Original Article

Foveal slope measurements in diabetic retinopathy: Can it predict development of sight-threatening retinopathy? Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS II, Report no 8)

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Aim: The aim was to assess the foveal slope configuration in subjects with type 2 diabetes in a population-based study. **Materials and Methods:** A subset of 668 subjects from Sankara Nethralaya Diabetic Retinopathy (DR) Epidemiology and Molecular Genetics Study II, a population-based study, were included in the current study. All the subjects underwent comprehensive ophthalmic evaluation including spectral domain optical coherence tomography. Foveal thickness was assessed in five central early treatment DR study quadrants from the three-dimensional scan and foveal slope was calculated in all the four quadrants. **Results:** Subjects with sight-threatening DR (STDR) had significantly shallow foveal slope in inferior quadrant (STDR: 7.33 ± 6.26 vs. controls: 10.31 ± 3.44; $P = 0.021$) when compared to controls and in superior (STDR: 7.62 ± 5.81 vs. no DR: 9.11 ± 2.82; $P = 0.033$), inferior (STDR: 7.33 ± 6.26 vs. no DR: 8.81 ± 2.81; $P = 0.048$), and temporal quadrants (STDR: 6.69 ± 5.70 vs. no DR: 7.97 ± 2.33; $P = 0.030$) when compared to subjects with no DR. Foveal slope was significantly shallow among the older age groups in subjects with no DR ($P < 0.001$) and non-STDR ($P = 0.027$). Average foveal slope in the diabetic subjects was independently and significantly correlated with increase in age ($r = -0.241$; $P < 0.001$) and central subfield thickness ($r = -0.542$; $P < 0.001$). **Conclusion:** Changes in foveal slope were seen with increasing age; however, in diabetes these segmental slope changes can be seen in late DR (STDR).

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.162578

Quick Response Code:

Key words: Diabetes, foveal slope, retinal thickness, spectral domain optical coherence tomography

Fovea is the specialized region of human retina that drives majority of our visual function.[1] Variation in foveal shape is related to the structural alterations of the retinal layers. Various parameters of the foveal structure have been found to be altered in subjects with diabetic retinopathy (DR)[2-4] and age-related macular degeneration.[5] Although foveal thickness has been used as marker of structural changes in various retinal diseases, there are evidences of using other foveal parameters such as foveal diameter, foveal slope, and foveal depth to assess the structural integrity of macula.[6]

It is known that the foveal avascular zone (FAZ) diameter enlarges in DR and further increases with severity of retinopathy due to the capillary dropout.[3,4] Early neuronal degeneration has also been reported in diabetic subjects even with no retinopathy.[7,8] Dubis *et al*.[9] have shown a strong relationship between FAZ and foveal pit morphology. Foveal slope measurement has been tried in macular diseases such as macular hole[6] and age-related macular degeneration,[5] and correlated with disease prognosis and macular pigment optical density.[10]

To the best of our knowledge, no study has looked into the foveal slope profile in subjects with diabetes and DR. The aim of this study was to assess the foveal slope in subjects with type 2 diabetes in a population-based cohort and to correlate foveal slope with visual function.

Materials and Methods

Sankara Nethralaya DR Epidemiology and Molecular Genetic Study II (SN-DREAMS II) was a follow-up study of SN-DREAMS I,[11] which was conducted between 2007 and 2010. In the follow-up study, of the 958 subjects, 668 subjects who underwent spectral domain optical coherence tomography (SD-OCT) were included in the analysis. The study was approved by the organization's institutional review board and was in accordance with the principles of Declaration of Helsinki, and informed consent was obtained from all subjects before participation.

All subjects underwent demographic, medical, and ocular history taking, which included comprehensive eye examination. Color vision was assessed monocularly using Farnsworth–Munsell 100 hue test, and the test results were reported as total error score calculated based on the classical method. Contrast sensitivity was assessed using Pelli–Robson chart at 1 m distance. The logarithmic contrast sensitivity value of the last triplet of which at least two letters are correctly seen was marked as the result. DR was graded clinically using Klein's classification (modified early treatment DR study [ETDRS] scales)[12] and the subjects were further classified as no DR, as nonsight-threatening DR (non-STDR) and as STDR. Non-STDR subjects included cases of mild and moderate nonproliferative DR and those with STDR included severe nonproliferative DR, proliferative DR, and clinically significant macular edema. Retinal photographs were obtained after pupillary dilatation using FF450 plus IR Fundus Camera (Carl Zeiss Meditec,

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Manuscript received: 22.09.14; Revision accepted: 27.05.15

Germany); all subjects underwent 45°, 4-field stereoscopic digital photography (posterior pole, nasal, superior, and inferior). For those who showed evidence of any retinopathy, additional 30°, 7-field stereo digital pairs were obtained. All photographs were graded by two independent observers in a masked manner; the grading agreement was high ($k = 0.83$).[9]

Retinal thickness was measured using SD-OCT (Copernicus; Optopol, Poland), following pupil dilation with 1% tropicamide. Retinal thickness was calculated automatically using an inbuilt topographic mapping software. A retinal map was acquired using the three-dimensional scan protocol with 50 B-scans and 1000 A-scans per B-scan, centered on the subject's fixation point. Central subfield thickness (CSFT) was noted. The temporal, superior, inferior, and nasal subfield thicknesses were noted at 3 mm radius. Foveal slope in all four quadrants was calculated at a distance of 500 µm from the foveal center [Fig. 1]. For example, foveal slope in nasal quadrant was calculated as the difference between nasal quadrant thickness in the 3 mm radius and CSFT divided by 500 µm, which is the distance of nasal quadrant thickness from foveal center.

Slope angle = Difference in thickness/horizontal distance

Slope (°) = $\tan^{-1}$ (slope angle).

Statistical analysis

Statistical analyses were performed using the statistical software SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). In newly diagnosed subjects with diabetes, the duration was considered as 0. Foveal slope (°) was represented as mean ± standard deviation independent *t*-test and one-way analysis of variance were used to compare the variables among groups and a *post-hoc* analysis was carried out using Bonferroni method. Correlation of variables with foveal slope was assessed using Pearson and partial correlation coefficients. A $P < 0.05$ was considered statistically significant.

Results

The average foveal slope values among subjects with diabetes in superior, inferior, temporal, and nasal quadrants were 8.94° ± 3.04°, 8.71° ± 3.14°, 7.86° ± 2.60°, and 8.07° ± 2.72°, respectively. Table 1 shows the foveal slope characteristics among the study subjects with varying severity of DR. In general, there is a trend of shallow foveal slope in all quadrants with increase in the severity of DR. Shallow foveal slope was found in subjects with STDR in inferior quadrant (STDR: 7.33 ± 6.26 vs. controls: 10.31 ± 3.44; $P = 0.021$) when compared to controls with no diabetes and in superior (STDR: 7.62 ± 5.81 vs. no DR: 9.11 ± 2.82; $P = 0.033$), inferior (STDR: 7.33 ± 6.26 vs. no DR: 8.81 ± 2.81; $P = 0.048$), and temporal quadrants (STDR: 6.69 ± 5.70 vs. no DR: 7.97 ± 2.33; $P = 0.030$) when compared to subjects with no DR.

Table 2 shows the distribution of average foveal slope among the demographic and systemic factors. Foveal slope was significantly shallow among the older age groups in subjects with no DR ($P < 0.001$) and non-STDR ($P = 0.027$) and was steeper in subjects with poor glycemic control ($P = 0.004$) and in subjects with no DR. No difference in foveal slope was found among the demographic and systemic factors in subjects with non-STDR and STDR.

Table 3 shows a gender-wise comparison of thickness and slope parameters among the study subjects. Mean retinal CSFT and all the quadrants of inner 3 mm radius of ETDRS subfields were significantly thicker in males compared to females. However, we did not find any significant difference in foveal slope in all the quadrants between the genders.

Table 4 shows Pearson and partial correlation between foveal slope and ocular variables. Foveal slope was significantly and inversely correlated with an increase in age, increase in duration of diabetes, best-corrected visual acuity, color vision, refractive error, and CSFT. Significant positive correlation was found between foveal slope and contrast sensitivity. However, when adjusted for all the parameters, partial correlation revealed significant relationship of foveal slope with increase in age ($r = -0.241$; $P < 0.001$) and CSFT ($r = -0.542$; $P < 0.001$).

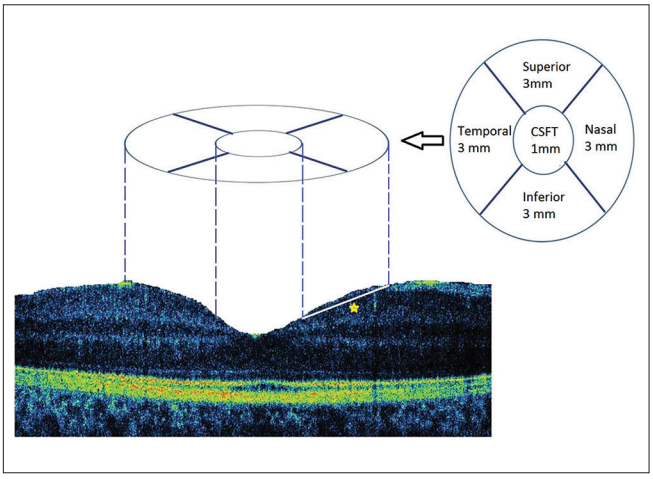

Figure 1: Measurement of foveal slope in all four quadrants

Table 1: Foveal slope characteristics among the study sample

Characteristics	Controls		No DR		Non-STDR		STDR		Trend *P*
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	
Duration of diabetes (years)	NA	NA	7.62±5.18	0–34	12.59±7.56	4-37	14.27±5.64	4-24.83	<0.001
Superior slope	8.51±2.35	4.01-12.61	9.11±2.82	(–3.44)-19.48	8.55±2.78	(–5.73)-13.75	7.62±5.81†	(–14.90)-14.90	0.019
Inferior slope	10.31±3.44	7.45-17.76	8.81±2.81	(–1.72)-25.21	8.50±3.14	(–6.88)-15.47	7.33±6.26*,†	(–18.91)-14.32	0.012
Temporal slope	8.24±2.07	5.73-13.18	7.97±2.33	(–2.86)-16.04	7.62±2.18	1.15-14.32	6.69±5.70†	(–17.19)-13.75	0.027
Nasal slope	9.70±4.08	4.01-18.91	8.14±2.52	(–2.86)-21.20	7.69±2.60	(–8.02)-14.32	7.41±4.65	(–7.45)-16.62	0.03

*Significant when compared with controls, †Significant when compared with no DR. DR: Diabetic retinopathy, STDR: Sight-threatening diabetic retinopathy, NA: Not applicable, SD: Standard deviation

Table 2: Average foveal slope and its relation with demographic data

Variables	No DR (*n*=532)	*P*	Non-STDR (*n*=102)	*P*	STDR (*n*=34)	*P*
Mean slope	8.50±2.25		8.09±2.23		7.26±4.46	
Age (years)						
40-49	9.09±2.30	<0.001	8.36±2.38	0.027	7.45±0.62	0.951
50-59	8.82±1.93		8.16±1.74		7.44±4.50	
60-69	8.01±2.30		8.52±1.69		6.92±5.12	
≥70	7.27±2.59		6.31±3.69		NA	
Gender						
Men	8.63±2.41	0.179	8.11±2.46	0.902	7.53±3.57	0.64
Women	8.37±2.04		8.05±1.91		6.77±5.92	
Duration of diabetes (years)						
≤5	8.57±2.25	0.582	8.53±1.78	0.363	9.02±2.15	0.409
>5	8.46±2.25		7.99±2.32		7.03±4.66	
HbA1c						
Normal (<5.6)	7.85±2.16	0.004	9.02±1.36	0.287	10.89±4.46	0.346
Good to fair (5.6-8.0)	8.48±2.27		7.83±1.98		6.29±5.35	
Poor (≥8.1)	8.93±2.25		8.25±2.70		7.69±3.47	

DR: Diabetic retinopathy, STDR: Sight-threatening diabetic retinopathy, NA: Not applicable, HbA1c: Glycated Hemoglobin

Table 3: Comparison of thickness and slope parameters among men and women

OCT variables	Male	Female	*P*
CSFT	196.98±31.94	187.17±29.53	<0.001
Inner ring superior quadrant	275.87±33.45	264.37±27.56	<0.001
Inner ring inferior quadrant	273.49±30.77	262.05±29.87	<0.001
Inner ring temporal quadrant	266.17±27.74	254.90±26.79	<0.001
Inner ring nasal quadrant	268.53±34.23	255.46±28.57	<0.001
Superior slope	9.02±3.05	8.85±3.05	0.467
Inferior slope	8.77±3.47	8.57±2.66	0.391
Temporal slope	7.92±2.79	7.76±2.35	0.423
Nasal slope	8.20±2.71	7.84±2.62	0.089

CSFT: Central subfield thickness, OCT: Optical coherence tomography

Table 4: Correlation between foveal slope and ocular parameters

Parameters	Foveal slope			
	Pearson correlation		Partial correlation	
	r	*P*	*r*	*P*
Age (years)	0.231	<0.001	0.241	<0.001
Duration of diabetes (years)	0.112	0.004	0.027	0.678
Visual acuity (logMAR)	0.122	0.002	0.007	0.918
Color vision (TES)	0.162	0.009	0.059	0.368
Contrast sensitivity (log units)	0.109	0.008	0.019	0.778
Refractive error (diopters)	0.082	0.034	−0.1	0.128
CSFT (μm)	0.499	<0.001	0.542	<0.001

Adjusted for age, duration of diabetes, visual acuity, color vision, contrast sensitivity, CSFT, DR. CSFT: Central subfield thickness, TES: Total error score, DR: Diabetic retinopathy

Discussion

In this study, we investigated the structural variability of the fovea in terms of foveal slope in patients with type 2 diabetes. Foveal slope was found to be significantly shallow in subjects with STDR compared to other group of subjects in superior, inferior, and temporal quadrants. No difference in foveal slope was found in nasal quadrant. Foveal slope was found to be significantly shallow in older subjects with no retinopathy and with without STDR, and poor glycemic control was associated with steep foveal slope. Mean retinal thickness was significantly thicker in men compared to women in all the quadrants. However, we did not find any significant difference in foveal slope between men and women in all quadrants. Average foveal slope was significantly and negatively correlated with an increase in age and CSFT after adjusting for other factors.

We found a trend of decreased foveal slope with an increase in severity of DR in all the quadrants. However, on Bonferroni correction, only subjects with STDR had a shallow inferior foveal slope compared to controls and shallower superior, inferior, and temporal slope compared to those with no DR. This could be explained by the fact that as the foveal slope was negatively correlated with CSFT, subjects with STDR with more CSFT had a shallow foveal slope. Shallower slope also relates to the disproportional increase in retinal thickness in parafoveal and foveal areas in STDR. It may also be related to thinner subfoveal choroidal thickness in STDR, which was reported in the study conducted by Unsal *et al*.[13]

We found a shallowing of slope with increasing age in No DR and Non-STDR groups. However, this age-related effect was not seen in STDR group. As it is known that the retinal thickness is increased in subjects with STDR, which includes cases with macular edema as well, in this group of subjects, the shallowing of foveal slope with increase in age might be compensated by the increased in retinal thickness.[14]

Our results are in agreement with those who reported reduced retinal thickness in women compared to men.[15-17] There have been reports on the effect of sex and race on foveal parameters such as foveal slope, foveal pit diameter, and foveal pit depth, and reports that there is no gender-based difference in these parameters.[18] These data taken together to support our finding that there is no gender-related difference in foveal slope.

In addition, we also assessed the correlation between the average foveal slope in the study sample and the ocular parameters. However, on adjusting for the variables using partial correlation, the factors that were found to be independently related to the foveal slope were increase in age and CSFT. Foveal slope was significantly and negatively correlated with age. This can be due to age-related neuronal loss.[19,20] Similarly, an increase in central macular thickness would shallow the slope.

This being a cross-sectional study, we could not see the changes in slope from no DR to non-STDR to STDR. However, we got some interesting clues that could have clinical significance. The first clue is a trend of shallowing of foveal slope with increase in the severity of DR. Thus, sequential OCT with slope measurements may predict progression of DR. The second clue is significant shallowing of slope in inferior quadrant of subjects with STDR when compared to controls, which again may help in predicting the onset of STDR. However, future longitudinal studies are required to validate these trends.

In conclusion, there are foveal slope changes specific for stages of DR, non-STDR, and STDR. Age and CSFT are independently related to slope. Further, longitudinal studies are required to confirm the utility of these measurements.

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Cite this article as: Gella L, Pal SS, Ganesan S, Sharma T, Raman R. Foveal slope measurements in diabetic retinopathy: Can it predict development of sight-threatening retinopathy? Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS II, Report no 8). Indian J Ophthalmol 2015;63:478-81.

Source of Support: Jamshetji Tata Trust, Mumbai, **Conflict of Interest:** None declared.