

CORRELATION OF VISUAL ACUITY WITH FUNDUS FLUORESCIN ANGIOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY IN DIABETIC MACULAR OEDEMA

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ABSTRACT

BACKGROUND

In India, according to International Diabetes Federation, the prevalence of diabetes in 2017 is 8.8%. Diabetes mellitus is a chronic disease caused by impaired metabolism of carbohydrate causing hyperglycaemia which results in multiple end organ damage like nephropathy, retinopathy and neuropathy. Increasing prevalence of this disease increases the burden of diabetic retinopathy. Diabetic retinopathy is an important and leading cause of visual disability. Most important and frequent cause of visual loss due to diabetic retinopathy is diabetic macular oedema. Patients with diabetic retinopathy will develop diabetic macular oedema at any stage of the disease. Patients with diabetic macular oedema mostly present with loss of vision, but vision loss can be prevented if it is diagnosed earlier. Early diagnosis, treatment, regular follow-up of diabetic eye disease can prevent vision loss.

The aim of the study is to correlate the visual acuity with the current tools of investigations- Fundus Fluorescein Angiography and Optical Coherence Tomography and incorporate routine investigation in screening protocol.

MATERIALS AND METHODS

Diabetic patients who attended the outpatient department at Karpaga, Vinayaga Institute of Medical Sciences, Chinnakolambakkam, Kanchipuram District, Tamil Nadu, during the period October 2015- 30th May 2018.

RESULTS

Visual acuity is best correlated with central foveal thickness. The mean best corrected visual acuity was $0.18 \pm 0.25SD$ at $257.36 \pm 82 \mu m$ mean central foveal thickness. Correlation is significant at $p < 0.01$ (2-tailed).

ROC curve was drawn based on macular thickness measured with OCT, it showed increased accuracy in diagnosing macular oedema at foveal thickness of $>235 \mu m$ and also thickening of nasal quadrant at the inner ring of ETDRS grid, with area under the curve 0.75 and 0.80 respectively. Significant correlation between different patterns of FFA and visual acuity. $p < 0.006$.

CONCLUSION

Functional impact of diabetic macular oedema is quantified by visual acuity, but it cannot be used as an indicator of development of diabetic macular oedema, since most of them had normal vision until involvement of foveal centre, in Ocular coherence tomography. Focal leaks at macula in Fundus Fluorescein Angiography away from fovea did not affect vision and OCT did not show associated thickening at macula. Therefore, it is concluded that inclusion of OCT, FFA in screening protocol along with routine evaluation can prevent vision loss in diabetic retinopathy.

KEYWORDS

Diabetic Macular Oedema, Optical Coherence Tomography (OCT), Fundus Fluorescein Angiography (FFA).

HOW TO CITE THIS ARTICLE: Govindan S. Correlation of visual acuity with fundus fluorescein angiography and optical coherence tomography in diabetic macular oedema. J. Evid. Based Med. Healthc. 2018; 5(37), 2675-2681. DOI: 10.18410/jebmh/2018/549

BACKGROUND

Diabetic retinopathy is an end vascular damage caused by chronic hyperglycaemia, oxidative stress, increased VEGF secretion which results in break down blood retinal barrier end vascular occlusion and proliferation of new blood vessels. It is estimated that cross sectional analysis showed

Financial or Other, Competing Interest: None.
Submission 20-08-2018, Peer Review 23-08-2018,
Acceptance 07-09-2018, Published 10-09-2018.
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DOI: 10.18410/jebmh/2018/549



that patients with diabetes mellitus have some degree of DR at any given time.¹

Diabetic retinopathy occurs both in type 1 and type 2 diabetes mellitus and has been shown that nearly all Type 1 and 75 per cent of Type 2 diabetes will develop diabetic retinopathy after 15 years duration of diabetes as shown in earlier epidemiological studies.^{2,3} In India with the epidemic increase in Type 2 diabetes mellitus as reported by the World Health Organization.⁴ Diabetic retinopathy is fast becoming an important cause of visual disability. Most common cause of visual loss in diabetic retinopathy is diabetic macular oedema.

Diabetic macular oedema is an ocular complication of diabetes mellitus Type 1 and 2. Diabetes may cause capillaries in the eye to become abnormally permeable and

leak fluid into the retinal tissue of the macula, causing diabetic macular oedema. This can result in vision loss and eventual blindness if left untreated.

The burden of Diabetic macular oedema is likely to increase as the prevalence of diabetes is expected to rise by more than 50% globally from 2000 to 2030, with the number of diabetes cases estimated to reach 300 million worldwide by 2025.⁴

According to Wisconsin diabetic retinopathy study prevalence of diabetic macular oedema varies with different stages of diabetic retinopathy about 3%, 38%, 71% in mild, moderate to severe and proliferative stages respectively. Also, according to various epidemiologic studies diabetic macular oedema prevalence varies between two types, management of diabetes and duration, 4.3% in insulin dependent type, 5.1% in non-insulin dependent, at 10 years duration 20.1% in Type I and 25.4% in Type II.⁵

In the past, the term "Clinically Significant Macular Oedema" was used to define patients who needed to be treated.⁶

However, these criteria were mostly discarded due to the emergence of Optical coherence tomography and fundus fluorescein angiography based diagnosis. Optical coherence tomography images are now used in the diagnosis, treatment, and follow up of Diabetic macular edema.⁷

Diabetic macular oedema can develop at any stage of diabetic retinopathy, it is frequently related with increase in duration and severity of diabetic retinopathy. Most of the patients have normal vision inspite of FFA leak and increased macular thickness in Optical coherence tomography. Therefore it is necessary for the patient to undergo OCT and FFA for the diagnosis of DME. The aim of this study is to find out if FFA or Optical coherence tomography correlates best with visual acuity.

Aim of the Study

To correlate visual acuity with Fundus Fluorescein Angiography and Optical Coherence Tomography characteristics of diabetic macular oedema.

Source of Data

Diabetic patients who attended the outpatient department at Karpaga Vinayaga institute of medical sciences, during the period of October 2015 to May 2018 and who fulfilled the inclusion and exclusion criteria.

Methods of Collection of Data

42 eyes of 23 patients with Type II diabetes with diabetic macular edema (based on clinical, angiographic, Optical coherence tomography classifications) at the time of presentation. Sample size calculated was 40.

Study Design

Observational, retrospective study.

Inclusion Criteria

42 Eyes with diabetic retinopathy at any stage with macular involvement in patients with clear media with blood sugar under control.

Exclusion Criteria

1. Patients with uncontrolled hypertension, dyslipidaemia and chronic renal failure.
2. H/o ocular surgery within 6 months.
3. Other ocular pathologies causing macular oedema.
4. Patients with hyperlipidaemia.
5. Previous history of photocoagulation and ocular surgery.
6. Previous history of intravitreal steroid administration
7. H/o topical medications.

MATERIALS AND METHODS

Forty-two eyes of twenty-three diabetic patients with age between (53-60 years) with type 2 diabetes with diabetic macular oedema presented to us were analysed, after approval of ethical committee. Data was collected meeting the objectives of the study after an informed consent from the patient. A detailed history of each patient was obtained regarding the age, duration of diabetes, antidiabetic treatment and any associated illness. All patients underwent visual acuity estimation by Snellen visual acuity chart, later converted to log(MAR) acuity, dilated slit lamp- 90D examination, indirect ophthalmoscopy, Fundus Fluorescein Angiography a (TRC 50 DX; Topcon, Tokyo, Japan) and Optical Coherence Tomography (3Dimensional Optical coherence tomography 2000; Topcon, Tokyo, Japan). Metabolic control was also assessed by measuring HbA1c.

Procedure

Patients were selected according to inclusion and exclusion criteria, with informed consent. All patients underwent ophthalmological examination, including a medical history review, best corrected visual acuity (Log MAR), Intraocular pressure measurement (Non-contact, Pneumotonometry), slit lamp examination with 90D and indirect ophthalmoscopy. After adequate pupillary dilatation Digital fundus photography and fundus fluorescein angiography were done, Optical coherence tomography was then done on the same day. The posterior pole colour fundus image was captured with 50 degree stereo angle and saved. The presence of hard exudates, haemorrhages and micro aneurysms in the foveal, perifoveal or para macular area were noted.

After the fundus camera was changed to the fluorescein angiography mode 3ml of 20% fluorescein sodium was injected intravenously and the early, mid, late phase pictures were taken analysed and saved. Leaks within macular grid were classified as focal, diffuse leaks in the foveal, perifoveal region or para macular region and compared with the colour pictures obtained with optical coherence tomography maps

All eyes underwent 3D imaging of macula with Topcon 3 Dimensional Optical coherence tomography (PC software edition, version 4.1×) using ETDRS GRID Overlay centred on macula. Analysis of the scans was done automatically by the PC software (version 4.1×). The retinal thickness data was displayed in two complementary manners. For quantitative interpretation the macula was divided into nine ETDRS type regions including disc of 500µm. diameter and an inner and outer ring, each divided into four quadrants, with outer radii

of 1 and 2DD. respectively. A false colour tomographic display also was developed. Macular thickness was converted to a false colour value for every point with bright colours indicating areas of increased retinal thickness. Cross sectional imaging provides foveal structural changes in macula.

Diabetic maculopathy is characterized by the accumulation of extracellular fluid in Henle's layer and the inner nuclear layer of the retina.

Clinically Significant Macular Edema (CSME)⁸

According to ETDRS clinically significant macular oedema (CSME), based on slit lamp biomicroscopy defined as "(1) thickening of the retina at or within 500µm of the centre of the macula; or (2) hard exudate at or within 500µm of the centre of the macula associated with thickening of adjacent retina; or (3) a zone of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the centre of the macula".

Diabetic macular oedema based on fluorescein angiographic pattern of leak is classified as,⁹ Focal, diffuse, ischemic and combined. Focal is a defined retinal thickening with rings of exudate. Focal leaks of fluorescein dye is seen in angiography at the macula. Diffuse macular oedema shows diffuse retinal thickening, along with cystoid changes in outer plexiform layer. Petaloid pattern of leak is seen in angiography. Ischemic macular oedema shows enlarged foveal avascular zone due to capillary non-perfusion. Combined macular oedema presents with mixed patterns as stated above.

OCT classification of diabetic macular edema¹⁰ is based on different characteristics like increased thickness (sponge), cystoid pattern, vitreomacular traction, epiretinal membrane and presence of subretinal fluid. (Fig. 1 to Fig. 4).

Data Analysis

Data analysis was performed using SPSS software version 15.0. The following parameters were collected at baseline, computed and compared between eyes /patients, age, sex, diabetes duration HbA1c, severity of diabetes, Descriptive analysis were performed Non-parametric Mann – Whitney test was used to correlate Visual Acuity with CSME and non –CSME group. Student t test, independent sample t test were also used. Pearson correlation test was used to test the correlation between visual acuity and central foveal thickness and ANOVA was used for the statistical comparison. ROC curve was used for analysis of macular thickness in various regions of macula to assess sensitivity and predictivity of Optical coherence tomography in the diagnosis of macular oedema.

RESULTS

42 eyes of 23 patients (7 female and 16 male) aged between 42 and 70 years were included in study. Duration of diabetes from diagnosis of these patients were minimum 4 years and maximum 23 years, a mean duration of 12.13 ± 4 SD. Glycemic control (HbA1C) among the study population, none

of them had good control, 8 patients (34.8%) had fair control, 15 patients (65.2%) had poor control. Visual acuity ranged between 0.00(6/6) to 1.30(<6/60) (Log MAR). Clinically CSME was detected in 25(59.5%) of 42 eyes as defined by ETDRS. There was no clinical evidence of macular oedema, but for few microaneurysms in the remaining eyes. 40 eyes (95.2%) of 42 eyes were classified as nonproliferative and 2 (4.8%) of 42 eyes as proliferative diabetic retinopathy after clinical and angiographic examination. FA demonstrated dye leakage either at the foveal, perifoveal or para foveal region in all eyes. Focal leakage observed in 27 (71.4%) eyes, Diffuse leakage in 11 eyes (35.7%) combined pattern in 4 eyes (9.5%). 3 eyes (7.1%) had enlarged FAZ with surrounding diffuse leakage. Two types of pattern petaloid and honeycomb were observed in diffuse type of leakage. (Fig. 5)

Optical coherence tomography imaging showed increased retinal thickness only in 30 eyes (71.4%). Optical coherence tomography failed to detect retinal thickness in 28.6% of eyes with focal leaks in FFA. (Table 4). Central foveal thickness ranged between 162 µm -525µm with a mean thickness of 257.36 ±82µm.

Cross sectional imaging of Optical coherence tomography showed sponge like oedema in 16(38.1%), cystoid pattern in 17 (40.5%), CME+SRD+ERM IN 4 eyes. All serous retinal detachment were associated with epiretinal membrane (ERM). Vitreomacular traction (VMT) were noted in 3 eyes* (7.1%). (Fig. 6).

Petaloid pattern of leak in FFA showed cystoid spaces in outer plexiform layer and honeycomb leak showed cystoid spaces in inner nuclear layer in Optical coherence tomography.

Central foveal thickness ranged between 162 µm - 525µm with a mean thickness of 257.36±82µm. Visual acuity is correlated with central foveal thickness. The mean BCVA was 0.18±0.25SD (6/9 to 6/18) at 257.36±82µm mean CFT. Correlation is significant at p<0.01(2tailed). (Fig. 8) (Table 2). Eyes with serous retinal detachment (SRD) had a mean central foveal thickness of 441.75±79µm, mean visual acuity of 0.67±0.41Log MAR) (6/24 to <6/60) and a mean HbA1c of 8.9. Significant correlation exist between central foveal thickness, glycemic control, (Fig. 7) and FFA features. (Table 5). Significant correlation exist between different patterns of FFA and Visual acuity. (p<0.006). (Fig. 9. Table 1) 23 of 25 CSME eyes and 7 of 10 Non CSME showed increased retinal thickness in Optical coherence tomography (Fig. 10a, 10b).

ROC curve was drawn based on macular thickness measured with Optical coherence tomography, it showed increased accuracy in diagnosing macula oedema at foveal thickness of >235µm and thickening of nasal quadrant at the inner ring of ETDRS grid, with area under the curve (AUC) 0.75 and 0.80. respectively. (Fig. 11, 12), (Table 3)

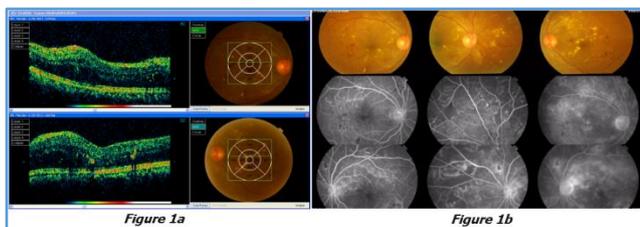


Fig. 1a - (OCT) DME with outer retinal thickening, (sponge), small cysts in inner nuclear layer), hard exudates
Fig. 1b - (FFA) Combined leak pattern. (Diffuse, petaloid)

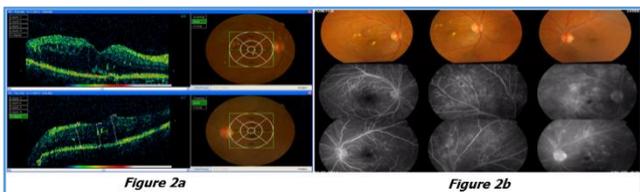


Fig. 2a - OCT. Cystoid macular oedema with sub retinal fluid with posterior hyaloid separation with perfoveal traction (top). Cystoid macular oedema (below).
Fig. 2b - FFA. Combined leak.

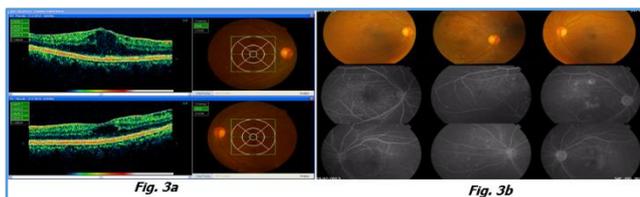


Fig. 3a - Cystoid macular oedema in OCT (above and below).
Fig. 3b - FFA, Petaloid in right eye, focal leaks in left eye.

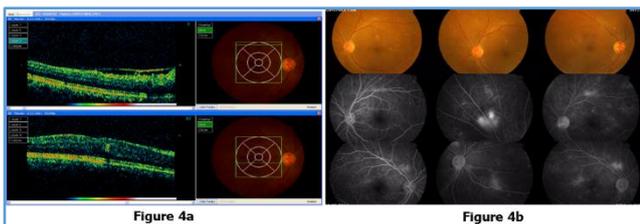


Fig. 4a - OCT. Right eye. Macular oedema with epiretinal membrane (above), sponge oedema.
Fig. 4b - Right eye enlarged Foveal avascular zone with focal leaks, left eye showing focal leaks.

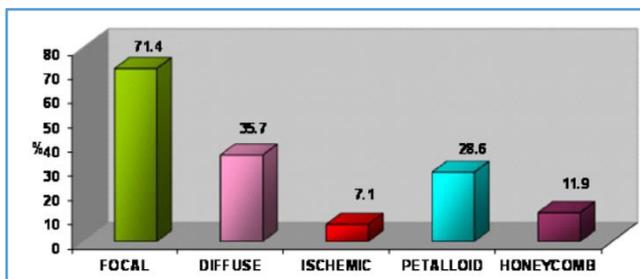


Figure 5. Patterns of Leaks in FFA

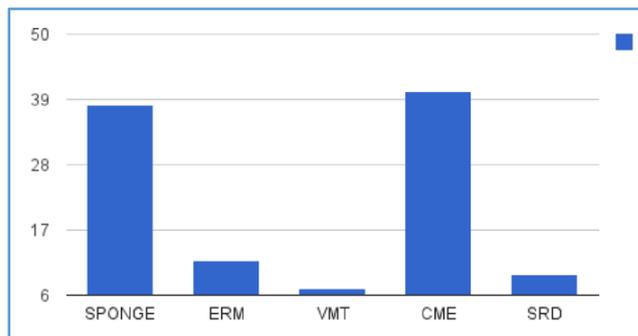


Figure 6. Morphologic Features in Optical Coherence Tomography

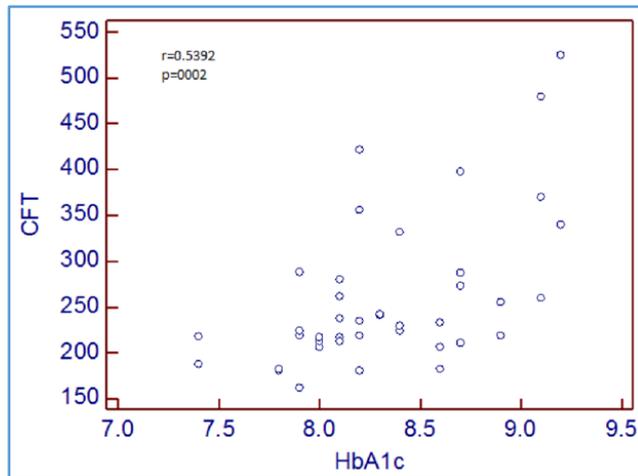


Figure 7. Correlation between Central Foveal Thickness and Glycemic Control

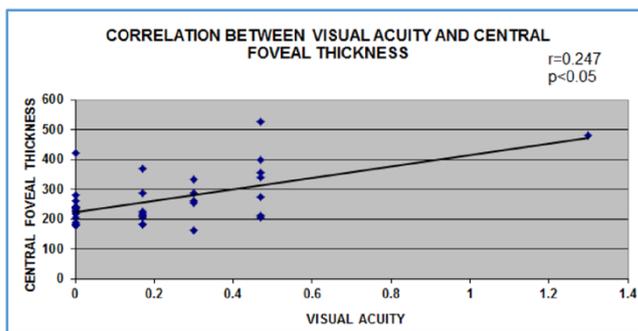


Figure 8. Correlation between Visual Acuity and Central Foveal Thickness

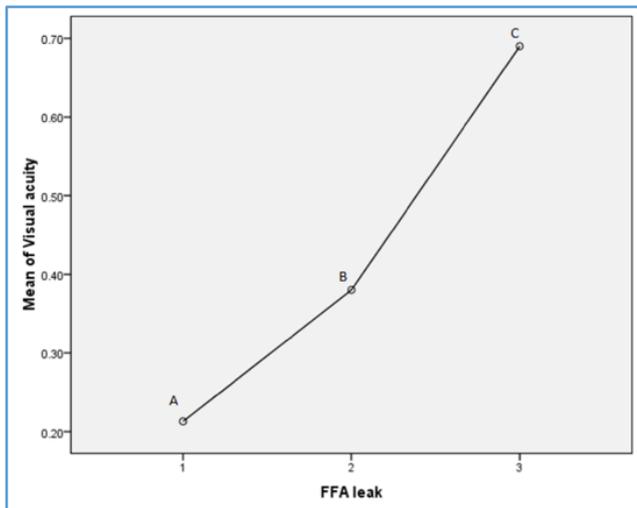


Figure 9. Correlation between Different Patterns of Fluorescein Leak at Macula Pattern in Angiography and Visual Acuity. A (1) - Focal Leaks; B (2)- Diffuse Pattern; C (3)-Combined Pattern

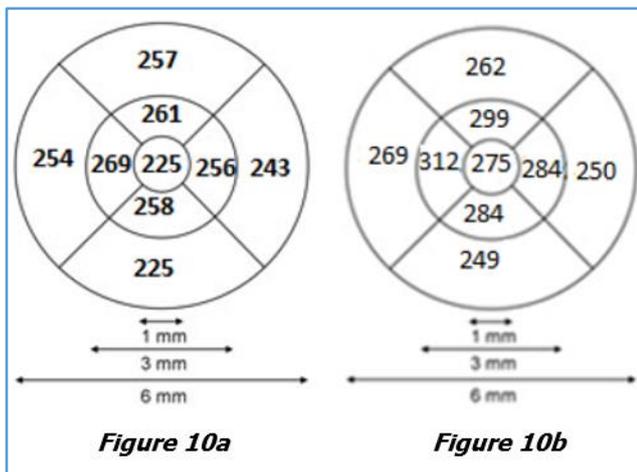


Fig. 10a and 10b - ETDRS grid showing Mean Macular Thickness in (µm) among Study Population in Non CSME and CSME Eyes Respectively.

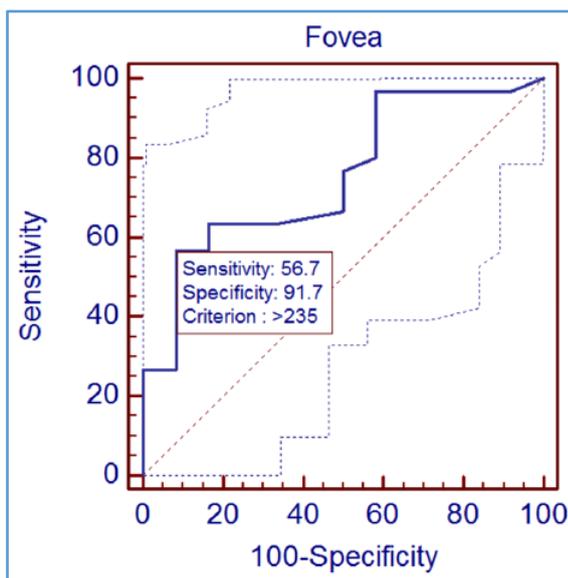


Figure 11. Comparison of ROC Curves of Various Foveal Thickness

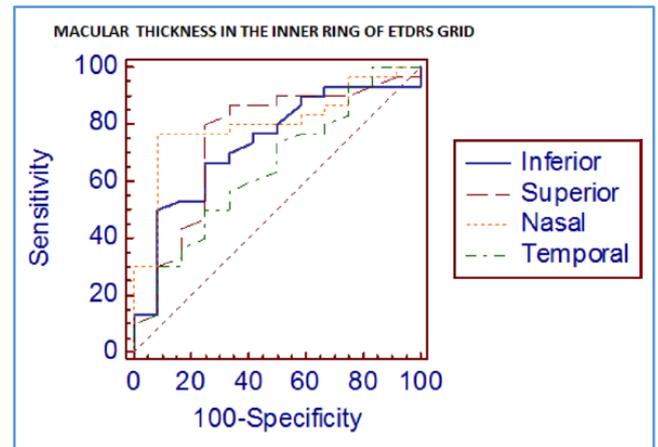


Figure 12. Comparison of ROC Curves of Four Quadrants of Inner Ring of ETDRS Grid

ANOVA

Visual Acuity-

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	0.542	2	0.271	6.736	0.006
Within Groups	0.765	19	0.040		
Total	1.307	21			

Table 1. Correlation between Different Patterns of FFA and Visual acuity. p<0.006

Parameters	Sponge	CME	SRD	NO Oedema
Central foveal thickness (µm)	207 ± 18	297 ± 49	441 ± 78	204 ± 24
Visual Acuity (logMAR)	0.08 ± 0.14	0.21 ± 0.16	0.67 ± 0.41	0.42 ± 0.07

Table 2. Results of Different Parameters according to OCT Patterns

	AUC	SE ^a	95% CI ^b
Inferior	0.733	0.0849	0.574 to 0.858
Superior	0.747	0.0910	0.589 to 0.868
Nasal	0.803	0.0722	0.651 to 0.909
Temporal	0.647	0.0940	0.485 to 0.788

Table 3. Comparison of Area Under Curve (AUC) for Macular Thickness in Inner Quadrants of ETDRS Grid

OCT Patterns	FFA Patterns			Total
	Focal	Diffuse	Combined	
NO EDEMA	12	0	0	12
SPONGY	12	0	0	12
CME	2	5	1	8
CME+SPONGE	0	2	1	3
CME+SRD+ERM	0	2	1	3
CME+VMT	0	1	1	2
CME+ERM+SRD+VMT	0	1	0	1
SPONGE+ERM	1	0	0	1
Total	27	11	4	42

Table 4. Comparison of OCT, FFA Patterns

FFA	CFT (Mean)	HbA1c (Mean)
Focal	213.11	8.14
Diffuse	333.91	8.61
Combined	339.00	8.87
P value	0.000	0.000

Table 5. Correlation of FFA Features with Central Foveal Thickness and Glycemic Control

DISCUSSION

Alkuraya et al¹¹ had reported positive correlation between Optical coherence tomography pattern and visual acuity. But Visual acuity was best correlated with central foveal thickness. In a retrospective observational study by Manpreet Brar et al.¹² Visual acuity correlates with the number, size, location of the cysts and not just the presence or absence of cysts. Our study showed significant correlation between cystoids macular oedema and visual acuity, $p < 0.01$ (2 tailed) with nonparametric correlation study. S. Nunes et al¹³ reported that visual acuity worse in the group of eyes that had oedema of the central 500- μm -diameter circle, the central foveal thickness. In this study also, visual acuity best correlated with central foveal thickness, moderate visual loss had occurred at central foveal thickness of $257.36 \pm 82 \mu\text{m}$. Gobel et al¹⁴ (60 of 61 eyes (98%) the diagnosis of macular oedema was confirmed by fluorescein angiography. There was only a minor correlation between visual acuity and foveal retinal thickness ($r = 0.32$, $p = 0.001$) in a study by Ozdek et al.¹⁵ Best-corrected visual acuity was significantly correlated with central foveal thickness ($R: -0.528$, $p \leq 0.01$). The Optical coherence tomography images demonstrated retinal swelling in 66.1% of eyes, cystoid macular oedema in 11.8% of eyes, serous foveal detachment with diffuse swelling in 6.2% of eyes, serous foveal detachment with diffuse swelling along with cystoid macular oedema in 3.6% of eyes and normal foveal structure in 12.3% of eyes. Comparing Optical coherence tomography and slit-lamp biomicroscopy, it's obvious that Optical coherence tomography can detect macular thickening while the clinic examination is still normal. Comparing OCT and FFA, OCT did not show increased retinal thickness in cases of focal leaks at the macula. In OCT retinal thickness at the macula other than increased central foveal thickness and increased nasal grid thickness did not affect visual acuity. In FFA focal leaks at macula did not affect visual acuity.

CONCLUSION

All patients should be encouraged to optimize treatment for adequate glycaemic control to keep HbA1c $< 7\%$. Though functional impact of diabetic macular oedema is currently quantified by visual acuity, it cannot be used as an indicator of development of Diabetic macular oedema since most of them had normal vision until involvement of foveal centre. FFA leakage and retinal thickness did not always correlate in this study. Early focal treatment of leaking microaneurysms detected by FFA prevents vision threatening complications due to diabetic macular oedema. In conclusion visual loss alone cannot be taken as an indicator of diabetic macular oedema, combination of optical coherence tomography and

FFA are needed for initial diagnosis and treatment planning of diabetic macular oedema; hence including these investigation in routine screening protocol can prevent vision loss due to diabetic retinopathy.

REFERENCES

- [1] Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. *Diabetes Care* 1998;21(1):143-156.
- [2] Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984;102(4):520-526.
- [3] Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984;102(4):527-532.
- [4] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27(5):1047-1053.
- [5] Klein R, Klein BE, Moss SE, et al. The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. *Arch Ophthalmol* 1994;112(9):1217-1228.
- [6] Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1987;94(7):761-774.
- [7] Zhang X, Zeng H, Bao S, et al. Diabetic macular edema: new concepts in pathophysiology and treatment. *Cell Biosci* 2014;4:27.
- [8] Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology* 1991;98:786-806.
- [9] Kanski JJ. Retinal vascular disease. In: *Clinical ophthalmology. A systematic approach*. 5th edn. London: Elsevier Science 2003:439-444.
- [10] Panozzo G, Parolini B, Gusson E, et al. Diabetic macular edema: an OCT-based classification. *Semin Ophthalmol* 2004;19(1-2):13-20.
- [11] Alkuraya H, Kangave D, Abu El-Asrar AM. The correlation between coherence tomography features and severity of retinopathy, macular thickness and visual acuity in diabetic macular edema. *Int Ophthalmol* 2005;26(3):93-99.
- [12] Brar M, Yuson R, Kozak I, et al. Correlation between morphological features on spectral domain optical coherence tomography and angiographic leakage patterns in macular edema. *Retina* 2010;30(3):383-389.
- [13] Nunes S, Pereira I, Santos A, et al. Central retinal thickness measured with HD-OCT shows a weak correlation with visual acuity in eyes with CSME. *Br J Ophthalmol* 2010;94(9):1201-1204.

[14] Goebel W, Kretzchmar-Gross T. Retinal thickness in diabetic retinopathy: a study using optical coherence tomography (OCT). *Retina* 2002;22(6):759-767.

[15] Ozdek SC, Erdinc MA, Gurelik G, et al. Optical coherence tomographic assessment of diabetic macular edema: comparison with fluorescein angiographic and clinical findings. *Ophthalmologica* 2005;219(2):86-92.