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Interrelationship between Clinical, Optical Coherence Tomography and Fluorescein Angiography Findings in Clinically Significant Diabetic Macular Oedema

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ABSTRACT
Background: Macular edema is an important cause of visual morbidity in diabetic retinopathy. It can be assessed by both fluorescein angiography (FA) and optical coherence tomography (OCT). Aims: To study, if any, interrelationship exists between OCT and FA patterns in Clinically significant macular edema (CSME). Furthermore, to associate macular thickness as determined by OCT to best-corrected visual acuity (BCVA). Materials and Methods: This was a prospective study which compared patterns in OCT and FA in patients with CSME. All the patients who were diagnosed as CSME underwent a complete ophthalmic examination and were subjected to OCT and FA. Those with a hazy media were excluded from the study. The results were analyzed by Fisher's exact test. Results: A total of 50 eyes were studied. FA revealed that most of the patients had diffuse leak (61%), followed by focal leak (31%) and combined leak (8%). On OCT, isolated sponge-like retinal swelling was seen among 67% eyes, spongy retinal swelling with cystoid macular edema/serous foveal detachment in 25% eyes, and 8% had a combined pattern. There was a statistical correlation between FA and OCT findings in our study (P = 0.038). The mean central foveal thickness in our study was 324.75 ± 98.30 µm, and there was a statistically significant correlation between central foveal thickness and BCVA (P = 0.043).
Material and Methods: This was a prospective study which compared patterns in FA and OCT in patients with CSME. All the patients who were diagnosed as CSME underwent a complete ophthalmic examination and were subjected to FA and OCT. Those with a hazy media were excluded from the study. The results were analyzed by Fisher's exact test.
Result: A total of 50 eyes were studied. FA revealed that most of the patients had diffuse leak (59%), followed by focal leak (31%) and combined leak (10%). On OCT, isolated sponge-like retinal swelling was seen among 66% eyes, spongy retinal swelling with cystoid macular edema/serous foveal detachment in 28% eyes, and 6% had a combined pattern. There was a statistical correlation between FA and OCT findings in our study (P = 0.038). The mean central foveal thickness in our study was 321.75 ± 98.30 µm, and there was a statistically significant correlation between central foveal thickness and BCVA (P = 0.043).
Conclusion: There is a significant correlation between OCT and FA findings for CSME. Furthermore, the foveal thickness correlates to BCVA.

Keywords: clinically significant diabetic macular oedema, fluorescein angiography, optical coherence tomography

I. INTRODUCTION

India is considered to be the diabetes capital of the world with a diabetic population which is predicted to hit 69.9 million by 2025 [1].All professional eye-care organisations advocate annual eye examinations for patients with diabetes [2].Screening over 12% of India' s population, distributed over a subcontinent is not easy. A nationwide cross-sectional study of diabetic patients by the AIOS for the first time in 2014 for diabetic retinopathy (DR), reiterated the findings of earlier regional studies, with a prevalence at 21.7% on a pan Indian scale [3].Macular edema is responsible for a significant degree of visual loss in diabetic patients [4] .Clinically significant diabetic macular edema (CSME) is diagnosed with ophthalmoscopy, slit lamp biomicroscopy using 78D/90D lens. The Early Treatment of Diabetic Retinopathy Study defined CSME and recommended treatment with focal photocoagulation using the following criteria: retina oedema located at or within <500µm from the center of the macula, hard exudates with thickening of the adjacent retina located at or within 500 µm from center of macula, a zone of thickening larger than 1 disc area if located within 1 disc diameter of the center of the macula [5].Macular thickening which is picked up by clinical examination does not reflect severity and extent of edema, source of fluid leakage, and affected layer of retina. Fluorescein angiography (FA) is used to assess vascular leakage qualitatively in macular edema, whereas optical coherence tomography (OCT) offers high-resolution

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cross-sectional images of the retina and thus aids in quantitative measurement of the retinal thickness [6-9].Thus, FA offers the physiological aspect of macular edema, and OCT provides the anatomical extent of macular edema such as extent of thickening and retinal layer involved. OCT can objectively measure retinal thickness and thus is an indispensable instrument in the diagnosis and management of macular edema [10].The aim of the study was to determine, if any, the correlation between FA and OCT in CSME and to find any association between foveal thickness as measured by OCT and best-corrected visual acuity (BCVA).

II. AIMS & OBJECTIVES

To study, if any, interrelationship exists between OCT and FA patterns in Clinically significant macular edema (CSME). Furthermore, to correlate macular thickness as determined by OCT to best-corrected visual acuity (BCVA).

III. MATERIALS & METHODS

This was a prospective study done on eyes with CSME from the period of May 2015 to Sept 2016 in a tertiary hospital in Kishanganj, Bihar. The study was conducted after seeking ethical clearance from the Institutional Ethics Committee. All diabetic patients with CSME and media clear enough to allow OCT and FA were included in the study. Furthermore, eyes with persistent CSME despite laser photocoagulation were included in the study. Exclusion criteria included any surgical intervention or any other vitreoretinal pathology. After taking written informed consent, a detailed history was taken. They underwent an ophthalmic examination in the form of BCVA, slit-lamp examination, and dilated fundus examination. Fundus was examined by slit-lamp biomicroscopy using + 78 diopter (D) Volk lens and indirect ophthalmoscopy using + 20D Volk lens. FA and OCT were done for patients diagnosed of CSME. Retinal photography and FA were performed using fundus camera. Angiography was performed under the supervision of an anaesthetist. Photographs of the fundus were taken of all quadrants up to 10 min following injection of the dye. Diabetic macular edema was classified based on Spigelman's classification [11] as:

a. Background maculopathy: Sparse microaneurysms, early ischemic foci, variable but small amount of exudates and hemorrhages with a relatively intact macula

b. Focal leakage: Focal beds of leaking microaneurysms, with variable accumulation of serous and lipid exudates, larger ischemic foci, and early distortion of macular anatomic structure

c. Diffuse leakage: Diffuse beds of leaking microaneurysms, marked accumulation of serous and lipid exudates, large ischemic foci, formation of microcysts, and severe distortion of macular anatomic structure

d. Cystoid degeneration: Diffuse beds of leaking microaneurysms and marked accumulation of serous and lipid exudates, large ischemic foci, macrocysts, and permanent damage of macular anatomy.

OCT was done using Spectral Domain OCT. Based on OCT, diabetic macular edema can be classified as[12] :

a. Sponge-like retinal swelling

b. Cystoid macular edema (CME)

c. Sponge-like retinal swelling + CME/serous foveal detachment

d. Combination of all types.

Ischemic maculopathy was considered in the presence of an enlarged foveal avascular zone on FA and if foveolar thickness (Ganglion cell layer) was <10 µm on OCT.[11] Statistical analysis was done using Fisher's exact test.

IV. RESULTS

A total of 50 eyes of diabetic patients with CSME were included in the study of which 82% were males and 18% were females. The sex ratio was 4.3:1. 58% percent had duration of diabetes mellitus more than 10 years, 36% had duration of diabetes of 5–10 years, and only 6% had duration of diabetes < 5 years. On FA, 61% of the eyes had a diffuse leak, 31% had a focal leak, and the remaining 8% had a combined leak. None of the eyes had Cystoid macular edema (CME) [Graph 1]. On OCT, isolated sponge-like retinal swelling was seen among 67% eyes, spongy retinal swelling with CME or serous foveal detachment in 25% eyes, and 8% had a combined pattern [Graph 2]. No eyes had isolated CME; however, it was detected in six eyes (12%), in association with spongy edema. Serous detachment was found in association with spongy edema in ten eyes (20%). Five eyes had vitreomacular traction (10%), and two eyes had epiretinal membrane (4%) [Figure 1]. Three eyes (6%) had undergone laser. The predominant pattern of macular edema was combined pattern (four patients), and two patients had a combination of cystoid and serous foveal detachment. No cases of ischemic maculopathy were encountered.

Correlation between FA and OCT findings in CSME are shown in Table 1. Eyes with focal leakage were found more likely to have sponge-like retinal swelling, whereas eyes with diffuse leak on FA were found to have sponge-like retinal swelling with CME with serous foveal detachment and combined pattern [Figures 2 and 3]. There was a statistical correlation between FA and OCT findings in our study (P = 0.038 by Fisher's exact test).

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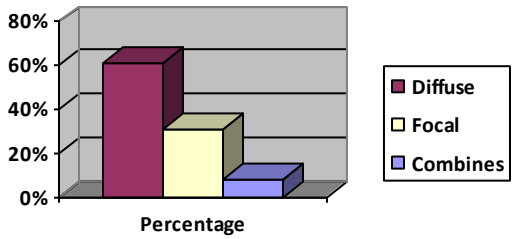
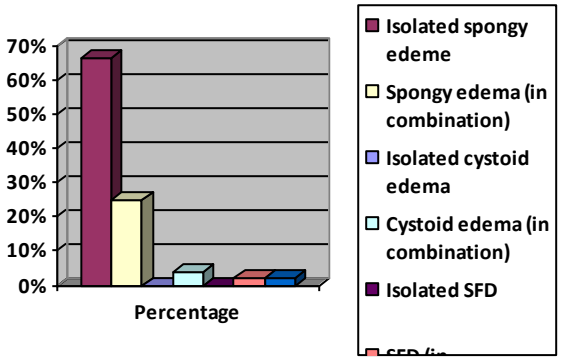
The distribution of BCVA in various groups is shown in Table 2. Only 8% of patients had a visual acuity less than 6/60. The central foveal thickness in our study ranged from 185 to 552 µm with an average of 324.75 ± 98.30 µm. The correlation between BCVA and central foveal thickness is shown in Table 3. There was a statistically significant correlation between central foveal thickness and BCVA (P = 0.043 by Fisher's exact test).

Graph 1: Fluorescein angiography pattern of macular edema in CSME



Graph 2: Optical coherence tomography pattern of macular edema in CSME



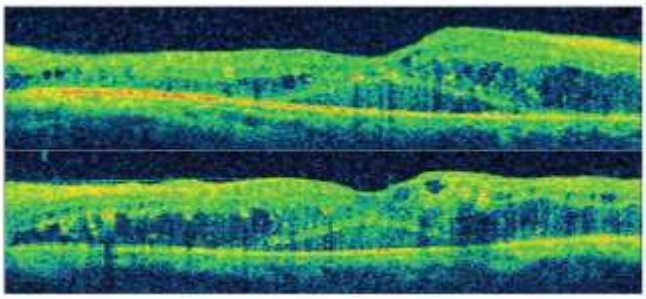


Figure 1: Spongy edema with serous foveal detachment (above insert) and combined pattern-spongy edema, cystoid, and serous foveal detachment with epiretinal membrane (above insert)

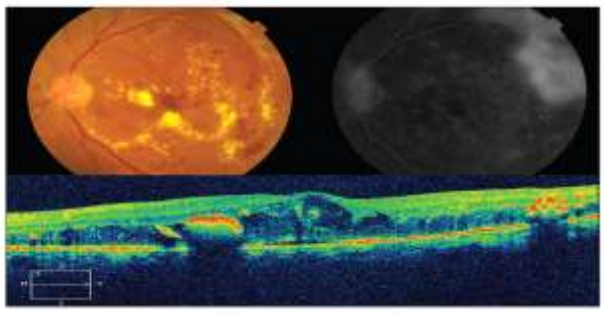


Figure2: Fluorescein angiogram showing diffuse leak at the macula and optical coherence tomography showing spongy edema and serous foveal detachment(above insert)

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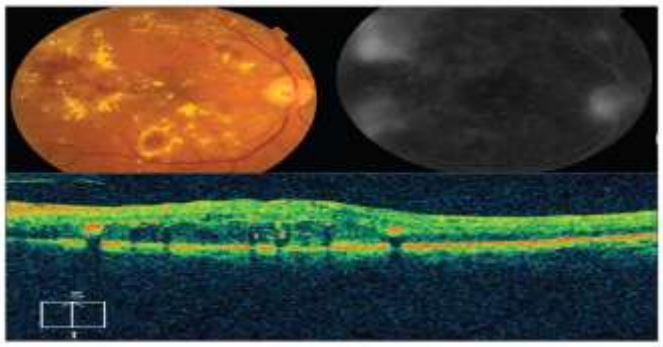

Figure 3: Focal leak at macula on fluorescein angiogram and spongy edema in optical coherence tomography(above insert)

Table 1: Correlation between fluorescein angiography and optical coherence tomography findings in clinically significant macular edema :

OCT Findings	FA findings (number of eyes)		
	Combined leak	Diffuse leak	Focal leak
Combined	2	2	0
Spongy	2	22	9
Spongy + CME/SFD	0	10	3

Fisher's exact test: P=0.038 significant. FA: Fluorescein angiography.
OCT: Optical coherence tomography. CME: Cystoid macular edema.
SFD: Serous foveal detachment.

Table 2: Best corrected visual acuity (BCVA)

BCVA	Number of eyes	Percentage
6/6 to 6/9	38	76%
6/12 to 6/18	2	4%
6/24 to 6/36	6	12%
≤ 6/60	4	8%
Total	50	100%

Table 3: Correlation between best corrected visual acuity and central foveal thickness

BCVA	Central foveal thickness in µm							
	<200	201-250	251-300	301-350	351-400	401-450	451-500	501-550
6/6 - 6/9	2	9	9	7	2	3	2	3
6/12 – 6/18	0	0	3	0	0	1	0	0
6/24 – 6/36	2	0	2	0	0	2	0	1
≤ 6/60	0	0	0	0	0	1	0	1

Fisher's exact test P=0.043, significant BCVA: Best corrected visual acuity.

V. DISCUSSION

The aim of this study was to determine whether there was a correlation between features of fluorescein angiography (FA) and optical coherence tomography (OCT) in clinically significant macular edema and whether there was any association between foveal thickness and BCVA.

The distribution of FA patterns showed

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diffuse leakage at macula as the most common pattern seen in 61% of eyes followed by focal leakage at macula seen in 31% of eyes and combined focal and diffuse leakage at macula was seen in 8% of eyes. CME was not seen in FA in our study. A comparison with another study has been shown in Table 4.

Otani et al., reported that OCT images showed three basic types of macular edema: Sponge-like retinal swelling, CME, and serous foveal detachment [12]. In our study, sponge-like retinal swelling was a universal finding on OCT seen in 100% cases of CSME either as an isolated entity or in combination with other findings. Out of the total 50 eyes studied, isolated spongy swelling was seen in 67% of eyes followed by sponge-like retinal swelling with CME or serous foveal detachment seen detachment seen in 25% of eyes. Combined pattern that is combination of three or more components (sponge- like retinal swelling ± CME ± serous foveal detachment ± vitreomacular interface abnormality) was seen in 8 % of eyes in OCT. A comparative analysis of our study to a study by Otani et al., has been shown in Table 5 [12]. Kang et al reported the incidence of each type in OCT as 55.2%, 30.3%and 14.5%, respectively [13].

CME (along with sponge-like edema was detected with OCT in 8% of eyes in our study which was not detected during slit-lamp biomicroscopy with a +78 D lens or with FA. This is a striking feature, demonstrating the importance of OCT in early detection of diabetic changes at fovea which are not evident clinically and angiographically. The great discrepancy between FA and OCT could also be the result of a masked cystoid staining pattern in eyes with severe focal and diffuse leakage. Ozdek et al., reported a slightly higher incidence of CME detected with OCT (15.4%)[14].

Serous foveal detachment was seen in 20% of eyes which was not detected during slit-lamp biomicroscopy or FA. This is also a very important finding detected on OCT, which may explain the cause of unexplained visual loss in patients with diabetic maculopathy. Serous foveal detachment determined with OCT was reported in 0–15% of diabetic patients in the literature.[12,13,15]Epiretinal membrane was seen in 4% of eyes in our study, the incidence of epiretinal membrane among diabetics was 6% in eyes with no diabetic retinopathy, 8.8% in patients with nonproliferative, and 41.6% in patients with proliferative diabetic retinopathy; [15] whereas 4–11% in general population [15-17]. Vitreomacular traction was detected using OCT in 10% of the study population. In general population, it has a prevalence of 0.35 in 100[18].

Eyes with focal leakage were more likely to have sponge-like retinal swelling, whereas eyes with diffuse leakage were more likely to have sponge-like retinal swelling with CME/serous foveal detachment and combined pattern on OCT. In our study, we found that distribution of FA types correlated significantly with OCT types in patients with CSME (P = 0.038 by Fisher's exact test). Our results were comparable to a similar study done by Kang et al., in Korea [13]. These findings imply that diabetic macular edema is a broad spectrum of disease, and its treatment is diversified according to the subtypes of macular edema. The interpretation of CSME with OCT as well as with FA would help select an appropriate treatment for diverse manifestations of the macular edema.

BCVA in our study was in a normal range in 76% of eyes, whereas 24% of eyes had BCVA of less than 20/30. Central foveal thickness in our study ranged from 185 to 552 µm with mean ± 2 standard deviation of 324.75 ± 98.30 µm. BCVA showed a statistically significant correlation with the central foveal thickness in our study (P = 0.043 by Fisher's exact test). Despite this modest correlation, there was a substantial variation in visual acuities at any given retinal thickness. Many eyes with a thickened macula had excellent visual acuity suggesting that OCT measurement alone may not be a good surrogate for visual acuity as a primary outcome in studies of diabetic macular edema. Assessment of macular thickness using OCT is certainly clinically useful, but macular thickness is just one of several variables affecting visual acuity in a complex and as yet not fully understood relationship. A study done by Hee et al., has found similar results; however, the strengths of correlation have varied widely [19].

Bhagat et al.,2009 noted in his study that diabetic macular edema tends to be a chronic disease [20]. Although spontaneous recovery is not uncommon, 24% of eyes with CSME and 33% of eyes with center involving CSME will have a moderate visual loss (15 or more letters on the ETDRS chart) within 3 years if untreated. The incidence of macular edema increses significantly with increasing severity of diabetes in both younger onset and older onset diabetic patients.

FA is known to be a sensitive method for qualitative assessment of fluid leakage in diabetic macular edema; however, actual macular thickening assessed by OCT is better correlated with the loss of visual acuity. Furthermore, FA is an invasive procedure, with side effects ranging from nausea to its rare complication of anaphylaxis and death. OCT is noninvasive, comfortable, safe, and fast and can be repeated as often as is required and offers an alternative to FA in the follow-up of changes in retinal thickness after laser photocoagulation and

intravitreal steroid injections. However, FA is still essential for the assessment of the foveal perfusion state which cannot be demonstrated by OCT. After an initial FA, OCT seems to be a useful noninvasive tool in the close follow-up of the effectiveness of treatment modalities in diabetic maculopathy.

Table 4: Comparison of Fluorescein Angiography patterns with other studies

Type of leak	Our study	Kang et al
Combined leak	8.375%	17.9%
Diffuse	60.375%	38.6%
Focal	31.25%	43.4%

Table 5: Comparison of Optical Coherence Tomography patterns with other studies

	Our study	Otani et al
Spongy edema (in combination)	68%	88%
Cystoid edema (in combination)	12%	47%
Serous foveal detachment (in combination)	20%	15%

VI. CONCLUSION

Our study revealed a significant correlation between the features of OCT and FA in CSME. The BCVA had a modest correlation with central foveal thickness measured with OCT in these patients. Some of the diabetic structural changes in fovea such as serous foveal detachment, CME, and foveal traction can be detected early with OCT, which may not be evident in ophthalmoscopy or FA. These results indicate that OCT can facilitate deciding on the treatment protocol (surgical or medical) and follow-up of diabetic patients, especially in the early stages of diabetic maculopathy when the structural changes are not yet evident with slit-lamp biomicroscopy or angiographically.

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Conflicts of interest :There are no conflicts of interest.

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