Original Article

Choroidal and retinal thickness variations in ocular albinism

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Purpose: To study the retinal and choroidal thickness variations on enhanced depth imaging optical coherence tomography scans in ocular albinism (OA) and compare with age-matched healthy subjects. **Methods:** This retrospective observational study had 48 eyes of 24 patients diagnosed clinically as OA and age, sex, and axial length-matched control healthy subjects. All patients underwent detailed ophthalmic examination and a single-line horizontal-raster enhanced depth imaging – optical coherence tomography scan (Spectralis, Heidelberg Engineering). Retinal and choroidal thickness was measured, compared, and analyzed between the two groups. Mann–Whitney U test was used for analysis between the two groups. $P < 0.05$ was considered significant. **Results:** The mean age was 28.3 ± 11.6 and 29.9 ± 10.6 years in the OA group and control group, respectively. Spherical equivalents ranged from −8.5D to +10.5D in the OA group and from −8.0D to +10.0D in the control group. The mean axial length between the two groups ($P = 0.652$) were comparable. The average retinal thickness (272 ± 34.3 vs. 213 ± 13.8 µm; $P < 0.001$) was greater in the OA group as compared to controls. The mean choroidal thickness (184 ± 78.4 vs. 287 ± 46.4 µm; $P < 0.001$) was significantly thinner in the OA group. **Conclusion:** Acquisition of OCT scans in OA can be challenging. This study showed that the subfoveal retinal thickness and choroidal thickness measured across the scans were significantly different in the OA group compared to controls. In the future, more studies are required to evaluate the role of the choroid and its relationship to emmetropization in albinism.

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Albinism is a genetic disease having an autosomal recessive or X-linked inheritance pattern. In albinism, the melanin biosynthesis in melanocytes is affected, resulting in absent or reduced melanin pigment. This, in turn, causes hypopigmentation of the skin, hair, and eyes.[1,2] Ocular features in albinism include poor vision, nystagmus, high refractive errors, iris and fundus hypopigmentation, foveal hypoplasia, and misdirection of the optic nerves.[3,4] All individuals with albinism have the abovementioned ocular features, but the amount of skin, hair, and iris pigment can vary depending on the gene and the mutation involved. A broad range of refractive errors has been noted in albinism, ranging from high myopia to high hyperopia. Wildsoet *et al*.[5] studied the refractive errors and their implications in albinism in the context of emmetropization and found hyperopia to be the most common refractive error in albinotic patients.

The choroid is a highly vascular tissue located between the retina and sclera and plays an active role in the process of emmetropization by adjusting its thickness and pushing the retina and sclera forward or backward.[6] Growth factors released from the choroid could play a potential role in remodeling the scleral extracellular matrix, thereby contributing to emmetropization.[6,7] Also, choroidal thickness has been shown to predict the normal ocular growth in chicks and thus can have a significant role in emmetropization.[8] The enhanced depth imaging – optical coherence tomography (EDI-OCT) image is useful for visualizing the structural abnormalities in the choroid and for measuring the retinal and choroidal thickness. The absent melanin pigment in the melanocytes in albinism can lead to structural changes in the choroidal layers. Also, a recent publication suggested that the changes in melanin quantity can play a significant role in the choroidal measurements on OCT.[9]

OCT findings in albinism are rarely documented. There is limited information in the literature regarding choroidal changes seen on OCT in albinism. This probably is due to the difficulties encountered in capturing images in albinotic patients due to poor fixation as a result of nystagmus, especially in the younger age group. One study from Turkey by Karabas *et al*.[10] noted decreased subfoveal choroidal thickness in 10 patients with ocular albinism (OA) compared to age-matched normal healthy children on EDI-OCT imaging. The major limitations in this study were the small sample size and the presence of nystagmus, thereby not allowing high-quality OCT scans to be acquired. Also, the technique used for obtaining the choroidal thickness at the fovea was different where they considered the average of the choroidal thickness measurement values obtained at 4000, 4500, and 5000 µm from the optic disc. The incorporation of eye tracking software in the newer-generation OCT machines helps to reduce the motion artefacts and may enable better centration of the scans on the expected fovea in albinism. In another study,

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Healey *et al*.[11] on OCT noted that in the presence of albinism, there was increased association of severe foveal hypoplasia with high hyperopia and poor visual acuity. They concluded that the failure of emmetropization was not attributable to the presence of foveal hypoplasia. Another study by Pillay *et al*.[12] noted higher central foveal thickness but thinner retinal thickness measurements in the parafoveal and perifoveal regions.

With this limited literature, the authors planned to study the retinal and choroidal thickness variations in albinotic patients and compared them with age, sex, and axial length-matched healthy control subjects.

Methods

In this retrospective study, clinical and imaging findings were compared between the eyes with albinism and age, sex, and axial length-matched control subjects at the Department of Retina in South India. The study protocol was approved by the institutional review board (C/20/10/010), and the research followed the tenets of the Declaration of Helsinki. All patients provided informed consent for participation before being included in the study.

Selection of cases

A diagnosis of OA was based on the presence of the following clinical features: presence of nystagmus and photophobia, iris transillumination, reduced fundus and/or skin and hair pigmentation, foveal hypoplasia with absent foveal reflex, and reduced visual acuity.[13,14] All patients underwent a detailed ophthalmic examination, including measurement of Snellen best-corrected visual acuity (BCVA), cycloplegic refraction with cyclopentolate 1% eye drops for patients with age <20 years or with tropicamide 1% eye drops for older patients and those having high refractive error or poor visual acuity, slit-lamp examination, non-contact tonometry (Topcon CT-80, Oakland, NJ, USA), and dilated fundus examination with either cyclopentolate 1% or tropicamide 1% eye drops. Axial length (AL) measurement was done using optical low-coherence reflectometry (Lenstar 900; Haag-Streit Diagnostics, Koeniz, Switzerland). Fundus findings were documented with ultrawide image color fundus photographs by using the Optos, Daytona (Marlborough, MA, USA) machine. Macular retinal and choroidal layer thicknesses were measured using spectral domain-OCT (Heidelberg Spectralis, Germany).

Selection of controls

The control group was selected from a cohort of patients having an anatomically normal fundus appearance. They were matched with the study group for age, gender, and axial length. The number of controls selected was in the ratio of 1:1 for the cases.

Retinal imaging using spectral domain-OCT

On OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), the macular retinal and choroidal layer thicknesses were measured. All OCT scans were performed by the same experienced operator during the morning hours from 9 a.m. to 12 p.m. A single-line horizontal raster scan using the EDI mode extending from the temporal margin of the optic nerve head and passing through the foveal center (either the actual fovea or expected foveal location when there was no visible pit identified with the help of the adjacent infrared image) was performed with 15 frames averaged to improve the image quality. OCT scans were obtained while the patient focused on the fixation target in their habitual head posture as this would allow for the null point of the nystagmus and their preferred retinal locus of fixation. The scan with no motion artifacts and a high signal-to-noise ratio with instrument quality score ≥20 dB was selected for further analysis.

All thickness measurements were made on the OCT by using the automated layer segmentation tool in the proprietary machine software. The retinal thickness was measured in an automated fashion from the internal limiting membrane to the outer border of the retinal pigment epithelium at the assumed fovea. The protocol for measuring the choroidal thickness was similar to that followed by Regatieri *et al*.[15] For measuring the choroidal thickness, the outer choroid-sclera junction was identified, cross-checked, marked, and measured by one of the authors in the study (SA). The choroidal thickness was measured manually from the outer border of the retinal pigment epithelium to the inner border of the sclera [Fig. 1]. The choroidal thickness was measured at the fovea and at intervals of 500 μm from the fovea and extending till 2000 μm of the scan nasally and temporally. The retinal thickness and choroidal thickness were measured at each of these points by using the 1:1-pixel protocol.

Statistical analysis

All data were analyzed with GraphPad Prism software (version 9.0.0 [121]) for Windows), San Diego, CA. The normal distribution of quantitative variables was checked using the D'Agostino & Pearson omnibus normality test. Refraction data were converted to the spherical equivalent, which was calculated as the spherical dioptric power plus one-half of the cylindrical dioptric power. BCVA was recorded in Snellen units and was converted to logarithm of the minimum angle of resolution (logMAR) for statistical analyses. Snellen equivalents of logMAR vision were recalculated for documenting in the tables. For nonparametric quantitative data, Mann–Whitney U test was used for analysis between the two groups. A generalized estimating equation model for both eyes was used for estimating the average response over the population to compensate for both eyes' inclusion of subjects. $P < 0.05$ was considered statistically significant.

Results

This study included 48 eyes of 24 cases with OA and 48 eyes of 24 control subjects for evaluation. Skin hypopigmentation and hair hypopigmentation was noted in 20 (83%) and 18 (75%) patients, respectively. There were 15 males and 9 females in each group. The mean age was 28.3 ± 11.6 years (range: 5–46 years) in the patients with OA and 29.9 ± 10.6 years (range: 7–48 years) in the normal control group. All the cases had spherical equivalents ranging from −8.5D to +10.5D, while in the control group, the spherical equivalent ranged from −8.0D to +10.0D. The mean axial length was 26.65 ± 4.32 mm and 25.98 ± 5.11 mm in the cases group and control group, respectively. The mean best-corrected visual acuity in the OA group was 0.655 ± 0.382 (Snellen equivalent: 20/90), and for the control subjects, it was 0.058 ± 0.152 (Snellen equivalent: 20/23). On examination, all cases showed iris transillumination, nystagmus, and photophobia, while none of the patients in the control group observed these features. Foveal light reflex was absent, and the choroidal vessels were prominent due to the absence of pigmentation in all of the patients with OA. Fundus examination was normal in the control group.

The mean retinal thickness was 272 ± 34.3 μm in the OA group and 213 ± 13.8 μm in the control eyes. The retinal thickness in the OA group was significantly thicker than in the control group ($P < 0.001$). The choroid was significantly thinner ($P < 0.001$) in the OA group compared to the control group at the fovea and at every point measured nasally and temporally. The mean subfoveal choroidal thickness was 184 ± 78.4 μm in the OA cases group and 287 ± 46.4 μm in the control group. The comparison of choroidal thickness between the two groups at every 500 μm of the scan nasally and temporally is mentioned in Table 1. We noted that the choroidal thickness was the greatest at the presumed fovea

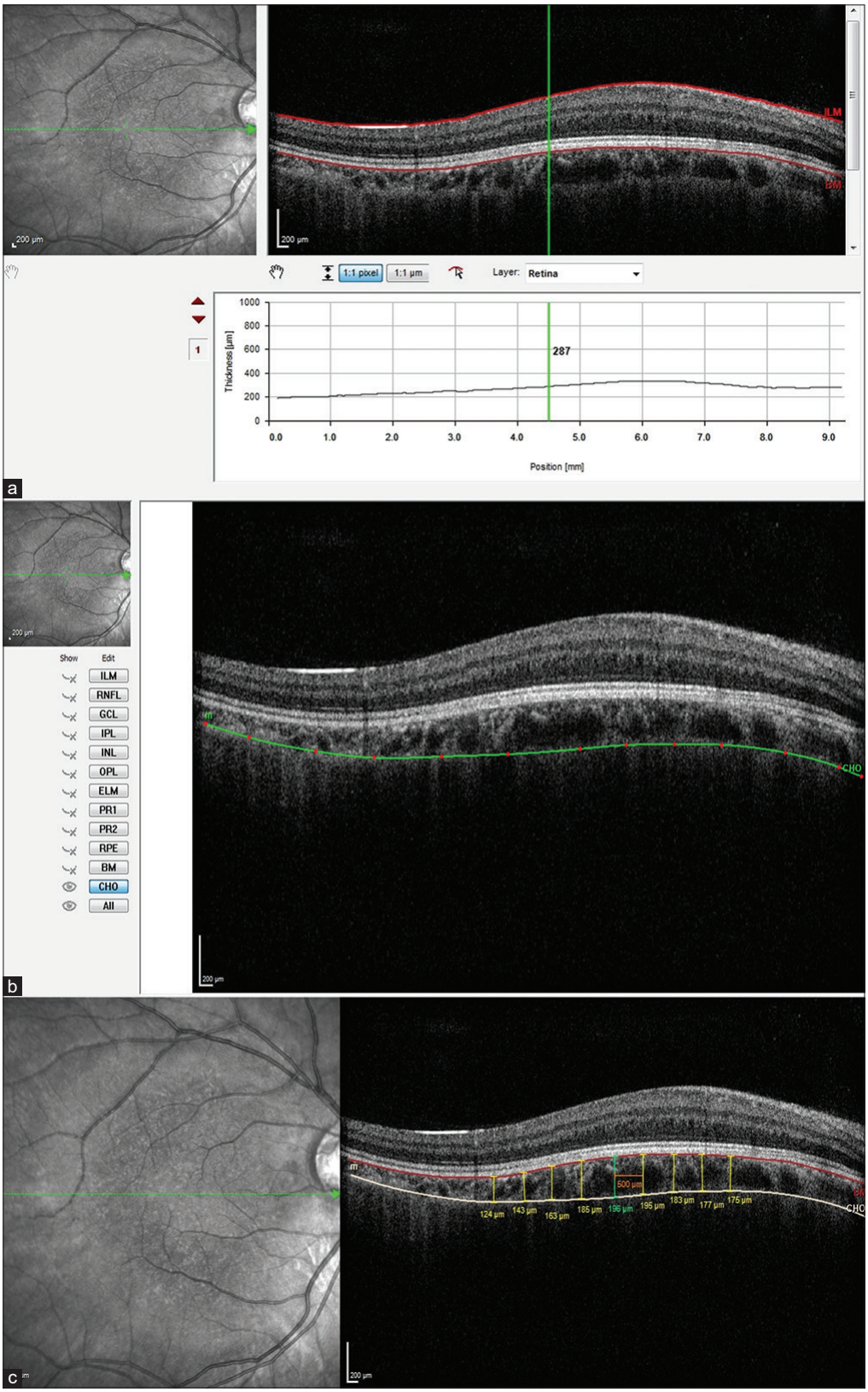

Figure 1: Single-line horizontal enhanced depth imaging optical coherence tomography (EDI-OCT) scan in a patient with ocular albinism (OA): This is the EDI-OCT scan of the right eye of a 19-year-old male patient (spherical equivalent = −3D and axial length = 22.1 mm) diagnosed with ocular albinism and nystagmus. Here, we also observe the absence of the foveal pit in the scan. (a) This is a representative OCT image measuring the retinal thickness at the presumed fovea. (b) This is a representative EDI-OCT image showing the manual marking of the choroid-sclera junction for measuring the choroidal thickness. (c) This is a representative OCT image measuring the choroidal thickness at the fovea and at 5000-µm intervals from the fovea and extending till 2000 µm nasally and temporally

and progressively reduced from the fovea toward the nasal and temporal sides of the OCT scan in both groups. No significant difference was noted upon comparing the choroidal thickness on the nasal and temporal parts of the scan. Comparisons between the choroidal thickness on the nasal and temporal sides of the scan in both groups is mentioned in Table 2.

Discussion

Previous studies on OA have shown that the choroid might play an important role in the process of emmetropization in albinotic eyes.[6,7] The deficiency of melanin pigment in the choroidal melanocytes can lead to choroidal anatomical and vascular abnormalities.[9] Before the availability of the EDI-OCT or swept-source technology, there were no other methods available for high-resolution visualization of the choroid. The findings of this retrospective EDI-OCT study on albinotic patients suggest that patients with OA have a wide range of refractive errors and have an increased retinal and reduced choroidal thickness compared to the age, sex, and refractive error-matched healthy controls. There was no significant difference in the choroidal thickness on the nasal and temporal sides of the macula, unlike healthy controls as seen in our study and literature.

These findings are agreeable to those reported by Karabas *et al*.,[10] where the subfoveal and peripapillary choroidal thickness was less than that in the normal control subjects. In their study, the subfoveal (measured as an average of values obtained at 4000, 4500, and 5000 µm from the optic disc) and peripapillary choroidal thickness was measured using enhanced depth imaging-OCT scans in a pediatric population in Turkey. However, the methodology used in the current study is different. Here, cases diagnosed with OA in the Indian population of varying age groups were included and the subfoveal retinal thickness and choroidal thicknesses were measured along the entire horizontal scan length at 500-µm intervals from the fovea on either side. In albinism, there is diffuse deficiency of the melanin pigment across the entire fundus. Thus, it would be more meaningful to measure the choroidal thickness across the entire length of the scan rather than measuring just at the subfoveal location, especially when the identification of the exact foveal location is difficult due to foveal hypoplasia. One of the limitations reported in the study by Karabas *et al*.[10] was the difficulty in capturing good quality scans due to poorer vision (20/154) and fixation in pediatric population with nystagmus. Older albinotic patients with better visual acuity (20/90) were a part of this study, thus allowing better-quality OCT scans to be acquired for measuring the retinal and choroidal thickness. A recent study by Pillay *et al*.[12] measured the retinal thickness at the fovea, perifoveal, and parafoveal regions in albinotic eyes. They noted that the retina was the thickest at the fovea and progressively became thinner in the perifoveal and parafoveal regions.

Several factors such as age, axial length, refractive error, and race can affect the choroidal thickness measurements.[16–18] In this study, the control subjects were matched with the cases for age, sex, and axial lengths. Thus, it is unlikely that the wide range of refractive errors in our cases could have contributed to the significant difference in the choroidal thickness between the case and control groups. Our results represent a true difference between the OA and control groups in regards to retinal and choroidal measurements.

Also, in this study, the mean choroidal thickness measurement in the healthy control group was slightly lower than the initial descriptive study of choroidal structure in the normal population done by Arora *et al*.[16] In this study, the choroidal thickness at the fovea measured in normal healthy subjects was 287 ± 46.4 µm compared to the subfoveal choroidal thickness measured in their study (301.80 ± 46.6 µm). This difference occurred mainly due to different instruments used for measuring the choroidal thickness. The comparisons are only meaningful when performed with the same instrument using the same imaging protocol.[16]

Another important probable theory responsible for the significant thinning of the choroid in albinotic patients may be based on the quantity of the melanin pigment present in the melanocytes of the iris, retinal pigment epithelium, and choroid and on the absorption properties of melanin to high wavelength light. The absorption spectrum of melanin is maximum for the visible light (short wavelength) while long-wavelength light (infrared spectrum) has the least absorption.[19,20] This

Table 1: Demographic, refractive error, visual acuity, retinal, and choroidal thickness changes between the ocular albinism group and control group

	Cases (*n*=48)	Controls (*n*=48)	*P*
Age	28.3±11.6	29.9±10.6	0.665
Sex (M:F)	15:9	15:9	
SE	0.565±4.25	-1.32±4.70	0.712
VA (logMAR)	0.655±0.382	0.058±0.152	<0.001
AXL (mm)	26.65±4.32	25.98±5.11	0.652
Mean RT	272±34.3	213±13.8	<0.001
SFCT	184±78.4	287±46.4	<0.001
Nasal 500	172±74.6	256±47.2	<0.001
Nasal 1000	157±63.4	229±39.8	<0.001
Nasal 1500	145±59.8	207±33.9	<0.001
Nasal 2000	132±56.3	187±39.5	<0.001
Temporal 500	168±68.3	255±42.1	<0.001
Temporal 1000	165±65.2	230±41.1	<0.001
Temporal 1500	160±64.3	223±46.5	<0.001
Temporal 2000	147±57.0	206±54.0	<0.001

Abbreviations: SE – spherical equivalent; VA – visual acuity; AXL – axial length, RT – retinal thickness; CT – choroidal thickness. *P*<0.05 was considered statistically significant

Table 2: Comparison of choroidal thickness between the nasal and temporal sides of the scan in both groups

Distance from fovea	Cases			Control		
	Nasal	Temporal	*P*	Nasal	Temporal	*P*
500 µm	172±74.6	168±68.3	0.935	256±47.2	255±42.1	0.951
1000 µm	157±63.4	165±65.2	0.469	229±39.8	230±41.1	0.932
1500 µm	145±59.8	160±64.3	0.159	207±33.9	223±46.5	0.213
2000 µm	132±56.3	147±57.0	0.092	187±39.5	206±54.0	0.252

would mean that in the absence of melanin pigment, the 870-nm wavelength light of the Spectralis OCT machine would pass easily through the choroid and allow visualization of the outer choroid-sclera junction. Based on this theory, a recent paper from our group explained an apparent increase in choroidal thickness in the depigmented areas of the fundus in a patient with choroidal melanocytosis.[9,21] Thereby, one would expect the choroid to be thicker in the albinotic patients as well. However, our study showed contrary results where the choroid was significantly thinner than the control group. The basic difference between the two scenarios is the presence of melanocytes in the albinotic cases and the absence of melanocytes in the depigmented areas of choroidal melanocytosis cases. Also, the retinal pigment epithelium melanin is unaffected in the choroidal melanocytosis cases, while it gets affected in the albinotic cases. All these reasons may contribute to the thinner choroid in the albinotic case group.

The literature search did not reveal any previous studies that measured the retinal thickness in OA patients. This could be due to the difficulty in accurately identifying the fovea on the OCT scan due to nystagmus. In this study, we selected an OCT line scan passing through the fovea after identifying it based on the adjacent infrared image. The retinal thickness measured across the scan at the presumed fovea was higher in the OA group compared to the normal control subjects. This may be due to the loss of the foveal pit and the presence of the inner retinal layers at the fovea in eyes with OA.

This study has several strengths and a few limitations. One of the major strengths is the relatively large number of cases compared to previously reported studies.[10] Also, cases of all age groups were included, and the study did not limit measurements only to the subfoveal location but measured the choroidal thickness along the entire length of the scan. The methodology used in the current study overcomes the limitations described by Karabas *et al*.[10] The major limitation of this study was that the changes based on the albinism subtype could be not evaluated as genetic testing was not performed for these patients. Second, the presence of nystagmus in patients resulted in poor-quality scans; this led to a further reduction in the total number of cases. Third, we neither did foveal hypoplasia grading nor measured the thickness of the individual retinal layers on the OCT scan. Finally, we could not do other choroidal biomarkers such as choroidal vascularity index due to the average quality OCT scans.

Conclusion

This study demonstrated that in patients with OA, obtaining high-quality OCT scans is difficult. The retina at the fovea was thicker while the choroid largely in OA cases was thinner compared to normal healthy controls. Solely based on the analysis of this data on EDI-OCT, it can be implied that the choroidal structural change is related to the failure of emmetropization in these patients. In the future, more studies are required to evaluate the role of choroidal metabolism and its relationship to emmetropization in albinism.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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