypertension and dyslipidemia (as shown in Table 1).

Characteristics of eye are 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 ~~6th months~~ 6-month follow-up 0.59±0.19 as compared to baseline visit 0.21±0.038. IOP was non-significantly improved at 3rd and 6th months visits, while CMT was significantly improved at 3rd and 6th months follow-up visits as compared to 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)	54±21.22
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 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 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: Frequency of patients with diabetic retinopathy and diabetic maculopathy

GRADES OF DR	DIABETIC RETINOPATHY N (%)	DIABETIC MACULOPATHY N (%)
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: Frequency of margin of foveal avascular zone (FAZ) to 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: Frequency of 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**	**3rd Month**	**6th 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.

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. Frequency of focal type of leakage was found higher compared with diffuse and mixed type of leakage. Collectively, BCVA, IOP and CMT were improved at ~~6~~th ~~months~~ 6-month follow-up as compared to baseline visit.

In our study, diabetic maculopathy was assessed by FFA. This method is used for many decades for evaluation of retinal vasculature. Although ~~currently~~ OCT is also currently used for detecting diabetic maculopathy, ~~but~~ FFA ~~is~~ still remains the gold standard for the evaluation of retinal vascular abnormalities. (17) Our study ~~inconsistent~~ is consistent with Rajappa A.S et al, who also used fluorescein angiography to diagnose macular disorders and further categorizing 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% diabetic maculopathy cases can be confirmed by using FFA.(19)

To our knowledge, our study is unique to present FFA in diabetic maculopathy in this part of the world, ~~is our~~ thus, high lightening the strength of our research. In our study, diffuse leakage was higher, similar to Mehboob et al study who observed diffuse leakage as common finding.(20) Syed SH et al also found increased prevalence of diffuse leakage of maculopathy in people with diabetic retinopathy, followed by ~~facal~~ focal and ischemic types of leakage.(21) However, a recent study by Rasquinha et al found high frequency of focal type of leakage, unlike ~~to~~ our study and other previous ~~studies~~ ones.(15) We also observed functional improvement in BCVA, IOP and CMT at ~~sixth~~ ~~months~~ 6-month 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 ~~have~~ had diabetes-associated risk factors such as hypertension and dyslipidemia, which are ~~a~~ 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, and no significant association with these kinds of parameters. However, most of our study subjects were males, had average age between 51-60 year and 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 programme should be developed for the early detection of diabetic maculopathy, as vision of diabetic patients can be saved. With advancement of technology, digital photography with telemedicine should also be promoted.(12)

~~With small sample size in large population, we did not find the correlation between FFA with OCT which is mostly used to quantify macular edema is our limitation.~~

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.

Conclusions

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

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