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Does outer retinal layer thickness correlate with the central visual field indices in early dry age-related macular degeneration?

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Abstract:

PURPOSE: Age-related macular degeneration (ARMD) is the leading cause of irreversible blindness worldwide and Nepal is one among them. We aimed to determine the relationship between outer retinal layer thickness parameters with central visual field indices in early dry ARMD cases among Nepalese population.

MATERIALS AND METHODS: The subjects for this descriptive, cross-sectional study comprised 40 patients with early dry ARMD from the ophthalmology department of a tertiary level hospital of Nepal. The retinal layer thickness was measured with spectral-domain optical coherence tomography (SD-OCT), and the visual field indices were assessed using the 10-2 protocol of Humphrey visual field analyzer (HFA). Thus, the retinal layer structures correlated with visual field indices among our population.

RESULTS: Among our early dry ARMD population, the foveal threshold (FT) was found to be significantly correlated with retinal pigment epithelium (RPE) elevation ($P < 0.01$, $r = -0.541$), outer segment (OS) length ($P = 0.02$, $r = 0.465$), and inner segment ellipsoid (ISe) band disruption ($P = 0.01$, $r = -0.499$), but not with presence of hyperreflective foci ($P = 0.464$), RPE thickness ($P = 0.612$), and central macular thickness ($P = 0.214$). However, no significant correlation between mean deviation and pattern standard deviation of visual field with retinal layer thickness parameters was identified.

CONCLUSION: In early dry ARMD, a reduced FT is significantly correlated with the integrity of the ISe band, thinning of OS length, and drusen-associated RPE elevation. The results highlight the utility of both SD-OCT retinal layer measurement and central visual field testing by HFA in ARMD to monitor the progression of the disease.

Keywords:

Age-related macular degeneration, microperimetry, Nepal, retinal layer thickness, visual field indices

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Introduction

Age-related macular degeneration (ARMD) represents 8.7% of irreversible blindness around the world and is the most widely recognized leading cause of blindness in the most developed nations, especially in individuals more than 60 years.[1-5] ARMD is also an emerging cause of retinal disease in developing country with the prevalence of 35.43% at age ≥60 in Nepal.[6]

Clinically, ARMD has been categorized as an early and late phase ARMD. In the very early phase, ARMD is described by some changes in retinal pigment epithelium (RPE) without significant vision loss in addition to intermediate-sized (≥63 μm to <125 μm) drusen deposition.[7] The series of harmful events occur in the RPE, outer segment (OS)

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layer of photoreceptors, and integrity of inner segment/OS junction (herein called the inner segment ellipsoid [ISe] band) and choroids which can be identified by optical coherence tomography (OCT) in any phase of ARMD.[8-10] Damage in these retinal tissue escort to the severe central visual loss which can be depicted in 10-2 program in humphrey field analyzer (HFA). In ARMD, few studies have reported decreased threshold visual field values like mean deviation (MD), pattern standard deviation (PSD), and foveal threshold (FT)[11,12] whereas others did not.[13,14]

This study is the first study of its type from Nepal which aims to correlate the structural and functional changes in early dry ARMD patients using spectral-domain (SD)-OCT and 10-2 HFA, respectively, among the senior citizens of Nepal.

Materials and Methods

This hospital-based, cross-sectional study was carried out in B. P. Koirala Lions Center for Ophthalmic Studies, Institute of Medicine, Kathmandu, Nepal between December 2018 and November 2019.

Patients diagnosed with early dry ARMD (stage of disease was determined by doing digital color fundus photographs according to the definition of clinical classification of ARMD)[15] attending general outpatient department (OPD) and retina clinic of BPKLCOS having best-corrected visual acuity category 0 visual impairment, i.e., ≥6/18 Snellen's visual acuity (WHO classification) were enrolled in the study. Each ARMD patients had one of the following stages of severity of AMD: stage 1a (soft distinct drusen ≥63 μm only), stage 1b (pigmentary abnormalities only, no soft drusen ≥63 μm), stage 2a (soft indistinct drusen ≥125 μm or reticular drusen only), stage 2b (soft distinct drusen ≥63 μm, with pigmentary abnormalities), or stage 3 (soft indistinct drusen ≥125 μm or reticular drusen with pigmentary abnormalities).[11] Strict exclusion criteria were followed and patients with late ARMD and wet ARMD, significant ocular media opacity, glaucoma, neurological disorders, diabetic retinopathy, macular diseases, and high refractive error (spherical equivalent exceeding ± 5.00 D sphere) were excluded. Age- and gender-matched healthy controls were randomly selected from the patients attending the general OPD of BPKLCOS. Their visual field indices and retinal layer thickness were compared with the early dry ARMD patients.

The structural changes of the central macula were evaluated with SD-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany, version 1.3 with SD-OCT segmentation and analysis software) using high-resolution settings and automated tracking. For each study eye, a detailed volume scan along the horizontal meridian of the central macular retina (15° × 10°) comprising 13–25 B-scans (200–242 μm distance between B-scans) was obtained with the greatest signal-to-noise ratio. SD-OCT images were segmented using a computer-aided, manual segmentation technique described previously[15] following ETDRS-style map, whereby the following measurements were taken from central 1.2 mm zone and each layer's length was determined by perpendicular line against slope of segmented area:

- Central macular thickness
- RPE thickness (separation between RPE and Bruch's membrane/choroid)
- RPE elevation (separation between lower RPE border and Bruch's membrane/choroid)
- OS length of photoreceptor layer (separation between ISe band and upper RPE border and >350 μm RPE elevation called as drusenoid pigment epithelium detachment is excluded)
- ISe band integrity and presence of hyperreflective foci.

All segmentations were performed by an experienced grader who masked to subject characteristics and clinical diagnosis.

The visual field sensitivity was assessed on the next day using 10-2 Swedish Interactive Thresholding Algorithm standard protocol of 2010 Carl Zeiss Meditec HFA II 750–41686 version 5.1.2 with 68 test locations in the central 20°, with a separation of 2°. The STATPAC software incorporated in HFA II of Carl Zeiss Meditec, Dublin, CA. into the perimeter of HFA allows for the probability analysis and displays that on standard HFA printout. 10-2 global indices like MD, corrected PSD, and FT were noted for the comprehensive analysis.

Written informed consent was taken from all the participants, ethical clearance was obtained from the Institutional Review Committee of the Institute of Medicine, Nepal, and the study adhered with the declaration of Helsinki.

Analysis

A comprehensive pro forma was made to record the data and relevant findings entered into spreadsheet (Microsoft Excel Sheet). Statistical analysis was carried out using SPSS software by IBM Corporation. The correlation among visual field parameters and retinal layer thickness parameters was done using Pearson's correlation test. $P < 0.05$ with 5% confidence interval was considered statistically significant.

Results

A total of 84 participants enrolled in this study, 44 were early dry ARMD patients and 40 were controls from age- and sex-matched normal population, the

demographic details of which is depicted in Table 1. However, 4 cases of early ARMD were excluded as they could not complete the visual field test reliability, so only 40 cases underwent detailed investigations.

Visual field findings like FT, MD, and PSD of ARMD patients and controls are shown in Table 2. Independent sample-*t*-test showed a statistically significant change in FT, MD, and PSD between ARMD cases and controls.

The mean thickness values for the central macular thickness, RPE thickness, OS of photoreceptor layer thickness, and RPE elevation are shown in Table 3 for early dry ARMD groups and controls. The RPE elevation, RPE thickness, and OS length were statistically significant difference between the two groups. Out of the total early dry ARMD group, 62.50% had <½% disrupted ISe band, 25.50% had normal integrity of the ISe band, and 15.00% had more than half percent disrupted ISe band. In the early dry ARMD group, the presence of hyperreflective foci was 15.00% and the rest of the group did not have HF above the drusen area.

Pearson's correlation test revealed that the RPE elevation was negatively correlated with the FT ($P < 0.01$), OS length was positively correlated with the FT ($P = 0.003$), and the integrity of the ISe band was negatively correlated with FT ($P = 0.001$), which is shown in Table 4. The FT was negatively correlated with RPE elevation ($r = -0.541$, $P < 0.01$), which is depicted in the scatter plot in Figure 1. The FT was reduced to the elevation of RPE. The FT was positively correlated with OS length of the photoreceptor layer ($r = 0.465$, $P = 0.003$), which is depicted in the scatter plot in Figure 2. The FT was reduced on the thinning of the OS length of the photoreceptor layer. The FT was negatively correlated with ISe band integrity ($r = -0.499$, $P = 0.001$), which is depicted in the scatter plot in Figure 3. The reduction in FT occurred to an increased degree of disrupted ISe band integrity.

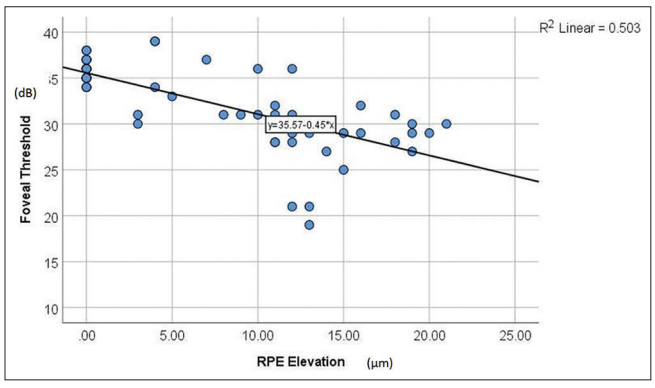

Figure 1: Scatter plot showing the correlation between foveal threshold and RPE elevation. RPE: Retinal pigment epithelium

Discussion

This was the first hospital-based comparative study conducted in the university hospital of Nepal, which correlated the retinal layer thickness with the central

Table 1: Demographic profiles of age-related macular degeneration patients and controls

Variables	ARMD patients, *n* (%)	Controls, *n* (%)	*P*
Gender			
Male	21 (52.50)	24 (60.00)	0.45[a]
Female	19 (47.50)	16 (40.00)	
Mean age in years (x±SD)	67.57±9.84	66.75±10.25	0.94[b]
Age range (years)	50-86	50-82	
Affected eye			
Right eye	19 (47.50)	18 (45.00)	0.64[a]
Left eye	21 (58.50)	22 (55.00)	
Status of lens			
Transparent	17 (42.50)	24 (60.00)	0.06[a]
Cataractous	12 (30.00)	16 (40.00)	
Pseudophakic	11 (27.50)	0	
History of smoking			
Smoker	9 (22.50)	0	0.03*[,c]
Past-smoker	14 (35.00)	2 (5.00)	
Nonsmoker	17 (42.50)	38 (95.00)	

[a]Chi-square test, [b]Independent sample *t*-test, [c]Fisher's exact test, *$P<0.05$ is considered statistically significant. ARMD: Age-related macular degeneration, SD: Standard deviation

Table 2: Distribution of visual field indices in age-related macular degeneration patients and controls

VF indices (dB unit)	ARMD patients	Controls	*P*
Mean FT	30.42±4.58	35.60±1.09	<0.01*
Mean MD	−4.36±5.52	−0.48±0.39	0.03*
Mean PSD	3.55±2.79	0.88±0.29	<0.01*

*$P<0.05$ is considered statistically significant. Independent sample *t*-test. VF: Visual field, ARMD: Age-related macular degeneration, MD: Mean deviation, PSD: Pattern standard deviation, FT: Foveal threshold

Table 3: Distribution of optical coherence tomography findings in age-related macular degeneration patients and controls

OCT findings	Mean thickness (µm)±SD	*P*
CMT		
ARMD patients	251.29±25.94	0.125
Controls	259.80±15.62	
RPE thickness		
ARMD patients	20.17±2.98	0.02*
Controls	17.80±2.04	
RPE elevation		
ARMD patients	17.72±5.66	<0.01*
Controls	0.00±0.00	
OS length		
ARMD patients	27.46±5.90	<0.01*
Controls	36.60±1.43	

*$P<0.05$ is considered statistically significant. Independent sample *t*-test. OCT: Optical coherence tomography, ARMD: Age-related macular degeneration, RPE: Retinal pigment epithelium, OS: Outer segment, SD: Standard deviation

visual field in early dry ARMD, which can help prognosticate the visual outcome. The increase in the life expectancy of Nepalese people has led to the significant increase in the prevalence of ARMD.[16,17] The population statistics in Nepal have reported that life expectancy over the past 20 years has raised from 55 and 53.50 years to 67.30 and 69.60 years in males and females, respectively.[18,19] Hence, increase longevity has led to occurrence of ARMD, which if not identified early can become a significant public eye health issue in Nepal as the progression to late ARMD leads to painless, progressive irreversible blindness.[16]

Our study depicted a statistically significant reduction in FT ($P < 0.01$) and MD (P-0.03) and increased PSD ($P < 0.01$) in early ARMD groups compared to the controls. Hence, it adds on information from our part of the world upon existing evidence of reduced retinal sensitivity parameters in automated perimetry in the different stages of ARMD versus normal subjects.[11,15] The 10-2 program of HFA identified significant visual field changes in our study population, which reflects the reliability of the use of 10-2 program to measure the central visual field changes in a macular disease like ARMD.[11] The correlation between the visual field changes and reduced retinal sensitivity may not be the direct effect of the drusen but rather due to the changes in retinal structures like RPE elevation and thinning of OS length of photoreceptors.[13]

Table 4: Correlation of optical coherence tomography parameters with visual field indices in age-related macular degeneration patients

OCT parameters	VF indices (*P*)		
	FT	MD	PSD
CMT	0.209 (0.214)	0.089 (0.597)	−0.088 (0.684)
RPE thickness	0.085 (0.612)	0.256 (0.121)	−0.173 (0.299)
RPE elevation	−0.541 (<0.01)*	0.160 (0.337)	0.298 (0.069)
OS length	0.465 (0.003)*	−0.086 (0.608)	−0.277 (0.092)
ISe band integrity	−0.499 (0.001)*	−0.010 (0.950)	0.265 (0.108)
Presence of HF	0.122 (0.464)	−0.152 (0.363)	−0.293 (0.074)

*Correlation is significant at 0.05 level, 1 tailed. Pearson's correlation test. FT: Foveal threshold, VF: Visual field, MD: Mean deviation, PSD: Pattern standard deviation, OCT: Optical coherence tomography, CMT: Central macular thickness, RPE: Retinal pigment epithelium, OS: Outer segment, ISe: Inner segment ellipsoid, HF: Hyperreflective foci

The foveal sensitivity parameters reduction develops much earlier and quicker than visual acuity changes. Hence, testing the central retinal sensitivity parameters even if in early ARMD cases irrespective of the drusen sizes is worthwhile.

Decreased central vision has serious impacts upon on the individual's daily living activities, substantial occupational impairment, and proper quality of life.[15,20] Thereby, early identification can be the best keys to suggest for the lifestyle modification among the early ARMDs cases.

The mean RPE thickness, RPE elevation, and OS length among our Nepalese senior citizen adds on to the similar thickness from ARMD patients from other part of the world.[21] This alteration in the thickness means the negative impact on the visual function among the ageing global population demanding pronounced public health concern.[22]

Our study identified the significantly thinner (P-0.01) OS of the photoreceptor layer among early ARMD cases compared to the controls. The diminishing of photoreceptor layer measured between the upper RPE fringe and the ISe band overlying the drusen can be responsible for the thinning of the OS of the photoreceptor layer.[23] Other auxiliary changes related to drusen are the diminished photoreceptor density and abbreviated OS of photoreceptor layer overlying the drusen.[24,25]

The overlying RPE can get thickened and elevated even in early ARMD groups compared to the controls as shown in our study. Similar study by Acton *et al*.[11] reported that the thickening and elevation of the RPE could be the result of the basal laminar storage

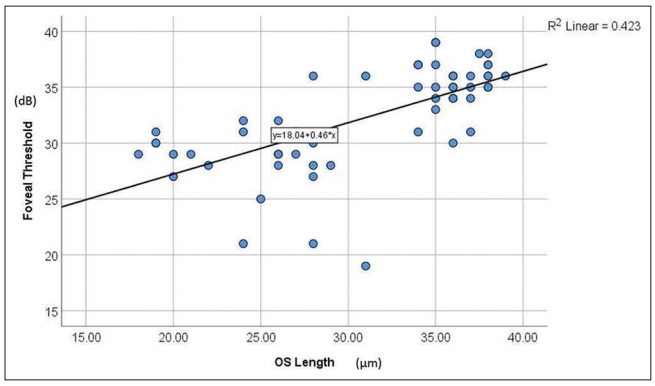

Figure 2: Scatter plot showing the correlation between foveal threshold and OS length. OS: outer segment

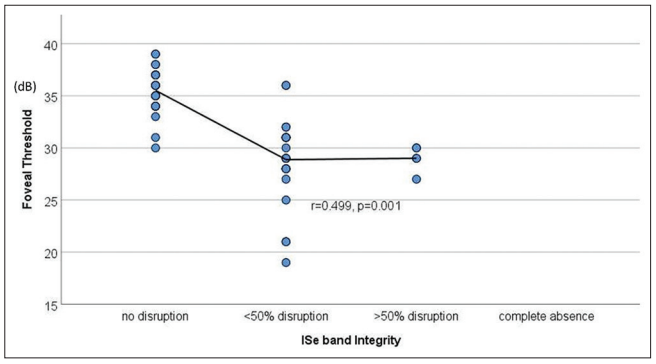

Figure 3: Scatter plot showing the correlation between foveal threshold and ISe band integrity. ISe: inner segment ellipsoid

underneath the RPE.[26-28] The aging RPE cells show an age-related accumulation of lipofuscin granule within the lysosomal compartment, as a product of the permanent phagocytosis of lipid-rich distal photoreceptors' OSs causing the elevation of RPE.[29]

Additional information identified in our study was, the disrupted ISe band even in early dry ARMD patients, while no disruption of the ISe band among the controls. Previous study from other part of the world had reported a significant disruption of IS/OS junction in both dry and wet ARMD with poor retinal sensitivity.[30] However, no previous reports had documented the similar retinal findings in our population.

The hyperreflective foci above and below the external limiting layer of the retina was found in 15% of our early ARMD patients which could be due to the presence of drusen and migrated RPE causing hyperreflective foci in SD-OCT.[31] The prevalence of the hyperreflective foci was lesser in our study group because the incidence of such foci increases with the severity of the ARMD and is more evident in late stage.[32]

In the correlation between the OCT findings and visual field indices, a significant relationship between RPE elevation, OS length, ISe band integrity, and the FT was established in our early ARMD patients. This adds on the significant relationship established between the retinal sensitivity and OCT changes in ARMD cases of various stages across the world.[30,33-35]

Pearson's correlation test identified that the FT was significantly correlated with RPE elevation ($r = -0.541$, $P < 0.01$) and ISe band disruption (Pearson's rho = –0.499, $P = 0.01$), but not with the presence or absence of HF ($P = 0.464$), RPE thickness ($P = 0.612$), and central macular thickness ($P = 0.214$). These findings rhymes with the reports of Landa *et al*.[30] and Hartmann *et al*.,[34] where they found that the integrity of the ISe band and RPE elevation are significant independent indicators of neighborhood changes in microperimetry retinal sensitivity, however not the RPE thickness or presence of HF.

The significant correlation between the FT and OS length of the photoreceptor layer ($r = 0.465$, $P = 0.02$) is in agreement with pace of disturbance in IS/OS interface in relation to the decreased microperimetric retinal sensitivity in early stages of dry ARMD.[33] The significant relationship between RPE elevation and OS length with the FT in our patients is similar to other global reports;[22,36] however, the estimation of RPE elevation better correlates with reduced FT. This may be due to the limited axial resolution of SD-OCT for measuring OS length and ineffectual to measure in areas where ISe band are absent to delineate the limits of the OS margin.

Contrary to the Midena *et al*.,[37] no significant correlation between the presence of the hyperreflective foci and VF indices was documented among our senior citizen, indicating that the reduced retinal sensitivity was not strongly influenced by the presence of the hypereflective foci. These hyperpigmentary changes commonly happen over the drusen;[22,31,38,39] however, we found using SD-OCT that they are additionally typically present in the region with ISe band interruption, profoundly elevated RPE, and diminished OS. Because of the concurrence of these retinal parameters, we found that ISe band integrity, RPE elevation, and OS length are significantly correlated with reduced FT but not with the presence of hyperreflective foci. In addition, this may be due to the early stage of disease resulting in lesser area of hypereflective foci. Hence, early ARMD must be cautiously followed up to establish the significant correlation of the microperimetric parameters with the OCT parameters in late stage.

Hence, comparison between outer retinal parameters and visual field indices has potential clinical utility for monitoring and prognosticating the early ARMD cases.

The limitation of this study was the sample size, as it was a single-center study; however, the strength of this study is being able to be the first study of its type to perform the subsequent analysis of both morphological and physiological parameters among early ARMD patients of Nepal.

Conclusion

The early ARMD cases of Nepal have elevated RPE, thin OS of photoreceptor layer, disruption of ISe band, and presence of hyperreflective foci along with a significant reduction in mean FT, increased PSD, and decreased MD compared to the controls. The macular morphological changes identified by the OCT findings like RPE elevation, thinned OS layer, and disrupted ISe band significantly correlate with the retinal physiological changes evident by the reduction of the FT. Hence, routine screening of the retinal microstructures change with the visual field changes in early stage of ARMD disease can be beneficial for early detection of disease, forecasting the visual function, and formulating the guidelines for future treatment.

Ethics approval and consent to participate

The study was approved by the Institutional Review Committee of the Institute of Medicine, Tribhuvan University (259 [6-11] E^2 076/077), and written informed consent was taken from all the participants.

Availability of data and materials

The authors confirm that the data supporting the findings

of this study are available within the article. The data can also be provided on request by the corresponding author.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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