

Comparative Study of Diabetic Retinopathy by Means of Clinical Evaluation of Fundus and Fundus Fluorescein Angiography among Diabetic Patients Less than 10 Years of Diabetic Age

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ABSTRACT

Introduction: Diabetic retinopathy is one of the leading causes of blindness. Up to 21% of patients with type 2 diabetes have retinopathy at the first diagnosis of diabetes and most develop some degree of retinopathy over time. Study objectives were to study diabetic Retinopathy clinically and angiographically, retinal changes in various duration of diabetes, observe the different stages of retinopathy and their analysis and to observe the advantages of fluorescein angiography

Material and methods: This analytical study was performed in Krishna Hospital, Karad for a period of 18 months. The fundus examination was done with indirect ophthalmoscope, 90D/78D lens after pupillary dilatation with a combination of phenylephrine and tropicamide eyed drops, and FFA was done

Result: The material for the present study consists of 100 diabetic patients who attended the outpatient department of, or who were admitted in Krishna Hospital, Karad

Conclusion: In patients less than 5 years of diabetic age or those who are at early stage of diabetic retinopathy, we observed that early pathological changes which could not be seen on ophthalmoscopy were evident on FFA. So by Early detection of diabetic retinopathy we can help to stop further progression of retinopathy. FFA is a better diagnostic tool for diagnosing retinopathy as compared to ophthalmoscopy.

Keywords: Diabetic Retinopathy, Clinical Evaluation of Fundus and Fundus, Fluorescein Angiography, Diabetic Patients, 10 Years of Diabetic Age

INTRODUCTION

The prevalence of diabetes among the population is varied and different in different parts of the world. In India it has been reported from 4-28%.^{1,2} 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 diabetic retinopathy is the duration of diabetes. For insulin dependent diabetes mellitus (IDDM) virtually there is no clinically apparent retinopathy for 4-5 years after the initial diagnosis of diabetes mellitus.

After 5-10 years, 25-30% develop some retinopathy while after 10-15 years it will be observed in 75-95% of patients.

After 20-25 years proliferative diabetic retinopathy is observed in 18-40% of patients. PDR is rare before 10 years and is unknown before 5 years duration of diabetes. In NIDDM Yanko and others have reported NPDR prevalence of 23% 10-13 years after the diagnosis of diabetes and

60% 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 41.7% and PDR in 10.3% of patients.

MATERIAL AND METHODS

A diagnostic cross sectional study was conducted in a tertiary care hospital and teaching institute in western Maharashtra. (Krishna Institute of Medical Sciences, Karad) between November 2016 – May 2018. 100 patients were included in our study i.e. 200 eyes were studied.

Source of Data and Data Collection: Diabetic patients of less than 10 years of diabetic age coming to the ophthalmology OPD and admitted in the wards of the parent medical college were included. An informed written consent of the patient was taken and proforma of study was explained to the patients. The data was collected using a pre-evaluated semi structured questionnaire. Demographic profile of the patients including age, gender was undertaken. History of the patients was taken and the examination was done. Required laboratory investigations were also done.

Patients were categorised as-

1. Patients of 0-1 year of diabetes
2. Patients of 1-5 year of diabetes
3. Patients of 5-10 year of diabetes

Inclusion criteria

1. Patients less than 10 years of diabetic age
2. Patients aged > 18 years

Exclusion criterion

1. Patients with Type 1 Diabetes Mellitus
2. Patients who are known cases of Hypertension
3. Patients suffering from Nephropathy
4. Patients of more than 10 year of diabetic age
5. Treated diabetic retinopathy patients with

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photocoagulation or any other surgeries

Ocular examination included

- Visual acuity assessment.
- Anterior segment examination
- Posterior segment examination includes vitreous and retinal examination

Visual acuity was recorded and retinoscopy was done in all the cases. Blood glucose and urine examination for albumin and sugar was done in all cases and recorded.

The initial examination was started with fundus examination with direct ophthalmoscope after pupillary dilatation with a combination of phenylephrine and tropicamide eye drops e.g. Tropicacyl plus eyedrops). Due care was taken to rule out hypertension in the patient before administration of this eyedrops to avoid cardiovascular complications.

The study of diabetic changes in the fundus was performed by non-invasive techniques like direct ophthalmoscopy, indirect ophthalmoscopy and slit lamp biomicroscopy using +90D Volk lens. keeler direct ophthalmoscope, Appasamy Wireless indirect ophthalmoscope with +20D Volk lens and topcon slit lamp along with +90D Volk lens were used throughout the study.

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, the procedure, and the possible adverse reactions, which are likely to occur during or immediately after the procedure. He was explained about the management of the likely adverse effect also.

Informed consent was taken from the patient. 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 eyedrops of a combination of tropicamide and phenylephrine (e.g. tropicacyl plus). The procedure was carried out during the outpatient department working hours of Krishna institute of medical sciences, Karad so that we could get the medical assistance of other specialists in the event of any untoward effects during the procedure.

For doing FUNDUS PHOTOGRAPHY and fundus fluorescein angiography, TOPCON TRC NW8F NON MYDRIATIC RETINAL CAMERA was used.

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 to loss of focus eventually leading to poor quality photographic frames. Sometimes an assistant was requested to fix the patient's head in order to prevent the involuntary movements of patient's head. On aiming and focussing the camera on the area of primary interest the patient was asked to fix the gaze by looking at the target (A red fixation light which is the part of fundus camera system). First patient's identification (name, IP/OP number)

photograph was taken. 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.

The fluorescein dye was injected into the antecubital vein and serial pictures were taken. All through the procedure, the patient's pulse and general condition was monitored and any reaction was attended to and noted. After the procedure the patient was made to lie down and relax for 15 to 30 minutes. He was also explained about the change in the color of urine and skin. The patient was asked to attend the outpatient department later on a specific date for the report.

The findings were recorded in the case sheet of the patient

The features, which were observed, were

- Presence of microaneurysms
- Presence of retinal edema
- Presence of capillary dropouts
- Presence of IRMA
- Presence of new vessels, Presence of maculopathies.-focal, diffuse or/and exudative

Early Treatment Diabetic Retinopathy Study (ETDRS) criteria was used for classifying Diabetic retinopathy

RESULTS

The material for the present study consists of 100 diabetic patients who attended the outpatient department of, or who were admitted to Krishna institute of medical sciences, Karad during the period from November 2016 to may 2018.

Age and sex - The study had most of patients from the age group of 51 -60 years (48%). There were 28% more than 60 years and 24% who belonged to 40-50 years of age. The mean age was 55.89 ± 6.10 years. Out of total 100 patients, there were 56% males and 44% females. The ratio was 1.27- Males: Females.

Duration - The study had majority 35% who suffered from diabetes < 1 year. There were 33% who had diabetes for 1-5 years and 32% had diabetes for 5-10 years duration. The mean diabetic age was 3.92 ± 3.00 years.

Glycemic control - Out of all the patients under our study, we had majority of the patients 67% with poor glycemic control, and rest 33% had good glycemic control. Mean of the HbA1c level was 7.02 ± 1.03 . In our study, we found majority 65% were having fasting blood sugar (FBS) levels >126 mg/dl, while few cases 14% with levels < 100, and rest 21% with FBS levels of 100 to 125 mg/dl. The mean FBS level was 141.72 ± 37.68 mg/dl. Our study witnessed majority (72%) cases were having Post Prandial blood sugar (PPBS) levels ≥ 200 mg/dl, while few cases (9%) with levels < 140, and rest (19%) cases with PPBS levels of 140 to 199 mg/dl. The mean PPBS level was 218.14 ± 59.67 mg/dl.

Visual acuity - In our study 51.5% eyes had visual impairment between 6 / 18 – 6 / 60, 40% eyes with no impairment and 17% eyes with severe visual impairment.

Ophthalmoscopy findings - In our study, we had majority 52% cases had no diabetic retinopathy and out of rest 48%

Ophthalmoscopy Findings		Ophthalmoscopy	FFA	P value*
No DR*		104 (52%)	94 (47%)	
Any DR		96 (48%)	106 (53%)	P = 0.317
	Mild NPDR	7 (3.5%)	16 (8%)	P = 0.045**
	Moderate NPDR	36 (18%)	31 (15.5%)	P = 0.864
	Severe NPDR	48 (24%)	51 (25.5%)	P = 0.511
	PDR	5 (2.5%)	8 (4%)	P = 0.326
Total		200 (100%)	200 (100%)	
*P values when compared with No any type of Diabetic Retinopathy. ** Significant				
Table-1: Comparison of Diabetic retinopathy findings on Ophthalmoscopy and FFA:				



Figure-1a: No changes seen on funduscopy

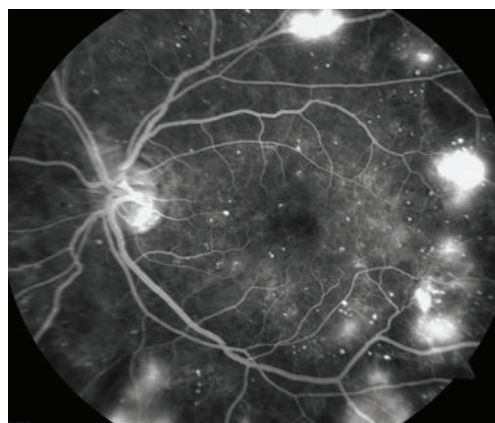


Figure-2b: NVE seen in periphery in FFA



Figure-1b: Few microaneurysms seen on FFA



Figure-2a: Only dot and blot hemorrhages seen

FFA findings - On FFA findings, 47% of cases had no retinopathy, the rest 53% had retinopathy. There were 15.5% with moderate NPDR, 25.5% with severe NPDR and 8% with mild NPDR. Proliferative retinopathy seen in 4% cases. Out of total 200 cases, on ophthalmoscopy, 96 cases (48%) were found to have Diabetic retinopathy, while on FFA 106 cases (53%) were found to have Diabetic retinopathy. These additional 5% cases were diagnosed on FFA. There was not a single case diagnosed as not having any Diabetic retinopathy on FFA which showed changes of Diabetic retinopathy on Ophthalmoscopy.

The table-1 shows similar findings of diabetic retinopathy on both ophthalmoscopic and FFA findings. The patients were divided into having retinopathy and absence of retinopathy by both the tests, almost always. The statistical test showed agreement to be 93.5% and kappa value was 0.88 which is referred to as strong agreement.

On ophthalmoscopy we found 96 eyes (48%) having any kind of Diabetic retinopathy, while on FFA, we found 106 eyes (53%) with Diabetic retinopathy. Mild NPDR was seen in 7 eyes (3.5%) in ophthalmoscopy while on FFA total 16 (8%) eyes had shown mild NPDR. Similarly severe NPDR was found in 48 (24%) eyes on ophthalmoscopy while on FFA, severe NPDR was seen in 51(25.5%) eyes. In case of PDR, 5 (2.5%) eyes were diagnosed as PDR on ophthalmoscopy while on FFA, we found 8 (4%) eyes of PDR. Only in case of Moderate NPDR, on ophthalmoscopy we found more cases as compared to FFA, 36 eyes (18%) and 31 eyes (15.5%) respectively. When we compared the association between absence of diabetic retinopathy and the types of retinopathy, we found significant association with the mild NPDR (p = 0.045), while there was no any significant association with

cases, there were 24% who had severe NPDR and 18% had moderate NPDR and 3.5% who had mild NPDR. Proliferative diabetic retinopathy was observe in 2.5% cases.

moderate NPDR ($p = 0.864$), severe NPDR ($p = 0.511$) or PDR ($p = 0.326$) as given in table no 1.

As we can see in figure 1a there are no diabetic retinopathic changes on fundoscopy but they are very well seen on FFA in figure 1b and also in figure 2a there are no NVE seen but they are visible on FFA (figure 2b).

Role of age, duration of diabetes on fundus findings

In our study we found out that there is strong association between age of the patient, duration of diabetes. P value was highly significant in both.

DISCUSSION

The World Health Organization (WHO) has estimated that, the number of adults with Fundus disorders in the world would increase alarmingly. Globally, it is estimated that there are 38 million people who are blind. In India: 9 million people are blind which comes to one fifth of the total in the world. (Approx. 8-9 blind people/ 1000 population) The prevalence of blindness in India, as determined by the three major population based surveys and one rapid assessment of avoidable blindness are as follows 1.38% in ICMR (1971 - 74), 1.49% in WHO-NPCB (1986-89), 1.1% in NPCB (2001-2002), 1% in RAAB (2006-2007). The prevalence of blindness due to posterior segment diseases in India was 4.7% of total blindness according to national survey (NPCB) of 2001-2002 and 3% of total blindness as per the rapid assessment of avoidable blindness (RAAB) 2006-07 survey. The trend of retinal blindness has changed its pattern over the years in developing countries. Diabetic retinopathy and ARMD are becoming one of the major causes of blindness.⁵⁻¹¹ The current study was planned to see for the diagnostic capacity of ophthalmoscopy and FFA in diagnosing the diabetic retinopathy findings as everywhere both facilities might not be available. So to see and provide better option for diagnosing the diabetic retinopathy. Diabetic maculopathy is an obvious finding even on direct ophthalmoscopic examination. We did not include the same in our study as we compared our clinical findings with ETDRS for staging of retinopathy and study diabetic maculopathy was not an objective of our research.

The study had most of the participants from the age group of 51 to 60 years with mean of 55.89 ± 6.10 years. Ramsevak V. et al¹², had higher age group and mean age was 72.1 years. While in Sumi S. et al²⁶, had younger age group and mean age was 52.9 years. Mulgund, et al¹³ had comparable age group of 55.65 years as in our study. SS Khalaf et al¹⁴ had mean age of 54.91 years similar to our study.

Majority that is 56%. patients were males And females were 44%. Similar findings were found in Mulgund et al¹³ study, but Gonzalez Villalpando C et al¹⁵ had more number of females as compared to males. SS Khalaf et al¹⁴ had equal number of males and females.

There were 35%, 33%, 32% with 0-1 year and 1-5 years and 5-10 years of diabetic age and the mean was 3.92 ± 3.00 years. The study by Mulgund et al¹³, had more patients (48%) who had 6-10 years of diabetes but there were less percent (20%) patients with 2-5 years of diabetic age as compared to our

study. The study by Sumi S et al²⁶, Gonzalez Villalpando C et al¹⁵ and Ramsevak V. et al¹² had higher diabetic age and mean was 10.7 years, 12.3 years, 11 years respectively. SS Khalaf et al¹⁴ also had higher diabetic age (duration of diabetes) and the mean was 11.57 years and standard deviation of 5.18.

In our study, we had 67% patients who had poor glycemic control, while remaining 33% patients had good glycemic control. In our study, we found majority (65%) of the cases were having deranged fasting blood sugar levels (>126 mg/dl), while few cases (14%) had levels < 100 , and rest (21%) had FBS levels of 100 to 125 mg/dl. Our study witnessed majority (72.00%) of the cases had deranged Post Prandial blood sugar levels (≥ 200 mg/dl), while few cases (9%) had levels < 140 , and rest (19%) had PPBS levels of 140 to 199 mg/dl. In our study, the mean HbA1c, FBS and PPBS levels were 7.02 ± 1.03 , 141.72 ± 37.68 mg/dl and 218.14 ± 59.67 mg/dl respectively.

Different studies have shown that early pathological changes of the retina mainly manifest as microangiopathies.¹⁶⁻¹⁸ Small haemorrhages and microaneurysms on the Retina cannot be accurately determined by direct ophthalmoscopy as well as indirect ophthalmoscopy which can be detected by FFA. FFA is a novel examination method in practice currently. Using FFA, the state and blood circulation of the retinal vessels can be accurately diagnosed by observing the state of fluorescein in blood circulation.¹⁹ Parallel findings were seen in our study, where FFA has diagnosed 10 cases (5%) more than ophthalmoscopy to be having Diabetic retinopathy.

We found out that 7 (3.5%) mild NPDR cases were seen on Ophthalmoscopy, while on FFA, 16 (8%) mild NPDR cases were seen, similarly severe NPDR findings were seen in 48 eyes (24%) and 51 eyes (25.5%) while PDR findings were seen in 5 eyes (2.5%) and 8 eyes (4%) on Ophthalmoscopy and FFA respectively. Only Moderate NPDR cases were seen more in Ophthalmoscopy than FFA 36 (18%) and 31 (15.5%) respectively. Our study showed that the FFA is a better diagnostic test as compared to ophthalmoscopy with respect to the number of cases diagnosed by both in different types of diabetic retinopathy. Wang S et al¹⁶ had shown similar results, they had considered that in patients who have suffered from diabetes for less than 5 years, FFA could discover earlier pathological changes which cannot be diagnosed by ophthalmoscopy, especially capillary fluorescence leakage. Therefore in those patients with diabetes who are not diagnosed as retinopathy by ophthalmoscopy, FFA should be done if possible.²⁰

On ophthalmoscopy we found 96 patients (48% of total 200) having Diabetic retinopathy, while on FFA, we found 106 patients (53%) with Diabetic retinopathy.

Mild NPDR was seen in 7 cases (3.5%) in ophthalmoscopy while on FFA total 16 (8%) cases had shown mild NPDR, these extra 9 (4.5%) cases have been diagnosed on FFA. In Y Yamana et al²¹ study, Early vascular changes due to DR can be elucidated by fluorescein angiography.

Similarly severe NPDR was found in 48 (24%) patients on ophthalmoscopy while on FFA, severe NPDR was seen in 51 (25.5%) cases that is 3 (1.5%) extra cases have

been diagnosed on FFA. In case of PDR, 5 (2.5%) cases were diagnosed as PDR on ophthalmoscopy while on FFA, we found 8 (4%) cases of PDR, that's 3 (1.5%) more cases with PDR have been found on FFA. Only in case of Moderate NPDR, on ophthalmoscopy we found more cases as compared to FFA, 36 cases (18%) and 31 cases (15.5%) respectively.

Overall FFA has diagnosed more cases of each subtype of DMR as compared to ophthalmoscopy, thus FFA was found to be a better diagnostic tool in our study.

A study by Sorath Noorani et al²², studied the role of Fundus Fluorescein Angiography in Pre-proliferative Diabetic Retinopathy. The study did Fundus fluorescein angiography of 25 patients having PPDR unilaterally or bilaterally was performed. In the study Fundus fluorescein angiography was used as an important diagnostic tool to show exact location and extent of vascular changes of PPDR. In current study also we did the same, used Fundus fluorescein angiography to check for the sensitivity for diagnosing early changes in fundus of diabetic patients.

In M Udayasridhar et al²³ study, they found out one important predictive factor that is poor blood sugar level.

The associations between HbA1c with Ophthalmoscopy Findings and FFA Findings were significant in our study (both with a $p < 0.0001$). Parallel results were given by diabetes control trial research group²⁴, who found out that increased levels of glycosylated haemoglobin were associated with a significant increase in the progression of DR.

Majority of the patients had impairment of vision which was 6/18 -6/60 who were 51.5% of these people. There were 40% with no impairment and 8.5% with severe vision impairment.

There were majority patients (52%) who had no diabetic retinopathy findings on ophthalmoscope. Severe non-proliferative diabetic retinopathy was seen among 24% patients and moderate and mild was seen among 18% and 3.5% patients respectively. There were 2.5% patients who had PDR. The study by Mulgund et al¹³, had higher percent (4%) finding of PDR compared to our study. Finding of severe NPDR was more in number than the study by Mulgund et al¹³, who had only 2% patients. But mild and moderate NPDR were more in study by Mulgund et al¹³. The study by Bertram et al²⁵ had 19% mild to moderate NPDR similar to the current study. The study by Sumi S et al²⁶, had higher percentage of mild to moderate NPDR (71%) and higher percentage of PDR (7%)

When seen under the fundus fluorescence angiography there were similar percent of patients with severe NPDR (25.5%). There was decrease in no of diabetic retinopathy patients who were 47% and also a decrease seen in patients with moderate NPDR (15.5%). But there was increase in mild NPDR (8%) and there were increased number of patients with PDR who were 4%. The study by SS Khalaf et al¹⁴ had similar findings that the ophthalmic and FFA findings were almost similar.

The study had significant association between age and ophthalmoscopic findings. Similar results were found in Mulgund et al¹³, which showed increase in severe category with increasing in age. Association was also seen with FFA

findings.

There was no statistical association seen between sex and ophthalmoscopic findings or sex and FFA. Similar results were found in study by Mulgund et al.¹³

While significant association was found between duration of diabetes and ophthalmoscopic findings. Similar association was seen in study by Mulgund et al.¹³ Association was also seen with duration of diabetes and FFA findings in our study. There was strong agreement seen between ophthalmic and FFA findings. The Mulgund et al¹³, study found ophthalmoscope to be more sensitive than FFA but in our study the findings were different. The study by S.S. KHALAF et al¹⁴, had similar findings as the current study of having a kappa value of 0.87 which shows strong agreement between the Ophthalmoscopy and FFA.

A study done by S.S. KHALAF et al¹⁴, however suggests that FFA is not needed for confirmation of diagnosis which has been already picked up on ophthalmoscopy in case of PDR. When we compared the association between absence of diabetic retinopathy and the types of retinopathy, we found significant association with the mild NPDR ($p = 0.045$), while there was no any significant association with other types of retinopathy.

CONCLUSION

In patients less than 5 years of diabetic age or those who are at early stage of diabetic retinopathy, We observed that early pathological changes which could not be seen on ophthalmoscopy were evident on FFA

Fundus fluorescein angiography (FFA) study of DM patients is more sensitive tool for early detection of Diabetic Retinopathy.

FFA is a better diagnostic tool for diagnosing retinopathy as compared to ophthalmoscopy.

So by Early detection of diabetic retinopathy we can help to stop further progression of retinopathy

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