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Corneal higher order aberrations in beta-thalassemia major

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HIGHLIGHTS

Corneal higher-order aberrations are significantly increased in beta-thalassemia major patients, likely due to disease pathology and iron chelation therapy, highlighting the need for regular ocular monitoring to prevent visual disturbances.

ABSTRACT

Purpose: This study aimed at evaluating the corneal higher order aberrations in beta-thalassemia major cases and comparing it to the healthy individuals.

Material and methods: It was a comparative cross-sectional study conducted on 56 beta-thalassemia major cases and 64 healthy controls from December 2023 to June 2024. All the participants received a standard ophthalmological examination subsequently followed by measurement of corneal higher order aberrations using Corneal Topography Galilei G5.

Results: The mean age of the cases and controls was comparable (P = 0.190). All the corneal higher order aberrations were significantly different among cases and controls (P <0.05), except for total coma, horizontal come, and spherical aberrations (P >0.05). Only fifth order aberrations were weakly positively correlated to thalassemia duration (r = 0.28, P = 0.033). The fourth order and spherical aberrations were weakly negatively correlated to hemoglobin levels (P = 0.029, P = 0.012 respectively). The fifth and sixth order aberrations were significantly different among the patients undergoing monotherapy and combined therapy (P = 0.006, P = 0.022 respectively).

Conclusions: Corneal higher order aberrations are greater in beta-thalassemia major cases potentially due to disease and its treatment-related factors. The findings of the study focuses the need for regular ocular monitoring in these patients to lessen potential visual disturbances and improve ocular health.

Key words: corneal higher order aberrations, beta-thalassemia major, hemoglobin, iron chelation therapy

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INTRODUCTION

High order aberrations (HOAs) are small imperfections in the optical surface of the eye that affects retinal image quality which cannot be corrected by spectacles or contact lenses [1, 2]. Unlike lower order aberrations (sphere and cylinder), which are common and correctable, HOAs are more complex and can significantly impact visual acuity and its clarity [3, 4].

These aberrations arise due to irregularities in the corneal shape often resulting from factors like corneal scarring, previous ocular surgeries, or pathologies like keratoconus [2, 5–7]. The cornea, being the most effective refractive component of eye, accounts for 90% of ocular aberrations [1]. The measurement of HOAs in normal eye is very considerate in early detection and grading of conditions like keratoconus [5–8]. HOAs manifest as distortions in the wavefront of light passing through the eye, causing symptoms like halos, glare, and reduced contrast sensitivity. Unlike lower-order aberrations that can be easily quantified using standard tests, HOAs require advanced diagnostic tools such as wavefront aberrometers for precise measurement of the anterior optical surface of eye which is found to be the most effective refractive ocular surface. The Galilei G4 corneal topographer assesses anterior and posterior corneal topography, corneal wavefront aberrations (from 2nd to 8th order aberrations), and corneal thickness effectively [3, 9, 10].

The understanding and correction of HOAs is very important in fields like refractive surgery, where achieving optimal visual outcomes depend on addressing these high-order distortions along with lower-order ones. Treatments such as wavefront-guided LASIK or custom contact lenses aim to minimize these aberrations, improving visual performance and patient satisfaction [11, 12].

This study aimed to compare corneal HOAs between beta-thalassemia major cases and normal healthy age-matched controls. This will help the ophthalmologists and optometrists in understanding the respective profiles of HOAs in thalassemia cases. The data of HOAs can be incorporated into the treatment profiles of such cases that can result in significant improvement in the quality of vision after refractive surgery and correction of surgically induced HOAs along with lower order ones. The management of these HOAs will significantly improve vision and quality of life of such patients. To the best of our knowledge, no such study has been conducted in the past to evaluate corneal HOAs in thalassemia individuals.

MATERIALS AND METHODS

This prospective comparative cross-sectional study was conducted on 140 individuals including 56 beta-thalassemia major cases and 84 age matched healthy controls. The study was performed for a duration of 7 months: from December 2023 to June 2024. The inclusion criteria included beta-thalassemia major cases and healthy controls of age group 10 years or above with spherical equivalent refraction (SER) ≤ ±6.00 DS. The cases having duration of thalassemia of 10 years or above, cases who were regularly receiving blood transfusions each month to maintain their hemoglobin (Hb) levels greater than 7 g/dL, cases who were taking iron chelation therapy inclusive of deferiprone, deferasirox, or deferoxamine (either monotherapy or combined therapy) were included. The individuals presenting with other systemic disorders, anemia, any other hemoglobin disease, SER greater than ±6.00 D, active or previous ocular infections, glaucoma, ocular trauma history, previous surgery, or contact lens use history were eliminated from the study. The cases fulfilling the inclusion criteria were taken from Jamila Sultana Foundation, Rawalpindi, Pakistan; whereas the healthy age-matched individuals were recruited from General OPD of Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan using purposive non-probability sampling technique.

After written consent, complete history of the included subjects was recorded. The history included demographics, systemic, ocular, surgical, medical and trauma history. The age at the onset of thalassemia, frequency of transfusions received, and iron chelating agent used by the cases was also recorded. The objective refraction was done using auto refractometer (Topcon) and retinoscopy (in patients aged less than 16 years), followed by subjective refraction using Early Treatment Diabetic Retinopathy Study vision chart (ETDRS). The intraocular pressure (IOP) was measured with Goldmann applanation tonometer and IOP was recorded. The anterior segment of eye was evaluated using slit-lamp biomicroscope by an ophthalmologist followed by measurement of corneal HOAs using Corneal Topography Galilei G4 by a trained optometrist. The posterior segment of the eye was evaluated using +90 D lens in conjunction with slit-lamp biomicroscope after complete mydriasis. The cases were then checked for their serum Hb and ferritin levels.

The procedure was carried out under strict conditions of ethical review board of the Institute and Declaration of Helsinki. A written informed consent was taken from the participants or their guardians where required before including them into the study and publication. The study was performed after taking permission from Ethical Committee of Lincoln University College, Malaysia (LUC/CPGS/FOS/20230517/002); and Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan (ERC-09/AST-24). The data of each participant was kept confidential and was used solely for research purposes.

DATA ANALYSIS

The data of the study was analyzed using statistical software named JASP (Jeffreys's Amazing Statistics Program) consid-

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ering p-value ≤0.05 as significant. The data normality was found using Shapiro-Wilk test with p-value ≥0.05 considered as significant representing the data was normally distributed. For normal distribution quantitative data, mean and standard deviation was reported; however, median and inter-quartile range (IQR) was reported if the data was not normally distributed. The categorical data was reported in terms of percentages and frequencies. The data was not having normal distribution, so, Mann–Whitney U test was used for comparing the mean values of the case and control groups. The correlation of corneal HOAs with thalassemia duration, frequency of transfusions, serum Hb, and ferritin levels was calculated using Spearman's correlation with P-value ≤0.05 as significant. Among the cases, the difference in the corneal HOAs in relation to iron chelation monotherapy and combined therapy was calculated using Mann–Whitney U test (with p ≤0.05 as significant).

RESULTS

The study involved 120 total subjects comprising 56 beta-thalassemia major individuals (26 males, 30 females) and 64 healthy controls (29 males, 35 females). The cases and controls were having the mean age of 18.42 (±4.05) years and 17.45 (±4.02) years respectively. The two study groups were comparable with respect to age (P = 0.190) (tab. 1).

TABLE 1

Demographic characteristics.

Study groups	n	Age			Gender			
					Males		Females	
		Mean	SD	P-value	f	%	f	%
Beta-thalassemia major cases	56	18.42	4.05	0.190	26	46.42	30	53.57
Controls	64	17.45	4.02		29	45.31	35	54.68

The spherical equivalent refraction (SER) in two study groups was not statistically different showing them to be comparable – cases: mean (±SD) = -0.67 (±1.78), median (±IQR) = -0.625 (±1.31); controls: mean (±SD) = -0.68 (±1.82), median (±IQR) = -0.65 (±1.39); P_{mean} = 0.21, P_{median} = 0.31. The IOP of the cases and controls was significantly similar to each other (P = 0.076). A significant difference was found with regard to Hb and serum ferritin levels among the two study groups (P_{Hb} = 0.039, $P_{ferritin}$ <0.001). The mean duration of thalassemia in the cases was 17.48 (±4.01) years and the mean transfusions received by the cases was 2.35 (±0.67) per month. 42 out of 56 cases were receiving iron chelation monotherapy, while remaining were using combined therapy (tab. 2).

TABLE 2

Distribution of clinical and laboratory parameters.

Parameters	Beta-thalassemia major	Controls	P-value
	Mean (±SD)	Mean (±SD)	
SER	-0.67 (±1.78)	-0.68 (±1.82)	0.21
	Median (±IQR) = -0.625 (±1.31)	Median (±IQR) = -0.65 (±1.39)	0.31
IOP	14.90 (±2.05)	15.1 (±2.04)	0.076
Hb (g/dL)	9.05 (±0.68)	13.12 (±0.98)	0.039
Ferritin (ng/dL)	5640.55 (±3264.22)	22.67 (±18.50)	<0.001
Duration of thalassemia (in years)	17.48 (±4.01)	N/A	
Number of transfusions (per month)	2.35 (±0.67)	N/A	

Hb – hemoglobin; IOP – intraocular pressure; SER – spherical equivalent refraction.

All the corneal HOAs were significantly different among the cases and healthy individuals (P <0.05) except horizontal coma, total coma, and spherical aberrations for which the P-value was >0.05. The details are given in table 3.

TABLE 3

Corneal higher order aberrations in beta-thalassemia major patients and healthy controls.

HOA (µm)	Beta-thalassemia major	Controls	Mann–Whitney U	P-value
	Median (±IQR)	Median (±IQR)		
Total HOA	0.51 (±0.21)	0.60 (± 0.28)	1252.00	0.005*
Total trefoil	0.18 (±0.11)	0.11 (±0.09)	2593.00	<0.001*
Vertical trefoil	0.13 (±0.08)	0.07 (±0.09)	2520.00	<0.001*
Oblique trefoil	0.07 (±0.11)	0.04 (±0.08)	2201.00	0.031*
Total coma	0.31 (±0.22)	0.28 (±0.16)	2152.00	0.059
Vertical coma	0.17 (±0.18)	0.09 (±0.11)	2408.00	0.001*
Horizontal coma	0.21 (±0.29)	0.23 (±0.19)	1724.50	0.724
Spherical	0.22 (±0.08)	0.23 (±0.07)	1939.00	0.440
Third order	0.37 (±0.22)	0.30 (±0.14)	2275.50	0.011*
Fourth order	0.28 (±0.10)	0.25 (±0.08)	2283.50	0.010*
Fifth order	0.11 (±0.10)	0.07 (±0.04)	2496.00	<0.001*
Sixth order	0.09 (±0.06)	0.05 (±0.02)	2717.50	<0.001*

HOA – high order aberration; IQR – inter-quartile range.
* P-value <0.05 as significant.

There was a significant weak positive correlation between fifth order aberrations and duration of thalassemia (r = 0.28, P = 0.033). A significantly weak negative correlation of Hb was found with fourth order and spherical aberrations (fourth order aberrations: r = -0.33, P = 0.012; spherical aberrations: r = -0.29, P = 0.029). No significant correlation of all other corneal HOAs with thalassemia duration, number of transfusions, Hb, and ferritin levels was found (P >0.05)

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as shown in table 4. In terms of iron chelation therapy received by thalassemia individuals, a significant difference among the cases receiving monotherapy and combined therapy was found for fifth and sixth order aberrations (P_{fifth} = 0.006, P_{sixth} = 0.022) (tab. 5).

DISCUSSION

The present study showed significantly high values of all the corneal HOAs (P <0.05) among the cases in comparison to controls other than total coma, horizontal coma, and spherical aberrations (P >0.05). There was a weak positive correlation of fifth order aberrations with thalassemia duration (P = 0.033). A weak negative correlation of Hb was found with fourth order and spherical aberrations (P = 0.012, P = 0.029). The cases receiving monotherapy of iron chelation showed significant difference in their fifth and sixth order aberrations from those using combined therapy (P = 0.006, P = 0.022).

Previous studies have revealed corneal HOAs in various ocular conditions including refractive errors [4], keratoconus [13, 14], hyperopic and myopic laser surgery [15], Descemet's membrane endothelial keratoplasty (DMEK), Descemet's stripping automated endothelial keratoplasty (DSAEK), penetrating keratoplasty (PK) [16], infectious keratitis [17], and corneal dystrophies [18].

In beta-thalassemia major, prolonged anemia causes tissue hypoxia which necessitates the thalassemic patients to have frequent blood transfusions. Although blood transfusions compensates for the Hb deficiency in those patients, however, the subsequent iron excess can lead to life-threatening conditions with most common being cardiac siderosis, hepatic, and endocrine dysfunction [19]. Iron is an important element of human body, and is essential for cell reactions in nervous tissues. Excessive iron, however, causes a misproportion of free radicals and antioxidants in the body leading to cell death [20–23]. To regulate the iron levels in the body, these patients require specified iron chelation therapy

TABLE 4

Correlation of corneal higher order aberrations with duration of thalassemia, number of transfusions, hemoglobin, and serum ferritin levels.

HOA (µm)	Duration of thalassemia (years)		Number of transfusions (per month)		Hemoglobin (g/dL)		Ferritin (ng/mL)	
	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
Total HOA	0.08	0.539	-0.005	0.972	-0.03	0.789	0.09	0.493
Total trefoil	0.09	0.487	0.01	0.937	0.11	0.413	0.02	0.844
Vertical trefoil	0.007	0.957	-0.06	0.654	0.10	0.441	0.002	0.989
Oblique trefoil	0.11	0.414	-0.07	0.610	-0.07	0.570	0.16	0.214
Total coma	-0.02	0.862	-0.04	0.767	0.09	0.488	0.24	0.073
Vertical coma	0.18	0.182	0.18	0.176	0.09	0.495	0.15	0.249
Horizontal coma	-0.10	0.455	-0.14	0.279	0.02	0.886	0.21	0.119
Spherical	0.05	0.701	0.12	0.348	-0.29	0.029*	-0.19	0.143
Third order	-0.00	0.995	-0.10	0.429	0.10	0.456	0.25	0.061
Fourth order	0.14	0.297	0.19	0.153	-0.33	0.012*	-0.16	0.233
Fifth order	0.28	0.033*	0.25	0.054	-0.22	0.097	-0.23	0.079
Sixth order	0.06	0.660	0.12	0.352	-0.17	0.201	-0.20	0.123

HOA – high order aberration.
* P-value <0.05 as significant.

TABLE 5

Corneal higher order aberrations in relation to iron chelation therapy.

HOA (µm)	Iron chelation therapy		Mann–Whitney U	P-value
	Monotherapy	Combined therapy		
	Median (±IQR)	Median (±IQR)		
Total HOA	0.50 (±0.13)	0.56 (±0.21)	215.50	0.140
Total trefoil	0.18 (±0.12)	0.17 (±0.06)	303.50	0.865
Vertical trefoil	0.13 (±0.07)	0.14 (±0.10)	296.50	0.970
Oblique trefoil	0.08 (±0.12)	0.07 (±0.08)	312.50	0.733
Total coma	0.30 (±0.21)	0.39 (±0.21)	232.50	0.248
Vertical coma	0.17 (±0.18)	0.12 (±0.17)	341.50	0.374
Horizontal coma	0.20 (±0.28)	0.23 (±0.30)	231.00	0.237
Spherical	0.22 (±0.09)	0.23 (±0.07)	242.00	0.329
Third order	0.37 (±0.18)	0.40 (±0.24)	267.00	0.616
Fourth order	0.27 (±0.09)	0.30 (±0.06)	195.50	0.063
Fifth order	0.10 (±0.07)	0.14 (±0.09)	150.00	0.006*
Sixth order	0.08 (±0.05)	0.11 (±0.10)	173.50	0.022*

HOA – high order aberration.
* P-value <0.05 as significant.

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either oral or intravenous which itself has its own complications [19].

The systemic and ocular effects of thalassemia are well known. To the best of our knowledge, the effect of thalassemia on corneal HOAs has not been studied yet. This is the first study to highlight the changes in corneal HOAs due to beta-thalassemia major. Moreover, we also evaluated these HOAs in terms of thalassemia duration, frequency of blood transfusions, Hb, ferritin and iron chelation therapy. The study was limited in terms of small sample size, which should be considered in future studies. Secondly, Corneal Topographer Galilei G5 was used to evaluate corneal HOAs in this study due to unavailability of corneal aberrometer, so, further studies should take this in to consideration. As it was a cross-sectional study, more follow-up studies are needed to evaluate the changes in corneal HOAs with increasing duration of disease, form of iron chelation, and Hb and ferritin levels at each follow-up.

CONCLUSIONS

Corneal HOAs are more evident among beta-thalassemia major cases in comparison to healthy individuals except for total coma, horizontal coma, and spherical aberrations. Spherical aberrations and fourth order aberrations were weakly negatively correlated to Hb, whereas fifth order aberrations were weakly positively correlated to thalassemia duration. The cases also showed significant difference in their HOAs when compared in terms of iron chelation therapy. Thalassemia patients should be closely monitored with more frequent ocular examinations to lessen the potential visual disturbances and improve ocular health.

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Authors' contributions:
Maryam Firdous – concept and idea, methodology & data collection, manuscript writing (original draft).
Muhammad Farooq Umer – supervision, validation, manuscript review and editing.
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