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CORRELATION OF OCT DRIL CHANGES WITH VISUAL ACUITY IN CENTRE INVOLVING DIABETIC MACULAR OEDEMA PATIENTS

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ABSTRACT

Aim: The aim of the present study was to determine whether disorganization of the retinal inner layers (DRIL), observed using Spectral Domain Optical Coherence Tomography (SD-OCT), is predictive of Visual Acuity in eyes with centre involving Diabetic Macular Oedema (DME).

Methods: The Cross-Sectional Observation Study was conducted at Dr. D. Y. Patil Medical college, Pune from June 2020 to May 2022 and 100 eyes of 80 patients were included in the study.

Results: Out of the 100 participants involved in our study, majority of the study participants were males (67.5%). Remaining 32.5% of the patients were female. 100 eyes affected with DRIL (80 patients) were selected for the study. Of the 80 study participants, 60 patients (75%) had unilateral involvement of eye. The remaining 20 participants (25%) showed presence of DRIL in both the eyes. Type II Diabetes was the most common diabetes (72.5%) associated with changes of disorganization of retinal inner layers (DRIL). There was not much difference between the laterality of the involved eye with DRIL changes. As per the ETDRS classification of diabetic retinopathy class, majority of the patients with DRIL had moderate Non-Proliferative Diabetic Retinopathy (moderate NPDR) (36%), while 24% reported PDR.

Conclusion: This study strengthens the potential utility of DRIL as a clinical marker to assess visual acuity in patients with diabetic macular oedema. DRIL represents a valuable, easily obtained and non- invasive biomarker of visual acuity in patients with macular oedema. Our study confirms that as the horizontal extent of DRIL increases, there is a decrease in visual acuity of the patients. This study also confirms that a correlation exists between macular thickness and visual acuity as well, with visual acuity decreasing as macular thickness increases.

Keywords: Diabetic Macular Oedema, Spectral Domain Optical Coherence Tomography, DRIL

INTRODUCTION

Diabetic macular edema (DME) is a sight-threatening manifestation of diabetic retinopathy, affecting almost 30% of individuals with more than 20 years of diabetes mellitus.[1] Standard treatment for DME involves repetitive, invasive intraocular injections, which place heavy burdens on the patient, physician, and health care reimbursement. No reliable methods exist to determine which individuals with DME will gain or lose vision over time, making such predictive biomarkers a major unmet need.[2] These tools would substantively enhance patient counseling, improve risk stratification, advance clinical management, and influence selection of eyes for clinical studies targeting DME. The noninvasive, readily performed imaging modality of spectral domain–optical coherence tomography (SD-OCT) provides reliable, high-resolution imaging of retinal anatomy and quantification of central retinal thickness. Previous investigations using OCT demonstrated that central retinal thickness is only modestly correlated withcurrent visual acuity (VA) or change inVA.[3] Various other SD-OCT anatomic findings have been studied, but these have not demonstrated adequate correlation to be useful as reliable predictors of VA in individual eyes with DME.[4-7]

Diabetic retinopathy (DR) is an important complication of diabetes and is closely associated with disease duration. DR is among the leading causes of acquired vision loss in adults worldwide. Diabetic macular edema (DME) is a serious and characteristic complication of DM-related maculopathy and is the most common cause of vision loss in these patients.[8,9] Optical coherence tomography (OCT) is a noninvasive, non-contact imaging method that allows in vivo, quantitative imaging of the human retina with high-resolution sections. It is the only method that provides cross-sectional images of the anatomic and topographic structure and pathologies of the retinal layers.[10,11] OCT has become an important diagnostic tool due to the information it provides about vitreoretinal relationships and the internal structure of the retina in the assessment and monitoring of DR. The use of OCT has not only made it possible to objectively evaluate DME, but also to make new descriptions such as serous macular detachment (SD). In addition, OCT has advanced our understanding of the importance of vitreoretinal interface pathologies in the pathogenesis of DME and their impact on treatment response. Thanks to newly described OCT findings, personalized information can be obtained about disease severity, treatment response, and prognosis.

Disorganization of the inner retinal layers (DRIL) is characterized by the absence of ganglion cell-inner plexiform layer or inner-nuclear-outer-plexiform layer boundaries in at least 50% of the 1 mm central subfield. It is linked to worse visual acuity and a reduced response to treatment with bevacizumab or ranibizumab.[12,13] The exact mechanism of DRIL formation still remains unknown. It is hypothesized that microvascular damages in the retina, resulting from elevated

glucose levels in diabetes, represent structural deformation identified as DRIL on optical coherence tomography (OCT) images.[14] DRIL is suggestive of damage to the various cells of the retina such as Müller cells, bipolar cells, horizontal cells, and amacrine cells, and is believed to affect the visual outcome of diabetic eyes.[15] DRIL is a finding observed on spectral-domain optical coherence tomography (SD-OCT) and not clinically. If the central part of the macula can be clearly visualized or the inner retinal layer boundaries can be manually segmented on SD-OCT, then there is no DRIL. However, inability to visualize the same on SD-OCT indicates presence of DRIL, which correlates strongly with a worse prognosis if the region involves a substantial portion of the central macula.

The aim of the present study was to determine whether disorganization of the retinal inner layers (DRIL), observed using Spectral Domain Optical Coherence Tomography (SD-OCT), is predictive of Visual Acuity in eyes with centre involving Diabetic Macular Oedema (DME).

MATERIAL AND METHODS

The Cross-Sectional Observation Study was conducted at Dr. D. Y. Patil Medical college, Pune from June 2020 to May 2022 and 100 eyes of 80 patients were included in the study.

Inclusion criteria: -

1. 18 years or above
2. History of diabetes mellitus (type 1 or type 2)
3. Presence of diabetic macular oedema on OCT

Exclusive criteria: -

1. Significant media opacity that precluded adequate images
2. Cataract surgery within 6 months of visit to the Out Patient Department
3. History of non-diabetic pathology (Branched Retinal vein occlusions, Central Retinal Vein Occlusions, Uveitic Cystoid Macular Oedema) that might cause macular oedema
4. History of advanced glaucoma, mature senile cataract, central posterior subcapsular cataract that might affect best corrected visual acuity

METHODOLOGY

All patients aged 18 years and above with Diabetes Mellitus were selected. Each patient's medical record will be reviewed and the following information were recorded: demographic details, Type of diabetes, Duration of diabetes, Treatment received/receiving, Any co-existing comorbidities, Family history of diabetes mellitus, Most recent glycosylated haemoglobin preceding first visit, Random blood sugar level at the time of visit

Participants with DM underwent comprehensive ophthalmic examination and spectral domain OCT. Retinal function shall be evaluated using visual acuity through the Snellen's Chart. Both aided and unaided vision of the eye was taken. Best Aided Visual correction is done. The pupil

of the patient was dilated using tropicamide dilating drops. Further evaluation of the fundus shall be done via 90D and Indirect Ophthalmoscopy in a dilated eye. The diabetic retinopathy severity in the patient at the first visit was then graded using Early Treatment of Diabetic Retinopathy Study (ETDRS).

Statistical Analysis

Analyses were performed using statistical software (SAS, version 9.2; SAS Institute Inc). Bivariate linear regressions were performed to establish the association of VA outcomes with SD-OCT parameters.

RESULTS

Table 1: Patient characteristics

Gender	**Frequency (n=80)**	**Percentage**
Male	54	67.5
Female	26	32.5
Eye involved		
Unilateral	60	75.0
Bilateral	20	25.0
Type of diabetes		
Type I	22	27.5
Type II	58	72.5
Use of insulin		
Yes	45	56.25
No	35	43.75
Family History of Diabetes		
Yes	66	82.5
No	14	17.5

Out of the 100 participants involved in our study, majority of the study participants were males (67.5%). Remaining 32.5% of the patients were female. 100 eyes affected with DRIL (80 patients) were selected for the study. Of the 80 study participants, 60 patients (75%) had unilateral involvement of eye. The remaining 20 participants (25%) showed presence of DRIL in both the eyes. Type II Diabetes was the most common diabetes (72.5%) associated with changes of disorganization of retinal inner layers (DRIL). Less commonly, it was seen in patients with type I Diabetes (27.5%) as well. 56.25% of the patients in the present study were using insulin as part of their treatment for the control of diabetes. Remaining 43.75% patients were using only oral hypoglycaemic agents as part of treatment regime for diabetes. Family history of Diabetes Mellitus was reported by 82.5% of the patients with DRIL. However, DRIL changes were also seen in patients who had no previous family history of Diabetes Mellitus (17.5%).

Table 2: Comparison of changes of DRIL between the eyes involved and Staging of Diabetic Retinopathy in study participants with DRIL (n=100 eyes) according to Early Treatment Diabetic Retinopathy Study (ETDRS)

Eye affected	Frequency (n=80)	Percentage
LE	52	52.0
RE	48	48.0
ETDRS Classification		
Mild NPDR	17	17.0
Moderate NPDR	36	36.0
Severe NPDR	23	23.0
PDR	24	24.0

There was not much difference between the laterality of the involved eye with DRIL changes. Left eye was affected in 52% of the patients, while 48% had their right eye affected. As per the ETDRS classification of diabetic retinopathy class, majority of the patients with DRIL had moderate Non-Proliferative Diabetic Retinopathy (moderate NPDR) (36%), while 24% reported PDR. This was followed by severe NPDR in 23% of the study participants and mild NPDR in 17 % of the patients.

Table 3: Visual Acuity (VA) and BEST CORRECTED VISUAL ACUITY (BCVA) observed on Snellen's chart in participants with DRIL

Visual Acuity	Frequency (n=80)	Percentage
6/9	8	8.0
6/12	18	18.0
6/18	13	13.0
6/24	11	11.0
6/36	8	8.0
6/60	16	16.0
5/60	6	6.0
4/60	5	5.0
3/60	10	10.0
2/60	5	5.0
BCVA		
6/9	13	13.0
6/12	18	18.0
6/18	12	12.0
6/24	11	11.0
6/36	9	9.0
6/60	17	17.0
5/60	2	2.0
4/60	5	5.0
3/60	12	12.0
2/60	1	1.0

Participants with DRIL changes showed variation in the visual acuity ranging from 6/9 to 2/60. Visual acuity was 6/9 among 8%, 6/12 among 18%, 6/18 among 13%, 6/24 among 11%, 6/36 among 8%, 6/60 among 16% of the patients, 5/60 among 6%, 4/60 among 5%, 3/60 among 10% and 2/60 among 5% of the patients. In the best corrected states, Visual acuity was 6/9 among 13%, 6/12 among 18%, 6/18 among 12%, 6/24 among 11%, 6/36 among 9%, 6/60 among 17%

of the patients, 5/60 among 2%, 4/60 among 5%, 3/60 among 12% and 2/60 among 1% of the patients.

Table 4: Relation between the horizontal extent of DRIL and Visual Acuity measured on Snellen's chart

VISUAL ACUITY	**HORIZONTAL EXTENT OF DRIL (micrometer)**				
	Mean	**SD**	**Median**	**IQR**	**Range**
6/9	185.85	50.86	169	155.5,199	139-324
6/12	389.39	296.51	281	217,390.5	164-1149
6/18	625.33	224	545	489.25,864.25	327-1050
6/24	905.91	233.77	750	736,1180	731-1350
6/36	1304.33	152.51	1255	1170.5,1451	1086-1470
6/60	1512.12	125.02	1558	1421.5,1609	1220-1637
5/60	1615	91.92	1615	1550,1680	1550-1680
4/60	1661	57.46	1680	1601,1711.5	1600-1728
3/60	1687	42.32	1691	1641,1725	1628-1750
2/60	1650	-	1650	1650,1650	1650

Since the continuous variables were skewed, spearman correlation was applied to assess the correlation between the visual acuity class and the Horizontal Extent of DRIL. There was significant high correlation between the visual acuity and the horizontal extent of drill (correlation co-efficient= 0.956, $p<0.001$). As the horizontal extent of DRIL increases, Visual Acuity becomes worse.

Table 5: Relation between Macular thickness and Visual Acuity measured on Snellen's chart

VISUAL ACUITY	**MACULAR THICKNESS (micrometer)**				
VA	Mean	SD	Median	IQR	Range
6/9	303.85	36.46	310	270,324	259-389
6/12	347.22	51.60	347	320.75,354.25	260-472
6/18	372.25	31.23	372.5	368.5,396.75	286-406
6/24	407	25.56	402	390,435	359-438
6/36	418	25.41	407	397,438.5	390-464
6/60	485.71	39.72	496	475,517.5	396-536
5/60	537.5	14.85	537.5	527, 548	527-548
4/60	549.2	3.9	547	547,552.5	547-556
3/60	548.33	14.58	553	534.25,558	523-564
2/60	561	-	561	561, 561	561

Since the continuous variables were skewed, spearman correlation was applied to assess the correlation between the visual acuity class and the Macular Thickness. There was significant high correlation between the visual acuity and the macular thickness (correlation co-efficient= 0.925, $p<0.001$). As the macular thickness increases, visual acuity becomes worse.

DISCUSSION

Disorganization of the retinal inner layers affecting 50% or more of the central 1-mm-wide zone centered on the fovea (foveal DRIL) is associated with worse VA. This holds true even in eyes with reduced vision despite edema resolution or, conversely, in eyes with good vision despite concurrent edema. The strong association of foveal DRIL with VA in a previous cross-sectional study supported longitudinal investigation of foveal DRIL as a potential biomarker of future VA in eyes with current DME.[16]

Sun et al (2014) conducted a prospective study among the DME patients from USA, where they evaluated the predictive capacity of the DRIL towards the visual function in terms of visual acuity at 4 & 6 months.[17] Das et al evaluated the role of DRIL as biomarker for visual function in the DME patients from United Kingdom.[18] The mean age of the patients in the present study was 61.74 years. Similar aged patients were included in the Sun et al (2014) study (mean=61 years) and Sun et al (2015) (mean=61.7 years).[15,18] Maheshwary et al included a slightly older diabetics in their study than ours (mean=65 years, 65 years and 67.9 years).[19] In the current study, majority of the study participants were males (67.5%). Das et al and Sun et al (2015) also concluded that majority of the patients were males (84%, 62.5% & 56%).[15,18] Type II was the most common diabetes (72.5%) reported in the present study. This was similar to the previous studies, where type 2 diabetes mellitus patients were included as the majority.[17,18] The mean duration of the DM among our patients was 19.35 years. Sun et al (2014) and Sun et al (2015) reported a slighter longer duration of DM in their patients (mean=23.9 years & 23.5 years).[15]

In the present study, left eye was affected in 52% of the patients. Sun et al (2014) and Sun et al (2015) also reported that predominantly left eye was affected (54.2% & 56.5%).[15,17] As per the diabetic retinopathy classification, majority patients in our study had moderate NPDR (36%), while 24% reported PDR followed by 23% reported severe NPDR and 17% reported mild NPDR in our study. The pattern of distribution was similar in the Sun et al (2014), who included 31.7% with moderate NPDR, 28.3% with PDR and 20% each with mild and severe NPDR.[17] Zur et al reported 51% with PDR and 49% with NPDR, however, grading of the severity was not reported.[20]

In the best corrected states, majority of our patients had vision acuity of 6/12 (18%), followed by 6/9 among 13%, 6/18 among 12%, 6/24 among 11%, 6/36 among 9%, 6/60 among 17% of the patients, 5/60 among 2%, 4/60 among 5%, 3/60 among 12% and 2/60 among 1% of the patients. Most of the previous studies assessed the VA in terms of the logMAR scale.[17,20]

The overall mean and median Horizontal Extent of DRIL was 977.68 µm and 1091 µm. Endo et al reported a lower length of DRIL values of 123 for the NPDR and 330 for the PDR patients.[21] DRIL has been reported to be the better marker for predicting the visual acuity in the DME patients.[22] The present study found that a significant and high correlation existed between the visual acuity and the horizontal extent of DRIL (correlation co-efficient= 0.956, $p<0.001$). The visual acuity becomes worsens as the horizontal extent of DRIL increases. Sun et al (2014) also reported similar findings between the baseline DRIL and the VA scores, and additionally, they also found DRIL to be significant marker to predict the future VA in the DME patients.[17]

It has not yet been identified how DRIL influences VA, and further research on histological association is required. The fact that retinal layer borders cannot be segmented, on OCT in

patients with DRIL, very certainly indicates that the visual transmission system has been anatomically disrupted. It has been proposed that disruption takes place as a result of bipolar axons snapping as a consequence of their elasticity limit being surpassed owing to oedema [96].

CONCLUSION

This study strengthens the potential utility of DRIL as a clinical marker to assess visual acuity in patients with diabetic macular oedema. DRIL represents a valuable, easily obtained and non-invasive biomarker of visual acuity in patients with macular oedema. Our study confirms that as the horizontal extent of DRIL increases, there is a decrease in visual acuity of the patients. This study also confirms that a correlation exists between macular thickness and visual acuity as well, with visual acuity decreasing as macular thickness increases. Future studies should include a large cohort to study the correlation between DRIL and VA more effectively. Also, a longitudinal analysis to determine whether DRIL can be used for early detection of diabetic retinopathy changes and as a prognostic marker of visual acuity and effectiveness of treatment should be considered.

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