Comparison of Retinal Sensitivity by Automated Perimetry in Middle Aged Type 2 Diabetic Patients with and without Diabetic Retinopathy - A Cross-Sectional Study in a Tertiary Care Centre in West Bengal

Abhinav Marlapati[1], Sambuddha Ghosh[2], Swati Majumdar[3]

[1, 2, 3] Department of Ophthalmology, Calcutta National Medical College, West Bengal, India.

ABSTRACT

BACKGROUND

We wanted to measure and compare retinal sensitivity in central 30 degree in diabetic patients, with and without diabetic retinopathy in different stages, evaluate changes in retinal sensitivity in relation to change in HbA1c values, measure and compare GCL thickness in various stages of DR with the help of optical coherence tomography (OCT).

METHODS

This observational, cross-sectional study involving 100 eyes of 100 middle aged (45 - 64 years) type 2 diabetes mellitus patients (50 eyes without DR - group 1 & 50 eyes with DR - group 2) without any other ocular abnormalities was conducted in the outpatient and in-patient departments of department of ophthalmology in a tertiary care centre in West Bengal. Non-randomised sequential sampling was performed with corrected visual acuity better than or equal to 6 / 12. Fasting and postprandial blood glucose and HbA1c were estimated. Detailed ocular examination was performed using direct and indirect ophthalmoscope with + 20 D lens and slit lamp bio-microscope using + 90D lens. Retinal sensitivity was assessed by Humphrey visual field analyser by Swedish Interactive Thresholding Algorithm (SITA) standard strategy (30 - 2 programme). Spectral domain optical coherence tomography (SD OCT) was performed in all patients. SPSS version 20 has been used for the analysis.

RESULTS

Among DR patients, 33 had mild non-proliferative diabetic retinopathy (NPDR) (male = 15, female = 18) and 17 had moderate NPDR (male = 7, female = 10). Mean age in DR (Gr. 2) and no DR (Gr. 1) group were 52.62 and 50.74 years respectively. Mean foveal sensitivity and mean retinal sensitivity decreased significantly (P-value 0.001 and 0.002 respectively) in group 2 patients. It further decreased with increased severity of DR. Mean ganglion cell + inner plexiform layer (GC + IPL) thickness in temporal quadrant decreased in DR group compared to no DR group with significant difference between the two (P-value < 0.001). Mean retinal nerve fibre layer (RNFL) thickness was significantly reduced in DR group (P-value < 0.001). HbA1c mean in no DR (6.7 %) and DR group (8.07 %) and in mild (7.5 %) and moderate NPDR (9.17 %) shows significant association of poor control of blood sugar with severity of DR.

CONCLUSIONS

Retinal sensitivity decreased significantly in diabetes even without retinopathy as detected by automated perimetry. Significant decrease in retinal thickness as detected by OCT suggested that neurodegeneration occurs in diabetes even without retinopathy. So automated perimetry and OCT could be helpful in identifying persons at an early stage who are at risk of future vision loss due to diabetes.

KEYWORDS

Diabetic Retinopathy, Retinal Neurodegeneration, Retinal Sensitivity, Automated Perimetry, GCL + IPL Thickness, RNFL Thickness

Corresponding Author:
Dr. Swati Majumdar,
 # 159 A, B. B Chatterjee Road, Kasba, Kolkata - 700042, West Bengal, India.
E-mail: swt.mjmdr@gmail.com

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BACKGROUND

Diabetes is a metabolic disorder characterised by hyperglycaemia secondary to a deficiency in insulin production (type 1 diabetes) or reduced insulin sensitivity (type 2 diabetes). It has early deleterious effects on retinal neurovascular structure and function. Neuro-inflammation, apoptosis, glutamate excitotoxicity, and / or a deficiency of neuroprotective factors may all contribute to retinal dysfunction in diabetic retinopathy. Alterations of neuro-retinal structure and function precede the clinically observable lesions traditionally associated with diabetic retinopathy such as microaneurysms, haemorrhages, and lipid exudates.[1] These changes appear to signify impairment of normal regulatory mechanisms throughout the neurovascular complex of the retina rather than isolated vascular or neuroglial alterations[2] occurring in the preclinical period. Identifying subclinical alterations in neurovascular unit function could help to identify persons at risk for future vision loss.

Retinal sensitivity in diabetic neurodegeneration leads to loss or decrease in retinal sensitivity that can be measured by automated perimetry.

Automated perimetry - It uses a standardised test procedure to assess retinal sensitivity and compares an individual test results to age adjusted normal population characteristics to identify whether various locations are within normal sensitivity limits or outside normal limits by a specific amount. Limited retinal damage with normal vision in eyes without retinopathy require identifying the relation between sensitivity in surrounding retina with fovea. It is critical for clinicians to know about alterations in retinal sensitivity in diabetic subjects to initiate a proper management which may affect quality of life.

Ganglion cell layer thickness in diabetic retinopathy - Retinal neurons, ganglion cells in particular begin to die by apoptosis within weeks of the onset of diabetes.[3] Loss of ganglion cell layer (GCL) is primarily caused by a prolonged disturbance of the glucose metabolism - so longer duration of DM even without DR can result in a relatively thin ganglion cell layer.

Nerve fibre layer thickness in diabetes - Ischaemia, reduced protein synthesis, depleted myoinositol and high sorbitol levels associated with DM may result in nerve fibre loss in peripheral nerves. Hence, it is possible that retinal nerve fibres also suffer due to DM. Studies of the retinal nerve fibre layer using green filter photographs have detected focal loss in diabetic patients.[4]

HbA1c and its relation to retinal sensitivity - Several randomised controlled trials and observational studies have showed that glycated haemoglobin is a good predictor of microvascular complications[5] and is highly correlated with fasting plasma glucose.[6] It has been shown that mild to moderate retinopathy are rare below HbA1c 6.6 to 7 and prevalence increased to 16 - 17 folds above this level of HbA1c.[7] Only a few studies have investigated the relationship between retinal sensitivity and diabetic retinopathy. So, there is a gap in knowledge regarding retinal sensitivity and progression of diabetic retinopathy from early to late stages.

We wanted to measure and compare retinal sensitivity in the central 30 degrees in diabetic patients without and with diabetic retinopathy in different stages and evaluate changes in retinal sensitivity in relation to change in HbA1c values. We also wanted to measure and compare GCL thickness in various stages of DR with the help of OCT.

METHODS

An observational, cross-sectional study in subjects without DR and subjects with DR who had no ocular abnormalities was conducted in outpatient and in-patient Department of Ophthalmology in a tertiary care centre in West Bengal from January 2019 to December 2019 with approval of the institutional ethics committee.

Non-randomised sequential sampling was performed which included 50 patients without DR and 50 patients with DR between 45 - 64 years of age with corrected visual acuity under subjective refraction more or equal to 6 / 12, with stable fixation and without ocular media opacity.

Those who had received any laser photocoagulation / anti vascular endothelial growth factor (VEGF) injections or had age-related macular degeneration, glaucoma, intraocular pressure (IOP) > 20 mm Hg, colour deficiencies and low reliability on automated perimetry were excluded. Patients without DR were assigned to group 1 and those with DR were assigned to group 2. In cases with DR in both eyes more severely affected eye was selected and in cases with DR of equal severity in both eyes the study eye was selected by tossing a coin. DR group were further subdivided into mild and moderate non-proliferative diabetic retinopathy as per Early Treatment Diabetic Retinopathy Study (ETDRS) classification.[6] Informed consent was taken from each patient. A detailed history about patient particulars (age, gender, address etc), any systemic illness, ocular disease, medications and duration of type 2 diabetes mellitus were noted. Fasting and postprandial blood glucose and HbA1c were estimated. Detailed ocular examination was performed. Fundus examination was done using direct and indirect ophthalmoscope with + 20 D lens and slit lamp biomicroscope using + 90 D lens and confirmed by a senior ophthalmologist. IOP was measured by non-contact tonometer.

The outcome variable was the retinal sensitivity which was assessed by Humphrey visual field analyser by SITA standard strategy, 30 - 2 programme. The device automatically determined the foveal sensitivity in decibels (dB); all tests were conducted by single observer. The test was considered reliable when fixation losses were fewer than 20 %. SD OCT was done in all patients. Three locations of the posterior pole were examined; peripapillary retinal nerve fibre layer (RNFL), the optic nerve head (ONH) and macular ganglion cell complex (GCL) were analysed.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD) and compared across the groups using Mann-Whitney U test. Categorical variables were expressed as

number of patients and percentage of patients and compared across the groups using Pearson's chi square test for Independence of attributes. Multivariate analysis was done using Binary Logistic Regression. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5 % has been taken, i.e. any P-value less than 0.05 has been considered as significant.

RESULTS

One hundred eyes (50 eyes with DR & 50 eyes without DR) of 100 middle aged type 2 diabetes mellitus patients were assessed. They were divided in two groups; group 1 without diabetic retinopathy (no DR) and group 2 with diabetic retinopathy (DR). Among DR patients, 33 had mild NPDR (male = 15, female = 18) and 17 had moderate NPDR (male = 7, female = 10). Mean age in DR (Gr. 2) and no DR (Gr. 1) group were 52.62 and 50.74 years respectively. The age and gender difference between two groups and between mild and moderate NPDR was not significant. Demographic data of subjects are shown in Table 1.

	NO DR (Group 1)			DR (Group 2)				Significance
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	P Value	
Age	50.74	49.50	5.64	52.62	52.00	5.23	0.074	Not significant
	Mild NPDR			Moderate NPDR				Significance
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	P-Value	
Age	51.76	50.00	5.26	54.29	55.00	4.87	0.075	Not significant

Table 1. Demographic Data of the Study Subjects

Retinal sensitivity (with foveal sensitivity) shown in Table 2.

	NO DR			DR				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	P Value (Mann-Whitney U Test)	Significance
Mean sensitivity	22.20	25.00	4.76	20.16	20.00	4.14	0.002	Significant
Foveal sensitivity	24.22	27.00	4.26	20.90	20.50	3.74	< 0.001	Significant
	DR							
	Mild NPDR			Moderate NPDR				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	P-Value	
Mean sensitivity	21.21	20.00	2.45	15.76	15.00	2.22	< 0.001	
Foveal sensitivity	22.91	22.00	2.80	17.00	17.00	1.66	< 0.001	

Table 2. Retinal Sensitivity

	NO DR			DR			(in Microns)	
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	P Value (Mann-Whitney U test)	Significance
GCL + IPL	71.56	71.00	4.44	69.40	68.00	8.20	0.029	Significant
RNFL thickness	81.86	85.00	6.07	79.23	80.25	4.40	< 0.001	Significant
GC+ IPL - T	70.86	70.00	4.14	66.42	65.00	7.17	< 0.001	Significant

Table 3. Retinal Thickness in Different Groups (No DR & DR)

OCT measurement of retinal thickness is shown in Table 3.

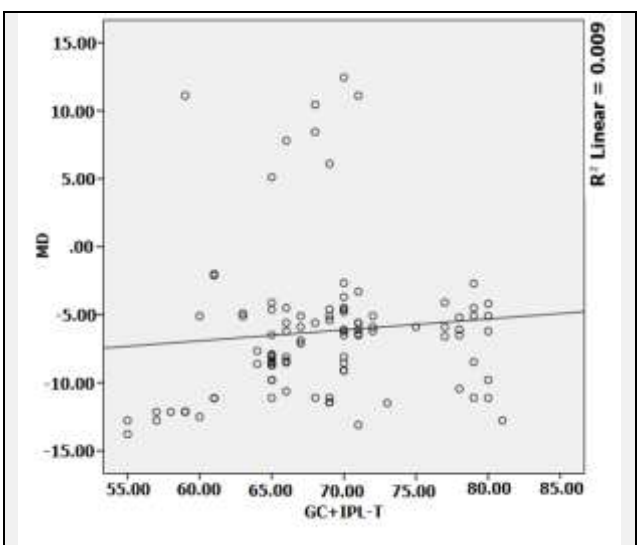
	Mild NPDR			Moderate NPDR				
	Mean	Median	Std. Deviation	Mean	Median	Std. Deviation	P Value	Significance
GCL+IPL	72.48	69.00	6.48	63.44	61.50	8.05	< 0.001	Significant
RNFL thickness	81.36	81.00	2.95	75.09	74.00	3.81	< 0.001	Significant
GC+ IPL - T	68.52	65.00	5.83	62.35	60.00	7.92	< 0.001	Significant

Table 4. Retinal Thickness in DR Gr. (in Microns)

	P-Value	Odds Ratio	95 % C.I. for Odds Ratio	
			Lower	Upper
MD	0.014	0.873	0.784	0.973
PSD	0.926	1.014	0.760	1.351
Mean sensitivity	0.036	1.494	1.027	2.173
Foveal sensitivity	0.016	0.639	0.444	0.922
GCL + IPL	0.758	1.016	0.917	1.127
RNFL thickness	0.595	1.052	0.873	1.268
GC+ IPL - T	< 0.001	0.115	0.039	0.343
HbA1c	< 0.001	5.775	2.550	13.077
Duration	0.235	0.816	0.584	1.141

Table 5. Binary Logistic Regression after Adjustment for Duration and HbA1c in No DR and DR

Significance persisted in mean deviation (MD) and in mean sensitivity and GC + IPL (T) after adjustment for HbA1c and duration between no DR and DR groups shown in Table 4.



Graph 1. Correlation between Mean Deviation and GCL + IPL (T) Thickness

Positive correlation noted between mean deviation and GC + IPL (temporal) thickness.

			MD
Spearman's RHO	GC+ IPL - T	Correlation coefficient	0.220
		P-value	0.028
	RNFL thickness	Correlation coefficient	0.445
		P-value	< 0.001
	GCL + IPL	Correlation coefficient	0.168
		P-value	0.094

Table 5. Correlation Coefficient between Mean Deviation and RNFL, GCL + IPL (Global), GC + IPL (Temporal)

There is a significant correlation between mean deviation and GC + IPL (T) and RNFL thickness.

DISCUSSION

The age and gender difference between two groups and between mild and moderate NPDR was not significant in this study. As the duration of diabetes increases severity of diabetic retinopathy increases. The difference of mean duration of diabetes was statistically significant among DR and no DR. Mean visual acuity in patients without DR is 0.13 log MAR and in diabetic retinopathy patients is 0.21 log MAR (P-value - 0.003). In mild NPDR patients it was 0.19 log MAR and in moderate NPDR patients it was 0.24 (P-value is not significant). There was significant reduction in visual acuity in DR compared to no DR though the difference was not significant between mild and moderate DR Sampson GP et al.[8] studied visual sensitivity in central 30° of visual field in patients with diabetic peripheral neuropathy and concluded that visual sensitivity reduces disproportionately with increasing eccentricity in type 2 diabetic patients. This sensitivity reduction within the central 30° of visual field may be indicative of more consequential loss in the far periphery. In this study mean foveal sensitivity decreased from 24 db in group 1 patients to 20.90 db in group 2 patients which was significant (Table 2). It further decreased in moderate NPDR when compared to mild NPDR with a significant difference between the two groups. Our findings are similar to the study done by Somilleda-Ventura et al.[9] Again, mean retinal sensitivity decreased significantly from 22.20 db in group 1 to 20.16 db in group 2 patients. It further decreased among moderate NPDR compared to mild NPDR with a significant difference between two groups. Our study findings are similar to Kaur S et al.[10] which showed significant decrease in total mean sensitivity at 10° for patients without DR and with DR (18.67 ± 0.83 db and 17.98 ± 1.42 db respectively). Nittala G Muneswar et al.[11] studied retinal sensitivity and fixation characteristics in participants with diabetes mellitus using the micro perimeter (MP-1) and showed that retinal sensitivity significantly decreased with increased severity of DR. In this study Mean deviation (MD) decreased in DR group (- 7.48) compared to no DR group (- 4.97) with significant difference (P-value 0.002) between two. MD further decreased among moderate NPDR compared to mild NPDR with a significant difference. Similar results were obtained by Henricksson M, et al.[12] who showed that in eyes without DR or mild disease mean deviation values were below the normal level in only 4 % of eyes whereas in severe non-proliferative and proliferative retinopathy there was significantly reduced MD in 44 % of eyes. This clearly indicates that retinal sensitivity decreases significantly as the severity of the disease increases.

On OCT measurement, mean GCL + IPL (temporal) thickness in no DR group and DR group was 70.86 and 66.42 microns respectively and again 68.52 micron in mild and 62.35 micron in moderate NPDR respectively (Table 3). There was a significant reduction in GCL + IPL (temporal) thickness in our study. G Montesano et al.[13] also studied correlation of the local ganglion cell layer-inner plexiform layer (GCL - IPL) thickness with corresponding retinal sensitivity in microperimetry in diabetic patients with no DR and observed higher GCL - IPL thickness and higher sensitivity in normal subjects compared to diabetic subjects.

In this study mean RNFL thickness decreased significantly in DR group (81.36 micron) compared to no DR group (81.86 micron) and again in moderate NPDR than in mild NPDR (P-value < 0.001). Srinivasan S et al.[14] showed the relationship between the markers of early retinal neuronal damage and peripheral diabetic neuropathy (DN) in subjects with no diabetic retinopathy (no DR) and they found significant association of neuroretinal dysfunction in presence of diabetic neuropathy among subjects with no DR. Structural changes included significant thinning of RNFL and significant thickening of retinal pigment epithelium (RPE) in subjects with DN when compared to those without DN. From the RNFL and GCL + IPL thickness loss it is suggested that retinal neurodegeneration occurs in diabetic patients even without retinopathy. HbA1c mean in no DR (6.7 %) and DR group (8.07 %) and in mild (7.5 %) and moderate NPDR (9.17 %) showed significant association of poor control of blood sugar with severity of DR. A study by Barr RG et al.[15] showed that mild to moderate retinopathy are rare below HbA1c level of 6.6 %.

Binary regression analysis in no DR and DR showed that significance persisted after adjustment for duration and HbA1c in MD, mean sensitivity, foveal sensitivity, GCL + IPL thickness in temporal quadrant and RNFL thickness (Table 4). Correlation coefficient between mean deviation and GCL + IPL (temporal) showed significant correlation between the two variables (P-value 0.028). This was also true for mean deviation and RNFL thickness (P-value < 0.001).

CONCLUSIONS

In this institution based cross sectional study involving 100 middle aged type 2 diabetes mellitus patients, decrease in retinal sensitivity was significant even without retinopathy. So, automated perimetry may be useful for early detection of retinal neurodegeneration in diabetic patients. Prevalence of loss of retinal sensitivity increases with increase in severity of diabetic retinopathy. Values of all the retinal sensitivity parameters (mean deviation, foveal sensitivity pattern, standard deviation) were significantly low in the presence of retinopathy which persisted after adjustment for age and duration of diabetes. From the RNFL and GCL + IPL thickness loss it was suggested that retinal neurodegeneration occurs before clinically detectable diabetic retinopathy changes. These OCT parameters could be helpful in identifying persons at risk for future vision loss due to diabetes at the earliest.

Limitations

It was a non-randomised study with a small sample size and presence of co-morbidities like hypertension and hyperlipidaemia and history of varied drug intake in some patients might have affected various parameters differently. A cohort study would be most appropriate to obtain more valuable information in future.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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