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Original Research Article

Quantification and Classification of Diabetic Macular Oedema Based on Optical Coherence Tomography in Non-Proliferative Diabetic Retinopathy Patients of Type 2 DM

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Conflict of interest: Nil

Abstract

Background: In this study, we wanted to evaluate the quantification and classification of diabetic macular oedema based on optical coherence tomography in non-proliferative diabetic retinopathy (NPDR) patients of type 2 diabetes mellitus (DM).

Methods: This was a hospital based cross sectional analytical study conducted among 100 patients who presented with diabetic history with symptoms of pain and vision complaints in the Department of Ophthalmology, Government Rajaji Hospital, Madurai, over a period of one year after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Results: Majority of the participants who were moderate to severe had problem in the right eye. Significant difference exists in mean para foveal thickness of study participants by one way ANOVA test ($p = 0.0001$). The OCT parameter - spongiform macular oedema with severity of fundus by Chi square test which was found to be statistically significant ($p = 0.03$). The OCT parameter - cystoid macular oedema with severity of fundus by Chi square test which was found to be statistically significant ($p = 0.02$). The OCT parameter - distorted inner retinal layers with severity of fundus by Chi square test which was found statistically significant ($p = 0.0001$) and there was 32 % positive correlation with positive status with severity of fundus ($p = 0.0001$). The OCT parameter - ellipsoid zone disruption with severity of fundus by Chi square test which was found statistically significant ($p = 0.003$) and there was 32 % positive correlation with positive status with severity of fundus ($p = 0.0001$). The OCT parameter – ERM/VMT with severity of fundus by Chi square test which was found to be statistically significant ($p = 0.02$).

Conclusion: Cystoid macular oedema is seen more commonly than spongiform macular oedema. Ellipsoid zone distorted inner retinal layers, inner retinal cyst parameters of OCT was measured and mostly seen in severe NPDR and indicates cystoid type of macular oedema. On calculating the parameters with the help of OCT, central and para foveal thickness were found to be more in the severe NPDR patients. VMT is predominantly seen in the severe NPDR

patients who have cystoid macular oedema, and the measured macular oedema is also found to be higher in this type of macular oedema.

Keywords: Diabetic Macular Oedema, Optical Coherence Tomography, Non-Proliferative Diabetic, Retinopathy, Type 2 DM.

Introduction:

Diabetic mellitus is a chronic systemic disease that increases the risk of developing many medical complications. So, patients will require screening, long term observation for diagnosis, treatment and prognosis. Diabetes mellitus is one of the major systemic causes of blindness in the world. It contributes 4.8 % of the 37 million cases of blindness in the entire world. Vision problem due to diabetes can be significantly reduced by proper glycaemic control, routine ophthalmological examination and timely treatment. Laser photocoagulation and intravitreal anti VEGF injections remains the mainstay of treatment for diabetic retinopathy. It has been shown to reduce visual loss due to diabetic macular oedema and proliferative diabetic retinopathy.

Aims and Objectives

- To quantify and classify the macular oedema with the help of spectral domain OCT in non-proliferative diabetic retinopathy patients of type 2 DM.
- To quantify the macular oedema at foveal and para foveal area in non-proliferative diabetic retinopathy patients of type 2 diabetes.
- To classify the types of macular oedema, and to understand the prevalence of types of macular oedema occurring in non-proliferative diabetic retinopathy patients of type 2 diabetes mellitus.
- To compare the amount of foveal and para foveal oedema with the degree of defective vision in non-proliferative diabetic retinopathy patients.
- To compare among the types of macular oedema causing defective vision in non-proliferative diabetic retinopathy patients.

Methods

This was a hospital based cross sectional analytical study conducted among 100 patients who presented with diabetic history with symptoms of pain and vision complaints to the Department of Ophthalmology OPD in Government Rajaji Hospital, Madurai, over a period of one year after obtaining clearance from Institutional Ethics Committee and written informed consent from the study participants.

Inclusion Criteria

- Age 20 – 70 years.
- Uncomplicated type 2 DM patients referred from medicine department without other co-morbidities.
- Non proliferative diabetic retinopathy patients with diabetic macular oedema confirmed on slit lamp biomicroscopy with 90D lens or with fundus fluorescein angiography.

Exclusion Criteria

- Age less than 20 and more than 70 years.
- Type 1 DM.
- Patients with proliferative diabetic retinopathy and advanced diabetic eye disease.
- Patients with hypertension.
- Patients with vascular diseases like CRVO, BRVO.
- Retinitis pigmentosa.

- Patients with nystagmus.
- Undergone cataract surgery, combined surgery, vitreoretinal surgery.
- Previous history of ocular surgery or trauma.
- Chronic usage of prostaglandins, timolol.
- Patients undergone laser photocoagulation and anti-VEGF therapy for macular oedema.
- Patients not given consent.

Sample size

$$\frac{\frac{z^2 \times p\,(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p\,(1-p)}{e^2 N}\right)}$$

p = confidence level
e = Margin of error (percentage in decimal form)
N = population size
Z score - 1.96 (for 95 % CL)
Confidence level - 95% p = (0.5)
Confidence interval – 9.8 % in decimal form (0.098) Margin of error

Population - 100000

With this formula and parameters, we derive sample size is 100

Statistical Methods

The information collected regarding all the selected cases were recorded in a master chart.

Data analysis was done with the help of computer by using Statistical Package of Social Sciences (SPSS16) software. Using this software, 'p' values were calculated through One-way ANOVA test for raw data and *Chi square test* for consolidated data to test the significance of difference between variables and correlation coefficient calculated through Pearson's correlation. A 'p' value less than 0.05 was taken to denote significant relationship.

Results

Table 1

Gender	**Frequency**
Male	67
Female	33
Total	100
Gender Distribution of Study Participants	
Side	**Frequency**
LE	37
RE	63
Total	100
Side of Eye Among Distribution	
Status	**Frequency**
Mild	5
Moderate	48
Severe	47
Total	100
Status of Severity Among Study Participants	
Spongiform Macular Oedema	**Frequency**
Negative	59
Positive	34
Para	7
Total	100
Spongiform Macular Oedema Among Study Participants	
OCT Parameters	**Frequency**
Cystoid macular oedema	56

Distorted inner retinal layers	69
Sub foveal fluid	23
Ellipsoid zone disruption	36
Intra retinal cyst	43
OCT Parameters Among Study Participants	
ERM/VMT	**Frequency**
Nil	83
ERM	5
VMT	12
Total	100
Distribution of ERM and VMT	

Majority were male 67 % followed by female patients who were 33 %. Majority had problem in right eye 63 % and in left eye it was 37 %. NPDR with CSME was observed to be mild in 5 %, moderate in 48 % and severe in 47 % among study participants. Majority were negative for OCT parameter of spongiform macular oedema; 34% had positives and 7 % had parafoveally. The OCT parameters - 69 % had positives for distorted inner retinal layers 56 % had positives for cystoid macular oedema, 43 % for intra retinal cyst, 36 % for ellipsoid zone disruption and 23 % for sub foveal fluid. Majority were negative (83 %); 5 % had positives for ERM and 12 % had VMT.

Table 2: Mean Comparison of Para Foveal Thickness with Severity Status of Fundus

Vision	**Mild**	**Moderate**	**Severe**	**Total**
3/60.	0	0	1	1
4/60.	0	0	7	7
5/60.	0	0	3	3
6/12.	4	0	0	4
6/18.	1	17	8	26
6/24.	0	24	12	36
6/36.	0	5	9	14
6/60.	0	2	7	9
Total	5	48	47	100
Comparison of Vision with Severity Status of Fundus				
Age	**N**	**Mean**	**SD**	**F**	**p**
Mild	5	46.6	5.03	9.52	**0.0001**
Moderate	48	52.44	7.841		
Severe	47	57.49	6.22		
Total	100	54.52	7.593		
Comparison of Mean Age with Severity Status of Fundus					
Central Foveal Thickness (microns)	**N**	**Mean**	**SD**	**F**	**P**
Mild	5	267.6	31.021	9.42	**0.0001**
Moderate	48	263.54	33.297		
Severe	47	321.89	90.315		
Total	100	291.17	72.122		
Mean Comparison of Central Foveal Thickness with Severity Status of Fundus					
Para Foveal Thickness (microns)	**N**	**Mean**	**SD**	**F**	**P**

Mild	5	255.4	15.076	10.02	**0.0001**
Moderate	48	302.04	28.817		
Severe	47	326.32	48.22		
Total	100	311.12	42.311		
Mean Comparison of Para Foveal Thickness with Severity Status of Fundus					

It describes the comparison of vision test with severity status of fundus. There was a significant difference in mean age of study participants by one way ANOVA test (p = 0.0001). This implies that patients with age more than 50 years may tend to have moderate and severe problems.

There was a significant difference in mean central foveal thickness of study participants by one way ANOVA test (p = 0.0001). This implies that severe group had more mean value (321.89 ± 90.3) than moderate and mild groups.

There was a significant difference in mean para foveal thickness of study participants by one way ANOVA test (p = 0.0001). This implies that severe group had more mean value (326.32 ± 48.22) than moderate and mild groups.

Table 3

Gender	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**P**
Male	1	35	31	67	5.78	0.06
Female	4	13	16	33		
Total	5	48	47	100		
Comparison of Gender with Severity Status of Fundus						
Side	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**P**
LE	0	23	14	37	6.44	**0.04**
RE	5	25	33	63		
Total	5	48	47	100		
Comparison of Eye Side with Severity Status of Fundus						
Spongiform Macular Oedema	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**
Negative	0	29	30	59	10.41	**0.03**
Positive	5	15	14	34		
Para	0	4	3	7		
Total	5	48	47	100		
Comparison of Spongiform Macular Oedema with Severity Status of Fundus						
Cystoid Macular Oedema	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**
Negative	5	22	17	44	7.59	**0.02**
Positive	0	26	30	56		
Total	5	48	47	100		
Comparison of Cystoid Macular Oedema with Severity Status of Fundus						

The gender wise comparison of severity of fundus by Chi square test was found to be statistically insignificant (p = 0.06).

The affected side of eye comparison with severity of fundus by Chi square test was found to be statistically significant (p = 0.04). It implies that majority of the participants who were moderate to severe had problem in the right side eye.

The OCT parameter - spongiform macular oedema with severity of fundus by Chi square test which was found statistically significant (p = 0.03).

The OCT parameter - cystoid macular oedema with severity of fundus by Chi square test which was found statistically significant (p = 0.02).

Table 4

Sub Foveal Fluid	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**
Negative	5	34	38	77	2.92	0.2
Positive	0	14	9	23		
Total	5	48	47	100		
Comparison of Sub Foveal Fluid with Severity Status of Fundus						
Intra Retinal Cyst	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**
Negative	5	27	25	57	4.06	0.1
Positive	0	21	22	43		
Total	5	48	47	100		
Comparison of Intra Retinal Cyst with Severity Status of Fundus						
ERM/VMT	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**
Nil	5	44	34	83	11.33	**0.02**
ERM	0	3	2	5		
VMT	0	1	11	12		
Total	5	48	47	100		
Comparison of ERM/VMT with Severity Status of Fundus						

The OCT parameter - sub foveal fluid with severity of fundus by Chi square test was found to be statistically insignificant (p = 0.2)

The OCT parameter - intra retinal cyst with severity of fundus by Chi square test was found to be statistically insignificant (p = 0.1)

The OCT parameter – ERM/VMT with severity of fundus by Chi square test was found to be statistically significant (p = 0.02).

Table 5

Distorted Inner Retinal Layers	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**	**Correlation**	**P**
Negative	5	18	8	31	16.37	**0.0001**	0.32	**0.0001**
Positive	0	30	39	69				
Total	5	48	47	100				
Comparison of Distorted Inner Retinal Layers with Severity Status of Fundus								
Ellipsoid Zone Disruption	**Mild**	**Moderate**	**Severe**	**Total**	**Chi sq**	**p**	**Correlation**	**p**
Negative	4	38	22	64	11.38	**0.003**	0.32	**0.0001**
Positive	1	10	25	36				
Total	5	48	47	100				
Comparison of Ellipsoid Zone Disruption with Severity Status of Fundus								

The OCT parameter - distorted inner retinal layers with severity of fundus by Chi square test was found to be statistically significant (p=0.0001) and there was 32 % positive correlation with positive status with severity of fundus (p = 0.0001).

The OCT parameter - ellipsoid zone disruption with severity of fundus by Chi

square test was found to be statistically significant (p = 0.003) and there was 32 % positive correlation with positive status with severity of fundus (p = 0.0001).

Discussion

In this study, a total of 100 subjects were taken, who had non proliferative diabetic retinopathy of T2 DM patients. The mean age of mild NPDR was 46.6, moderate NPDR was 52.44, and severe NPDR was 57.49. Age and sex had no statistical significance with the diabetic macular oedema, which is in concordance with the previous studies.

Vision is less affected in mild NPDR, moderate NPDR had vision between 6/18 and 6/60, severe NPDR had vision between 6/18 and 3/60, indicating the severity of macular oedema. Studies shows BCVA was significantly lower in the group with cystoid macular oedema (P < 0.001) Participants had equal distribution of moderate and severe NPDR with macular oedema.

Cystoid macular oedema is more common than spongiform macular oedema among the participants. Studies have shown that the most common type of DME was cystoid macular oedema (68.5 %). No statistically significant difference was found between groups in sex (P = 0.40), type of diabetes (P = 0.50), or diabetic retinopathy (P = 0.78).

Central foveal thickness of patients shows that severe group had more mean value (321.89 ± 90.3) than moderate and mild groups. Previous studies have shown that retina thickness in early DME is (232.9 +/- 7.9 micron).

The para foveal thickness of severe NPDR group had more mean value (326.32 ± 48.22) microns than moderate and mild groups.

The cystoid macular oedema is more common in severe NPDR and was found statistically significant (p = 0.02). The spongiform macular oedema is almost equally distributed between moderate and severe NPDR and was found to be statistically significant (p = 0.03) studies have not compared the severity of diabetic retinopathy with macular oedema.

The distorted inner retinal layers are found to be associated mostly with severe NPDR and was found statistically significant (p = 0.0001).

Ellipsoid zone disruption is calculated and is mostly seen with severe NPDR which was found to be statistically significant (p = 0.003).

Sub foveal fluid is seen mostly with moderate NPDR, which was found to be statistically insignificant (p = 0.2). Intra retinal cyst is almost equally distributed between moderate and severe NPDR which was found to be statistically insignificant (p = 0.1).

ERM is almost equally distributed between moderate and severe NPDR. VMT is seen more in the severe NPDR.

Which was found to be statistically significant (p = 0.02). Previous studies show that macular traction with retinal distortion was detected in 31.5 % of the eyes with DME.

Recently, Arf et al. [1] developed another classification system categorizing DME into 3 types: type 1, diffuse macular oedema; type 2, cystoid macular oedema (CME); and type 3, cystoid macular degeneration (CMD). Each type was subcategorized into (a) the presence of serous macular detachment (SMD), (b) the presence of vitreomacular interface abnormalities (VMIA), and (c) the presence of hard exudates (HE). The authors emphasized the importance of the distinction between CME and CMD-the former occurred in the early stage of DME, and the latter was a result of chronic oedema, associated with a poorer functional and morphological outcome. As opposed to previous studies, this classification did not consider SMD as a morphological pattern of DME, rather a co-morbid finding,

considering its prevalence regardless of morphology. The authors reported that SMD and hard exudates were found in the early stage of DME while the epi-retinal membrane (ERM) was present in the later stage of DME.

Otani et al. [2] first described 3 morphological patterns of DME and categorized them in 3 subtypes: sponge-like diffuse retinal thickening (DRT), cystoid macular oedema (CME), and serous retinal detachment (SRD) the first study to put forward the significance of DRIL (disorganization of retinal inner layers) in DME was published in 2015 by Sun et al [3]. The study demonstrated that DRIL is a robust indicator of VA, which correlated more consistently than any other OCT parameters, including CST and even the current glycemic status. Studies have demonstrated that the eyes with DRIL were at a nearly 8-times greater risk of poor visual recovery, resolution of DRIL [3] was indicative of better visual improvement, and persistent DRIL after resolution of DME was associated with a less favourable outcome.

Maheshwary et al. [4] showed a statistically significant correlation between percentage disruption of the IS/OS junction and the BCVA. Disruption of ELM and EZ acts as a predictor for poorer final BCVA.

There is conflicting evidence in the literature regarding the value of SFCT. Many studies reported a substantial reduction of SFCT in DME eyes, but this phenomenon was not observed in some studies. A study by Eliwa et al. [5] states that though SFCT was significantly thinner in DME patients, it was thicker in those with DME and sub-retinal fluid. A study by Kim et al. [6] claimed that eyes with DME tended to have thicker SFCT than eyes without DME. Other studies, however, demonstrated no significant difference in choroidal thickness in DME eyes. The confounding factors related to the interpretation of SFCT, including age, axial length, systemic diseases, and previous pan retinal photocoagulation, may be the reasons for this discrepancy.

For decades, the criteria for CSME from the ETDRS classification and the international guidelines for the center-involved and non-center-involved macular oedema have been widely used in guiding patient selection in treating DME. However, these traditional classification systems lack prognostic indicators which are essential in the treatment decision. With the advancement of OCT technology, an updated protocol with comprehensive inclusion of OCT biomarkers which possess high level of evidence in their prognostic value is needed in DME management as the advancement of OCT technology has allowed the search of novel biomarkers in DME eyes. These imaging parameters may reflect cellular changes in the pathogenesis of DME. In particular, DRIL and EZ/ELM layer changes were shown to have a strong prognostic value, which can act as a surrogate marker for neuronal changes in the presence of DME. These OCT-based biomarkers will be essential for DME management, especially for selection of treatment for patients.

Conclusion

Cystoid macular oedema is seen more commonly than spongiform macular oedema. Ellipsoid zone distorted inner retinal layers, inner retinal cyst parameters of OCT was measured and mostly seen in severe NPDR and indicates cystoid type of macular oedema. On calculating the parameters with the help of OCT, central and para foveal thickness were found to be more in the severe NPDR patients. VMT is predominantly seen in the severe NPDR patients who have cystoid macular oedema, and the measured macular oedema is also found to be higher in this type of macular oedema.

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