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Original Research Article

To Study the Diagnostic Value of Disorganization of Retinal Inner Layers as a Predictor of Macular Capillary Non-Perfusion and Vision Loss in Patients with Center Involving Diabetic Macular Edema

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Abstract

Aim: The aim of the present study was to assess the diagnostic value of disorganization of retinal inner layers as a predictor of macular capillary non-perfusion and vision loss in patients with center involving diabetic macular edema.

Methods: This study was conducted in sant parmanand hospital, Delhi. Total 65 patients of either sex, age > 35 years with center involving Diabetic Macular edema were included.

Results: 32.31% of the patients were in the age group less than 50 years and 51-60 years each; and 35.38% of the patients were in the age group 61-70 years. In this study, 64.62% were males and 35.38% were females. In this study, distribution of left and right eye was 50% each. Majority (76.92%) of patients were diabetic for less than 5 years. Fasting blood sugar of 50.77% of study subjects were below 110 mg/dl, 27.69% of study subjects had fasting blood sugar between (110-126) mg/dl and 21.54% had blood sugar level more than 126mg/dl at baseline. Fasting blood sugar of 78.46%% of study subjects were below 110 mg/dl and 21.54% of study subjects had fasting blood sugar between 110-126 mg/dl at 3 months. In this study, 32.50% of patients had mild non-proliferative diabetic retinopathy, 45% of patients had moderate non-proliferative diabetic retinopathy and 22.50% of patients had severe non-proliferative diabetic retinopathy. Disorganization of retinal inner layers was present in 32.50% of study subjects at baseline. Disorganization of retinal inner layers was newly present in 3.75% of study subjects, stationary in 27.50% of patients and increased in 5% of patients at 3 months.

Conclusion: The present study concluded that DRIL is a predictive tool in identifying macular CNP but its absence does not rule out CNP. DRIL is modestly correlated with vision loss. It is helpful in predicting future visual outcomes. Significant association was seen between DRIL, blood sugar levels (fasting and post prandial) and Hb1Ac. Significant association is seen between DRIL activity and treatment profile of patients.

Keywords: diagnostic value, retinal inner layers, macular capillary non-perfusion, vision loss, diabetic macular edema

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease causing macular edema (ME) and an important cause of visual deterioration. [1,2] Blocked venous drainage may induce an increase in the permeability of vessels and initiate a breakdown of the blood-retinal barrier. Eventually, cystoid ME, capillary nonperfusion (CNP), and ischemia occur. Ischemia is a crucial parameter in the prognosis of the disease. Traditionally, fundus fluorescein angiography (FFA) has been used to assess ischemia in these patients.

Optical coherence tomography angiography (OCTA) is a noninvasive imaging technique that uses motion contrast imaging to obtain high-resolution volumetric blood flow information and generate angiographic images. [3] It also allows us to quantitatively measure the CNP area and the foveal avascular zone (FAZ). Spectral domain optical coherence tomography (SD-OCT) is a reliable, high-resolution imaging technique that allows us to evaluate the retinal anatomy and quantify different prognostic parameters in patients with RVO, diabetic retinopathy, and uveitic cystoid ME.[4-6] Central macular thickness and the disorganization of the retinal inner layers (DRIL) are examples of these prognostic parameters. [4-6]

ME is most often the clinical result of an accumulation of serous fluid in the retinal layers (the light-sensitive inner lining of the eye, which is

caused by the disruption of the blood-retinal barrier. The pathogenesis of ME is still not completely understood; however, it is associated with the alteration of the functional cell relationship in the retina and promotion of inflammatory reparative responses. To improve the best-corrected visual acuity (BCVA), the management of ME via amelioration of both anatomical (by reducing central retinal thickness) and functional parameters is necessary. [7,8] Appropriate local and systemic use of corticosteroids may be the most widely used treatment for uveitic macular edema (UME), but resorting to other immunosuppressive drugs is also common. Delays in treatment can lead to worse visual outcomes.

Approximately 55% of patients with diabetic macular edema have co-existent macular capillary non- perfusion. Co-existent macular edema may masks angiographic evidence of capillary non-perfusion. Using fluorescein angiography, capillary non-perfusion was defined as the absence of retinal arterioles and/or capillaries and was detected by characteristics such as pruned appearance of adjacent arterioles and darker appearance of choroid. Areas of CNP on FA are seen as hypofluorescent areas within the normal ground-glass appearance of perfused retina. Angiographic evidence of macular CNP indicates a decrease or absence of retinal blood circulation to the inner retina, which in turn may compromise inner retinal integrity. [9]

The aim of the present study was to assess the diagnostic value of disorganization of retinal inner layers as a predictor of macular capillary non-perfusion and vision loss in patients with center involving diabetic macular edema.

Materials and Methods

This study was conducted in Sant Parmanand Hospital, Delhi. Total 65 patients of either sex, age > 35 years with center involving Diabetic Macular edema were included.

Inclusion Criteria

1. Patients 18 yrs. Or above with history of diabetes mellitus (type 1 or type 2) and baseline center involving diabetic macular edema (Spectral domain optical coherence tomography central subfield thickness, >320 micrometer for men and >305 micrometer for women)

2. Patients able to co-operate with the protocol

Exclusion Criteria

1. Significant media opacity that precludes adequate imaging such as presence of cataract etc.

2. History of non-diabetic pathology that may affect visual acuity or causes macular edema such as central retinal vein occlusion , branch retinal vein occlusion , epiretinal memberane , vitreomacular traction.

3. Optic disc pathology affecting visual acuity.

4. Any systemic illness that interferes with procedure such as renal diseases etc.

5. Fluorescein angiography images of foveal avascular zone.

6. Presence of macular pathology other than disorganization of retinal inner layers on optical coherence tomography.

7. Non co-operative patients.

OCT images are generated by measuring the reflectance of light from retina. This information is processed by a computer, and artificially coloured based on the degree of reflectance. Standard convention is to colour the image with a spectrum ranging from red(white if black and white) for the most reflective tissues, to green (black if black and white) for the least reflective tissues. Although spectral domain(SD) OCT technology permits 3-dimensional imaging of tissue by combining hundreds of nearly instantaneous laser scans, each scan is performed in a single plane, permitting a cross sectional view of structures. In the retina, this allows visualization of each unique layer, as shown below for a normal eye.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Diagnostic test was used to calculate sensitivity, specificity, NPV and PPV. Inter rater kappa agreement was used to find out the strength of association between disorganization of retinal inner layers and macular capillary non-perfusion and vision loss in patients with center involving diabetic macular edema. A p value of less than .05 was considered as significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Table 1: Baseline characteristics

Age distribution in years	Frequency	Percentage
<=50	21	32.31%
51-60	21	32.31%
61-70	23	35.38%
Gender distribution		
Female	23	35.38%
Male	42	64.62%
Total	65	100.00%
Eye		
Left eye	40	50.00%
Right eye	40	50.00%
Total	80	100.00%
Duration of diabetes mellitus		
<5 years	50	76.92%
>5 years	15	23.08%
Total	65	100.00%

32.31% of the patients were in the age group less than 50 years and 51-60 years each; and 35.38% of the patients were in the age group 61-70 years. In this study, 64.62% were males and 35.38% were females. In this study, distribution of left and right eye was 50% each. Majority (76.92%) of patients were diabetic for less than 5 years.

Table 2: Distribution of baseline parameters of study subjects

Baseline bio-chemical parameters	Frequency	Percentage
Baseline blood sugar fasting in mg/dl		
<110 mg/dl	33	50.77%
110-126 mg/dl	18	27.69%
>126 mg/dl	14	21.54%
Baseline blood sugar post prandial in mg/dl		
<140 mg/dl	23	35.38%
140-200 mg/dl	18	27.69%
>200 mg/dl	24	36.92%
Baseline glycosylated haemoglobin		
<6%	16	24.62%
6-7%	27	41.54%
7-8%	21	32.31%
>8%	1	1.54%

Fasting blood sugar of 50.77% of study subjects were below 110 mg/dl, 27.69% of study subjects had fasting blood sugar between (110-126) mg/dl and 21.54% had blood sugar level more than 126mg/dl at baseline. Post prandial blood sugar levels of 35.38% of patients were below 140 mg/dl,27.69% of patients had post prandial blood sugar level between (140- 200) mg/dl and 36.92% of patients had post prandial blood sugar levels more than 200 mg/dl at baseline. HbA1c levels of majority of patients were between 6-7% followed by 7-8%. Only 1 patient had HbA1c level more than 8%.

Table 3: Distribution of bio-chemical parameters at 3 months of study subjects

Bio chemical parameters at 3 months	uency	Percentage
Blood sugar fasting at 3 months in mg/dl		
<110 mg/dl	**51**	**78.46%**
110-126 mg/dl	**14**	**21.54%**
Blood sugar post prandial at 3 months in mg/dl		
<140 mg/dl	**45**	**69.23%**
140-200 mg/dl	**20**	**30.77%**
Glycosylated haemoglobin at 3 months		
<6%	**23**	**35.38%**
6-7%	**24**	**36.92%**
7-8%	**18**	**27.69%**

Fasting blood sugar of 78.46% of study subjects were below 110 mg/dl and 21.54% of study subjects had fasting blood sugar between 110-126 mg/dl at 3 months. Post prandial blood sugar levels of 69.23%

of patients were below 140 mg/dl and none of the patient had post prandial blood sugar levels more than 200 mg/dl at 3 months. HbA1c levels of majority of patients were between 6-7% followed by <6%. No patient had HbA1c level more than 8%.

Table 4: Distribution of fundus and baseline disorganization of retinal inner layers at baseline and 3 months of study subjects

Fundus	Frequency	Percentage
Mild non-proliferative diabetic retinopathy	26	32.50%
Moderate non-proliferative diabetic retinopathy	36	45.00%
Severe non-proliferative diabetic retinopathy	18	22.50%
Total	80	100.00%
Baseline disorganization of retinal inner layers		
Absent	54	67.50%
Present	26	32.50%
Total	80	100.00%
Disorganization of retinal inner layers status at 3 months		
Absent	51	63.75%
Increased	4	5.00%
Newly Present	3	3.75%
Stationary	22	27.50%
Total	80	100.00%

In this study, 32.50% of patients had mild non-proliferative diabetic retinopathy, 45% of patients had moderate non-proliferative diabetic retinopathy and 22.50% of patients had severe non-proliferative diabetic retinopathy. Disorganization of retinal inner layers was present in 32.50% of study subjects at baseline. Disorganization of retinal inner layers was newly present in 3.75% of study subjects, stationary in 27.50% of patients and increased in 5% of patients at 3 months.

Table 5: Association of baseline disorganization of retinal inner layers with baseline capillary non-perfusion

Baseline disorganizationof retinal inner layers	Baseline capillarynon-perfusion		Total	P value
	Absent	Present		
Absent	40 (100.00%)	14 (35.00%)	54 (67.50%)	<.0001
Present	0 (0.00%)	26 (65.00%)	26 (32.50%)	
Total	40 (100.00%)	40 (100.00%)	80 (100.00%)	

Significant association was seen between baseline disorganization of retinal inner layers and baseline capillary non-perfusion. (P<.05) All the patients who did not have capillary non-perfusion also did not have disorganization of retinal inner layers and 65% of patients with capillary non-perfusion had disorganization of retinal inner layers.

Table 6: Association of disorganization of retinal inner layers with capillary non-perfusion status at 3 months

Disorganization of retinal innerlayers status at 3 months	Capillary non-perfusion status at 3 months		Total	P value
	Absent	Present		
Absent	40 (100.00%)	11 (27.50%)	51 (63.75%)	<.0001
Increased	0 (0.00%)	4 (10.00%)	4 (5.00%)	
Newly Present	0 (0.00%)	3 (7.50%)	3 (3.75%)	
Stationary	0 (0.00%)	22 (55.00%)	22 (27.50%)	
Total	40 (100.00%)	40 (100.00%)	80 (100.00%)	

Significant association was seen between disorganization of retinal inner layers and capillary non-perfusion at 3 months. (P<.05) All the patients who did not have capillary non-perfusion also did not have disorganization of retinal inner layers and 55% of patients with capillary non-perfusion had stationary (no change) disorganization of retinal inner layers,8% of patients developed disorganization of retinal inner layer at 3 months, these patients did not have disorganization of retinal inner layer at baseline,10 % of patients showed increase in extent of disorganization of retinal inner layer at 3 months in comparison to baseline.

Table 7: Inter-rater kappa agreement between baseline disorganization of retinal inner layers and baseline capillary non-perfusion

Baseline disorganizationof retinal inner layers	Baseline capillarynon-perfusion		Total	P value	Kappa
	Absent	Present			
Absent	40 (50.00%)	14 (17.50%)	54 (67.50%)	<.0001	0.650
Present	0 (0.00%)	26 (32.50%)	26 (32.50%)		
Total	40 (50.00%)	40 (50.00%)	80 (100.00%)		

Strength of agreement between baseline disorganization of retinal inner layers and baseline capillary non-perfusion was good with kappa value of .65.(P<.05) Agreement between baseline disorganization of retinal inner layers and capillary non-perfusion was seen in 82.50% of patients.

Discussion

Diabetic retinopathy is a leading cause of blindness and visual disability. Diabetic retinopathy is multifactorial complication of diabetes, and sustained hyperglycemia is considered a major cause of slow and cumulative damage to the small blood vessels in the retina. [10,11] The major determinant for development and progression of diabetic retinopathy are duration of diabetes and the degree of glycemic control maintained over the years. [12]

32.31% of the patients were in the age group less than 50 years and 51-60 years each; and 35.38% of the patients were in the age group 61-70 years. In this study, 64.62% were males and 35.38% were females. In this study, distribution of left and right eye was 50% each. Majority (76.92%) of patients were diabetic for less than 5 years. Luke Nicholson et al concluded that the presence of DRIL is a reliable predictor of areas of macular CNP. However, DRIL is not a universal finding of non-perfusion, with some cases exhibiting absence of DRIL despite angiographic CNP.[9] Sun JK, Lin MM, Lammer J et al concluded that disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. [13]

Fasting blood sugar of 50.77% of study subjects were below 110 mg/dl, 27.69% of study subjects had fasting blood sugar between (110-126) mg/dl and 21.54% had blood sugar level more than 126mg/dl at baseline. Fasting blood sugar of 78.46%% of study subjects were below 110 mg/dl and 21.54% of study subjects had fasting blood sugar between 110-126 mg/dl at 3 months. In this study, 32.50% of patients had mild non-proliferative diabetic retinopathy, 45% of patients had moderate non-proliferative diabetic retinopathy and 22.50% of patients had severe non-proliferative diabetic retinopathy. The exact pathogenesis of DRIL and the mechanism by which DRIL affects BCVA is unknown. The main potential causes of DRIL in UME are inflammation and ischemia. Nicholson et al [9] revealed that DRIL was strongly correlated with retinal capillary nonperfusion on fundus fluorescein angiography. The intact organization of retinal cellular pathways determines the quality of visual function. Because bipolar cells constitute the only transmission pathway between ganglion cells and photoreceptors, any destruction of bipolar cells will compromise visual acuity. Sun et al [13] suggested that the possible mechanism of DRIL may be a disruption of pathways that transmit visual information from the photoreceptors to the ganglion cells. It has been shown that the higher the increase in DRIL, the greater the number of axons of bipolar cells that stretch or even break. [14] Given the elasticity of biological material, the continuity of bipolar cells will be maintained within elastic limits. However, if sufficient swelling exceeds the elastic limits, neuronal axons may be disrupted, leading to the loss of the transmission pathway.[15] This concept may explain why DRIL was strongly associated with visual acuity. The range of DRIL was the most important parameter correlated with a worse BCVA prognosis, indicating that worse BCVA may result from long-term overstretching of bipolar axons. Disorganization of retinal inner layers was present in 32.50% of study subjects at baseline. Disorganization of retinal inner layers was newly present in 3.75% of study subjects, stationary in 27.50% of patients and increased in 5% of patients at 3 months.

Conclusion

The present study concluded that DRIL is a predictive tool in identifying macular CNP but its absence does not rule out CNP. DRIL is modestly correlated with vision loss. It is helpful in predicting future visual outcomes. Significant association was seen between DRIL, blood sugar levels (fasting and post prandial) and Hb1Ac. Significant association is seen between DRIL activity and treatment profile of patients.

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