Original Article

Foveal slope measurements in subjects with high-risk of age-related macular degeneration

Rajiv Raman, Sayalee Lahane, Aditi Gupta, D Sandeep[1], Tarun Sharma

Background: Recent reports indicated that the slope of the foveal depression influences the macular pigment (MP) spatial profile. MP has been shown to confer possible protection against age-related macular degeneration (ARMD) because of its antioxidant properties. **Aims:** To study the configuration of foveal slope and the foveal thickness in fellow eyes of subjects with unilateral neovascular ARMD. **Settings and design:** Case-control series. **Materials and Methods:** The study population consisted of 30 cases aged >50, who had unilateral choroidal neovascular membrane (CNVM) or disciform scar in the fellow eye and 29 controls aged >50, who had no sign of ARMD in the either eye. Using spectral-domain optical coherence tomography, foveal thickness at different locations including the central subfield foveal thickness (CSFT) was noted. The foveal slopes were calculated in the six radial scans (between 0.25° and 1° retinal eccentricity) as well as the 3D scan. **Results:** Cases had a significantly higher CSFT when compared to controls (215.1 ± 36.19 μ vs. 193.0 ± 17.38 μ, $P = 0.004$). On the 3D scan, the cases had shallower superior (cases 1.32 ± 0.32 vs. controls 1.45 ± 0.13, $P = 0.04$) and temporal slopes (cases 1.27 ± 0.21 vs. controls 1.39 ± 0.12, $P = 0.01$) in comparison to the controls. **Conclusions:** We noted a shallower superior and temporal foveal slope and a higher CSFT in the fellow eyes of subjects with a unilateral neovascular ARMD. Prospective studies observing the development of CNVM in subjects with altered foveal slope might provide more information on this optical coherence tomography finding.

Key words: Configuration, choroidal neovascular membrane, foveal slope, foveal thickness, neovascular age-related macular degeneration, macular pigment

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The neovascular form of age-related macular degeneration (ARMD) accounts for the majority of patients with severe visual loss from this disease.[1] The incidence of developing neovascular disease in the second eye of the participants with unilateral neovascular ARMD has been reported to be as high as 35% over a median follow-up of 6.3 years.[2]

Although the precise etiopathogenesis of ARMD remains a matter of debate, there is compelling evidence to indicate that oxidative damage plays a crucial role.[3-5] In recent years, there has been a growing interest on studying macular pigment (MP) optical density because of possible protection against ARMD conferred by the antioxidant properties of MP.[6,7] This protective effect of the MP may be of therapeutic value as it has been reported that MP can be augmented with the dietary modification.[8]

MP has been shown to be significantly related to central retinal thickness in the healthy subjects as well as in some types of retinal degeneration.[9-12] Liew *et al*. have shown a significant positive relationship between the central retinal thickness and the MP optical density.[9] More recently, Kirby *et al*. showed that the slope of the foveal depression influences the MP spatial profile, with a steeper MP spatial profile being associated with a steeper foveal depression.[13]

Shri Bhagwan Mahavir Department of Vitreoretinal Services, and [1]Department of Optometry, Sankara Nethralaya, Chennai, Tamil Nadu, India

Correspondence to: Dr. Tarun Sharma, Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18 College Road, Chennai - 600 006, Tamil Nadu, India. E-mail: drtaruns@gmail.com

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The purpose of the present pilot study was to determine whether fellow eyes of patients with unilateral neovascular ARMD have altered foveal slope, an indirect evidence of altered MP spatial profile. We also aimed to study the foveal thickness in fellow eyes of subjects with an unilateral neovascular ARMD.

Materials and Methods

This is a pilot study, the study population consisting of 30 cases aged >50, who had no sign of the ARMD in one eye and a choroidal neovascular membrane (CNVM) or disciform scar in the other eye and 29 controls aged >50, who had no sign of the ARMD in the either eye. An ocular history and examination was performed on all subjects to exclude those with any previous ocular surgery or retinal pathology (including early age related maculopathy in both eyes of controls and study eye of cases). Research procedures followed the tenets of the Declaration of Helsinki and were approved by the institutional ethics committee.

Retinal thickness was measured using spectral domain optical coherence tomography (SD-OCT) (Copernicus, Optopol, Polland), following pupil dilation with 1% tropicamide. Retinal thickness was calculated automatically using the inbuilt topographic mapping software. A single retinal map was acquired using the 3D scan protocol, centered on the subject's fixation point. Central subfield foveal thickness (CSFT) was noted. The temporal, superior, inferior, and nasal subfield thicknesses were noted at 3 mm radius. The measurements were carried out in the normal eye in cases and in the right eye in controls.

Calculation of foveal slope: The calculation of foveal slope was carried out as described by Kirby *et al*. in the six

radial scans.[13] Measurements were carried out between 0.25° and 1° retinal eccentricity [Fig. 1]. The values, in micrometers, corresponding to these retinal eccentricities, were used as x-values. The foveal thickness values (caliper function-OCT) were taken as the perpendicular distance between the horizontal lines drawn from the foveal center to the vitre-oretinal interface. The thickness (micrometers) at both 0.25° and 1° retinal eccentricity, measured subjectively, using the built-in caliper function were used as y-values. The slope equation $m = (y_2 - y_1)/(x_2 - x_1)$ was then applied. Thus, the slope of the foveal pit profile curve was approximated with the slope of the line segment joining (x_1, y_1) and (x_2, y_2). Similar calculation was carried out in all six macular scans and average of all the six readings was taken as the overall foveal slope. The slope was also calculated in the 3D scan. The individual slopes on the 3D scan were calculated as a ratio of temporal/nasal/superior/inferior and CSFT.

Statistical analyses were performed using SPSS for Windows version 14.0 software (SPSS Inc., Chicago, IL, USA). The retinal thickness and foveal slope measurements for cases and controls were adjusted for the age and gender.

Results

Fig. 2 shows, the comparison of mean retinal thicknesses in cases and controls. There was a statistically significant difference in the CSFT in cases and controls (215.1 ± 36.19 μ vs. 193.0 ± 17.38 μ, $P = 0.004$). However, there were no significant differences in temporal, superior, inferior, and nasal subfield thicknesses.

Table 1 shows, the comparison of foveal slopes between the cases and controls as measured in the six radial scans. There was no statistically significant difference between the cases and controls.

Table 2 shows, the comparison of foveal slopes between cases and controls as measured in the 3D scan. Cases had a

Table 1: Foveal slope measurements at six radial scans in cases and controls

Parameters	Cases	Controls	*P* value
Average slope	0.067 (0.055-0.078)	0.077 (0.066-0.088)	0.200
Slope at 0°	0.073 (0.055-0.092)	0.077 (0.059-0.095)	0.789
Slope at 30°	0.059 (0.046-0.072)	0.075 (0.062-0.088)	0.093
Slope at 60°	0.067 (0.051-0.083)	0.087 (0.071-0.102)	0.085
Slope at 90°	0.067 (0.051-0.084)	0.085 (0.068-0.101)	0.141
Slope at 120°	0.061 (0.046-0.076)	0.068 (0.053-0.083)	0.537
Slope at 150°	0.072 (0.053-0.090)	0.071 (0.052-0.089)	0.947

Table 2: Comparison of foveal slopes from 3D scans in cases and controls

Parameters	Cases	Controls	*P* value
Superior slope	1.31 (1.22-1.41)	1.46 (1.36-1.55)	0.036
Inferior slope	1.33 (1.25-1.41)	1.40 (1.33-1.48)	0.180
Nasal slope	1.29 (1.21-1.37)	1.37 (1.29-1.45)	0.165
Temporal slope	1.28 (1.21-1.34)	1.39 (1.32-1.45)	0.018

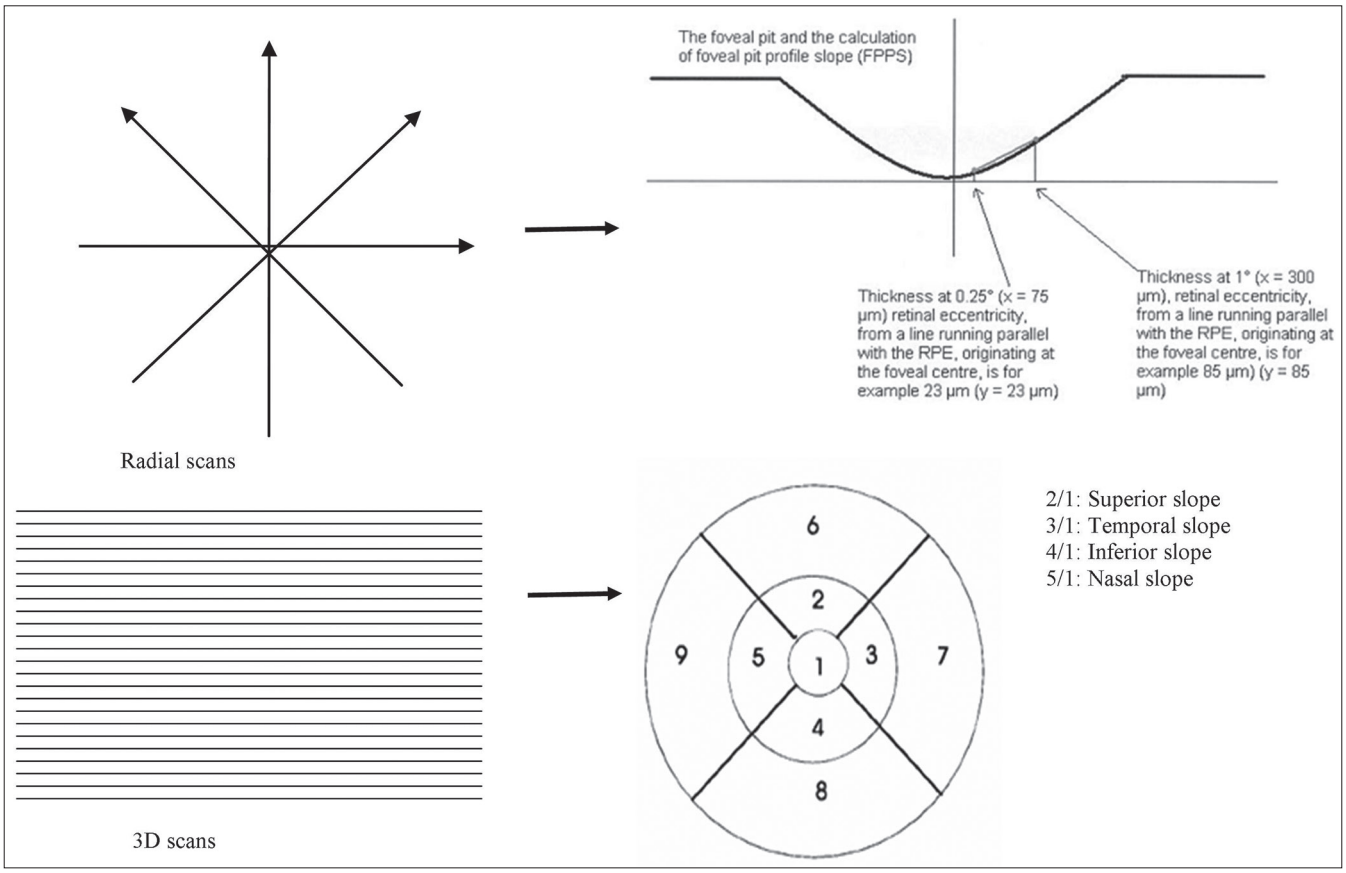

Figure 1: Calculations of foveal slope using radial scans and 3D scans

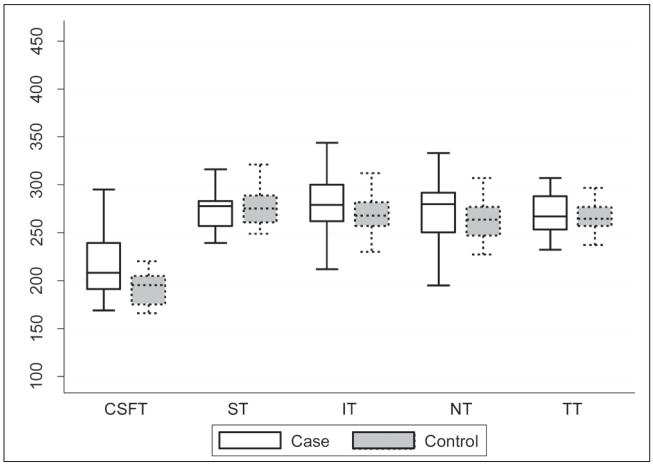

Figure 2: Comparison of retinal thickness measurements in cases and controls (CSFT: Central subfield foveal thickness, ST: Superior subfield thickness, IT: Inferior subfield thickness, NT: Nasal subfield thickness and TT: Temporal subfield thickness)

statistically significant difference in the superior (cases 1.31 vs. controls 1.46, $P = 0.036$) and the temporal slopes (cases 1.28 vs. controls 1.39, $P = 0.018$), the respective slopes being found to be shallower in comparison to controls. There were no significant differences in the nasal and inferior slopes in the two groups.

Discussion

Age-related eye disease study report no. 19 has indicated the risk of developing CNVM in fellow eyes of subjects with unilateral neovascular ARMD to be as high as 35%.[2] Since the patients with the identifiable risk factors for development of CNVM in fellow eyes would benefit from closer monitoring the risk factors have been extensively studied in the literature. Recently, many reports have focused on studying in detail the MP optical density in ARMD because MP has been hypothesized to have a protective role against the development of ARMD.[6,7,14,15] An association has been reported between MP and retinal thickness[9-12] and between MP and foveal slope;[13] hence, studying these parameters can also prove useful. Moreover, recent reports have even cited the possibility that a thin retina may be an independent risk factor for ARMD, with the association of ARMD and low MP being secondary to this.[9]

In the present study, we aimed to study the configuration of foveal slope and the foveal thickness in fellow eyes of subjects with unilateral neovascular ARMD, and compare the corresponding findings with those of healthy controls without any sign of ARMD in the either eye. We noted a shallower superior and temporal foveal slope in the cases, whereas, there were no significant differences in the thickness of nasal and inferior slope. One way to explain these differences can be the altered density of the MP over different parts of fovea. MP has been shown to peak at the center of the fovea and to decline in an exponential fashion with increasing retinal eccentricity, for the most individuals.[16] Snodderly *et al*.[17] and Delori *et al*.[18] initially hypothesized that foveal architecture may contribute to the variability seen in MP distribution. Nolan *et al*. found that MP was positively and significantly associated with a distinct feature of foveal architecture—namely, foveal width.[19] However, the variation in the distribution of MP over nasal or temporal slopes of fovea has not been reported earlier.

In the present study, we could not find any focal differences in the foveal slope when measured in radial scans. In the healthy subjects, no significant difference in retinal thickness measurements has been reported between the radial and 3D scans on SD-OCT.[20] Hence, the differences in foveal thickness (as noted between cases and controls in the present study) would not be responsible for variation in the foveal slopes noted only in 3D scans. Furthermore, radial scans calculate the retinal thickness based only on the 6 lines while 3D scans calculate from the data of 128-200 scans over the same area. Thus, radial scans only image a small proportion of the macula while the 3D scans image almost the complete area. Hence, changes in foveal slope as found on 3D scan, but not on radial scan, may imply that the changes in foveal slope are more regional than focal.

We also observed that the CSFT in cases was significantly higher in comparison to controls. Factors that might influence the retinal thickness include age, gender, and axial length.[21,22] The retinal thickness and foveal slope measurements for cases and controls were adjusted for age and gender in the present study. We did not measure axial length in the two groups, and this is a limitation of our study. In a report by Wagner-Schuman *et al*.[23] the differences in the retinal thickness observed only in the central subfield were more likely due to differences in foveal pit morphology, whereas, the differences including multiple Early Treatment Diabetic Retinopathy Study segments represented real differences in retinal thickness. In our study, the differences in retinal thickness were observed only in the central subfield and hence, are more likely to reflect altered foveal pit morphology. Such a finding is significant because altered pit morphology in subjects with unilateral ARMD might indicate an association between the two.

Until now, the relationship between the MP and foveal thickness remains controversial. Previous studies have found that MP optical density in patients with retinal degeneration (choroideremia, retinitis pigmentosa, Usher syndrome) is a significantly and inversely related to retinal thickness.[11,12] However, studies performed in healthy subjects reported a positive association between the central foveal thickness and MP optical density.[9,10] However, these studies evaluated the foveal thickness on stratus time domain OCT (TD-OCT) because it was the most common commercially available OCT instrument in the past decade. Foveal thickness measurement on TD-OCT averages six values and has large variability since it becomes difficult to image the same point on the retina repeatedly. To overcome this difficulty, studies have defined the central subfield, which is an average of 512 values and also distributes any change in the location over a wider area.[24,25] Furthermore, TD-OCT calculates the retinal thickness based on the 6 radial line scans while SD-OCT calculates from the data of 3D scan with 128-200 scans over the same area.[20] In our study, we measured the retinal thickness on SD-OCT. Hence, we cannot relate our results with the reported associations between retinal thickness on TD-OCT and MP. One study used SD OCT (Topcon 3D OCT 1000) and reported no correlation between the foveal thickness and MP optical density in early ARMD subjects.[26] In our study, since we did not measure the MP optical density, it is difficult to comment

whether the MP optical density is higher in the cases than the control group. Altered central retinal thickness in cases may represent a change in foveal pit morphology or a change in MP. As reported previously by Nolan *et al*.[19] MP optical density is related to the foveal architecture of the individual; however, even in healthy subjects, the relationship is complex.

The limitations of the present study include the lack of measurement of MP optical density in cases and controls, and unavailability of data regarding the smoking status of the cases and controls. Furthermore, we did not assess the relationship between CSFT and foveal slope in this study.

Prospective studies observing the development of CNVM in subjects with altered foveal slope might provide more information on this OCT finding. It would be fascinating to demonstrate the presence or absence of a quantitative relationship between foveal slope and development of wet ARMD in future studies.

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