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Investigation of anterior scleral thickness in patients with corneal stromal dystrophies using swept-source anterior segment optic coherence tomography

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Abstract

Aim: The distinctive feature of corneal dystrophies is the existence of abnormal deposits that are insoluble and found in different layers of the cornea. While corneal thickness has been investigated in corneal stromal dystrophies, anterior scleral thickness has not yet been evaluated. We aimed to investigate anterior scleral thickness and corneal and anterior segment parameters in corneal stromal dystrophies in this study.

Materials and Methods: The study was conducted with 35 eyes with corneal stromal dystrophies from 19 patients and 35 healthy controls. We calculated the anterior scleral thickness 4 mm posterior to the scleral spur in the nasal and temporal quadrants, by anterior segment optic coherence tomography (Triton, Topcon, Japan). Scheimflug corneal tomography (Sirius, CSO, Italy) was performed to assess corneal and anterior segment parameters.

Results: The mean age was 36.5±12.1 years in the dystrophy group. The mean temporal scleral thickness was 556.67±15.11 µm, and the mean nasal scleral thickness was 565.83±15.18 µm, statistically similar to those of the control group (p=0.81, p=0.51, respectively). However, the difference between temporal and nasal scleral thickness values was not statistically significant in the dystrophy group (p=0.53, p=0.57). Intraocular pressure was higher in lattice stromal dystrophy than in other dystrophies (p=0.005). There was found to be a moderate, positive correlation between age and nasal scleral thickness in the control group. (r=0.432; p=0.010).

Conclusion: In conclusion, we found that scleral thickness did not change in corneal dystrophies. Further histological studies are needed to conclusively exclude microstructural alterations of scleral thickness in patients with corneal stromal dystrophies.

Introduction

The distinctive feature of corneal dystrophies is the existence of abnormal deposits that are insoluble and found in different layers of the cornea [1]. According to the IC3D classification system, granular and macular corneal dystrophies fall under the category of epithelial-stromal TGFBI dystrophies, whereas lattice corneal dystrophies fall under the category of stromal dystrophies [2].

The sclera consists of collagen fibrils embedded in a hydrated matrix of proteoglycans [3]. The anterior scleral layers can be imaged non-invasively and with high quality with anterior segment optical coherence tomography (AS-OCT) [4]. Various studies have shown that anterior and posterior segment diseases can cause changes in anterior scleral thickness [5-9]. Although corneal thickness has been evaluated in corneal dystrophies to our knowledge, anterior scleral thickness has not been evaluated previously [10].

In the present study, we purposed to investigate anterior scleral thickness in corneal stromal dystrophies and explore its relationship with corneal and anterior segment parameters.

Materials and Methods

Thirty-five eyes with corneal stromal dystrophies (15 granular, 10 macular, and 10 lattice) from 19 patients and 35 healthy controls were involved. This study adhered to the principles of the Declaration of Helsinki. We obtained approval from the research ethics committee of the hospital (Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee, 2023/KK/109) and

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informed consent from each participant.

Diagnoses of corneal stromal dystrophies were made by experienced corneal specialists based on the morphology of the deposits using slit lamp biomicroscopy. Patients with ocular diseases other than corneal dystrophies, such as retinal disorders, uveitis, glaucoma, and a history of intraocular surgery, were excluded. In addition, patients with drug use that could alter the sclera and those with systemic diseases were also excluded. The patients with intraocular pressure (IOP) between 10 and 21 mmHg, a normal cornea, optic disc, and retina, and no history of ocular trauma, ocular surgery, or drug use were involved in the control group.

All patients underwent BCVA evaluation, slit lamp biomicroscopy, IOP measurement, fundus examination, and axial length (AL) measurement (IOL Master, Carl Zeiss Meditec, Dublin, CA, USA). The measurement of scleral thickness was performed with AS-OCT (Triton, Topcon, Japan) in nasal and temporal cornea-scleral sections within a 16-mm diameter using a compatible anterior segment lens. The anterior scleral border was determined as episcleral vessels. The posterior scleral border was defined as the line of intersection between the hyperreflective sclera and hyporeflective ciliary muscle.6 We calculated scleral thickness 4 mm posterior to the scleral spur (Figure 1). All measurements were performed at 9:00–12:00.

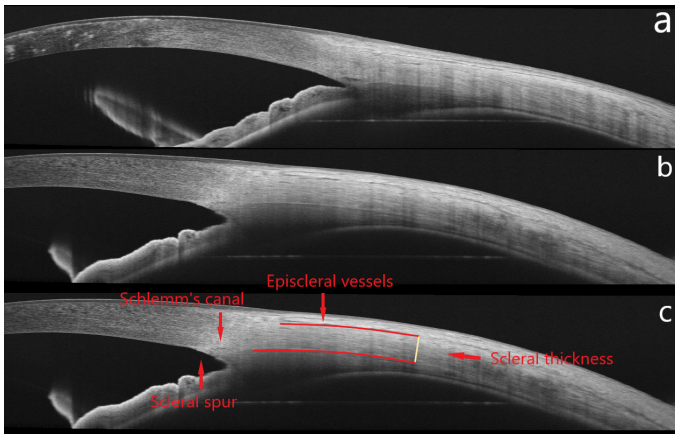

Figure 1. Anterior segment optical coherence tomography images of the cornea and anterior sclera. a. Optical coherence tomography image of the cornea and anterior sclera of a patient with granular corneal dystrophy b. Optical coherence tomography image of cornea and anterior sclera of a healthy eye c. Determination of the anterior and posterior scleral boundaries and measurement of scleral thickness vertically, 4 mm posterior to the scleral spur.

Corneal tomography was taken using a Scheimpflug-Placido disc camera (Sirius, CSO, Italy) in all patients. Horizontal visible iris diameter, thinnest pachymeter, central corneal thickness, anterior chamber depth and volume, corneal volume, iridocorneal angle, horizontal anterior chamber diameter, and keratometry 1 and 2 (K1 and K2) were evaluated.

We determined that the difference in the anterior scleral thickness between the corneal dystrophy and control groups had a large effect size, and we calculated the total number of patients required to be 70 (35 for each group) to achieve a power of 0.90 at an effect size of 0.88 and a type 1 error of 0.05.

Statistical analysis

IBM SPSS Statistics Standard Concurrent User v. 26 (IBM Corp., Armonk, New York, USA) was utilized for statistical analysis. The suitability of the quantitative data for normal distribution was assessed with the Shapiro–Wilk test. Descriptive statistics were provided as the number of units (n), percentage (%), mean, standard deviation, and standard error values. While the chi-square test was used to compare the groups in terms of gender, the independent samples t-test was preferred to compare based on age. Generalized estimating equations were utilized to compare the eye parameters between the groups since some patients had one eye with dystrophy while others had bilateral dystrophies, resulting in missing data. Association between numerical variables was assessed using the Pearson or Spearman correlation coefficients according to the data distribution. The significance level for statistics was determined as 0.05.

Results

The mean age was 36.5 ± 12.1 years for the stromal corneal dystrophy group and 36.8 ± 11.3 years for the control group. There were 10 (52.6%) female participants in the patient group and 18 (51.5%) in the control group. In terms of age or gender, the groups were found to be similar ($p = 0.94$ and p=0,99 respectively).

The mean BCVA values of the dystrophy group were found to be lower than those of the control group ($p<0.001$), whereas the K2 values were higher in the dystrophy group ($p = 0.04$). Nasal and temporal anterior sclera thicknesses were found to be similar (Table 1).

The BCVA values differed between the dystrophy subgroups ($p<0.001$). The BCVA values of the macular corneal dystrophy group were statistically significantly lower compared to those of the lattice and granular corneal dystrophy groups. Nevertheless, the difference in BCVA values between the lattice and granular corneal dystrophy groups was not found statistically significant. In the subgroup analysis performed according to dystrophy type, the IOP values were higher in the lattice corneal dystrophy group than in the macular and granular dystrophy groups (p=0.005). The IOP values of the macular and granular corneal dystrophy groups were similar (Table 2).

When all patients were evaluated together (Table 3), nasal scleral thickness values were revealed to be higher than temporal scleral thickness values ($p<0.001$). In the control group, nasal scleral thickness was higher than temporal scleral thickness ($p<0.001$). However, the difference between nasal and temporal scleral thickness values was not statistically significant in the dystrophy group (p=0.53, p=0.57).

The relationship between age and temporal scleral thickness in both groups was not found to be statistically significant (Table 4). A slightly positive correlation was found between nasal scleral thickness and age in all patients (r

Table 1. Comparison of parameters between groups.

	Control group n = 35	Dystrophy group n = 35	p values*
Spherical equivalent (D)	0.14 ± 0.13	0.31 ± 0.37	0.073
Astigmatism (D)	0.21 ± 0.09	2.27 ± 0.62	0.088
BCVA (logMAR)	0.00 ± 0.00	0.47 ± 0.08	**<0.001**
Intraocular pressure (mmHg)	13.70 ± 0.42	13.82 ± 0.84	0.533
Axial length (mm)	23.49 ± 0.11	23.25 ± 0.24	0.421
HVID (mm)	12.15 ± 0.11	12.10 ± 0.12	0.709
Thinnest pachymeter (µm)	540.04 ± 6.18	477.51 ± 15.69	0.072
CCT (µm)	544.36 ± 5.75	495.76 ± 13.04	0.090
ACD (mm)	3.48 ± 0.07	3.38 ± 0.09	0.970
ACV (mm^3)	153.34 ± 4.72	141.95 ± 7.73	0.705
Iridocorneal angle (degrees)	41.37 ± 1.04	41.13 ± 1.59	0.605
HACD (mm)	12.11 ± 0.07	11.96 ± 0.23	0.607
Corneal volume (mm^3)	57.52 ± 0.64	56.86 ± 1.34	0.914
K1 (D)	42.77 ± 0.27	42.53 ± 0.34	0.353
K2 (D)	43.52 ± 0.25	44.65 ± 0.50	**0.043**
Temporal scleral thickness (µm)	557.39 ± 6.99	556.67 ± 15.11	0.814
Nasal scleral thickness (µm)	577.71 ± 8.03	565.83 ± 15.18	0.517
Mean scleral thickness (µm)	567.55 ± 7.03	561.25 ± 14.92	0.822

Data are given as mean ± standard error, *generalized estimating equations. BCVA: best-corrected visual acuity, HVID: horizontal visible iris diameter, K1: keratometry 1, K2: keratometry 2, CCT: central corneal thickness, ACD: anterior chamber depth, ACV: anterior chamber volume, HACD: horizontal anterior chamber diameter.

Table 2. Comparison of parameters between dystrophy subgroups.

	Dystrophy group			
	Lattice n = 10	Macular n = 10	Granular n = 15	p values
Spherical equivalent (D)	2.34 ± 1.35	- [c]	0.64 ± 0.57	0.138
Astigmatism (D)	2.99 ± 1.34	- [c]	3.54 ± 1.10	0.395
BCVA (logMAR)	0.213 ± 0.064[a]	1.038 ± 0.182[b]	0.324 ± 0.055[a]	**<0.001**
Intraocular pressure (mmHg)	16.98 ± 1.14[a]	12.89 ± 0.50[b]	12.18 ± 1.17[b]	**0.005**
Axial length (mm)	22.78 ± 0.38	23.35 ± 0.55	22.99 ± 0.25	0.218
HVID (mm)	11.75 ± 0.27	12.31 ± 0.14	12.28 ± 0.08	0.233
Thinnest pachymeter (µm)	455.13 ± 18.79	- [c]	494.47 ± 6.65	0.066
CCT (µm)	485.96 ± 16.80	- [c]	507.03 ± 7.14	0.950
ACD (mm)	3.31 ± 0.06	- [c]	3.32 ± 0.09	0.373
ACV (mm^3)	135.47 ± 9.91	- [c]	142.26 ± 8.29	0.441
Iridocorneal angle (degrees)	41.04 ± 2.27	- [c]	40.38 ± 1.91	0.727
HACD (mm)	12.33 ± 0.39	- [c]	11.81 ± 0.24	0.649
Corneal volume (mm^3)	57.17 ± 2.27	- [c]	56.66 ± 0.87	0.833
K1 (D)	42.03 ± 0.51	42.99 ± 0.48	42.45 ± 0.55	0.304
K2 (D)	43.80 ± 0.91	45.36 ± 1.36	44.74 ± 0.88	0.548
Temporal scleral thickness (µm)	612.28 ± 25.33	521.18 ± 30.07	554.45 ± 20.43	0.532
Nasal scleral thickness (µm)	615.45 ± 29.06	542.30 ± 28.85	562.59 ± 20.28	0.572
Mean scleral thickness (µm)	613.87 ± 27.02	531.74 ± 29.27	558.52 ± 20.01	0.554

Data are given as mean ± standard error, *generalized estimating equations, [a] and [b] superscripts indicate differences between groups in each row (no statistically significant difference between the groups with the same superscripts). [c] superscripts indicate that we were unable to evaluate due to the small number of patients and the insufficient quality of corneal topography images in some cases of macular dystrophy BCVA: best-corrected visual acuity, HVID: horizontal visible iris diameter, K1: keratometry 1, K2: keratometry 2, CCT: central corneal thickness, ACD: anterior chamber depth, ACV: anterior chamber volume, HACD: horizontal anterior chamber diameter.

= 0.239; p = 0.047). There was found to be a moderate, positive correlation between age and nasal scleral thickness in the control group (r = 0.432; p = 0.010). Nonetheless, no relationship was detected between age and nasal scleral thickness in the dystrophy group.

When the control and dystrophy groups were evaluated separately, there was no statistically significant difference between males and females regarding nasal or temporal

Table 3. Comparison of nasal and temporal measurements within the same eye.

	Temporal scleral thickness	Nasal scleral thickness	p*
All participants	564.1 ± 8.5	580.3 ± 9.1	<0.001
Control group	562.2 ± 11.5	584.3 ± 11.8	<0.001
Dystrophy group	564.2 ± 13.4	574.1 ± 14.5	0.104

Data are given as mean ± standard error, *generalized estimating equations.

Table 4. Correlation of temporal and nasal scleral thicknesses with age.

	Temporal scleral thickness		Nasal scleral thickness	
	r	p	r	p
All participants	0.151	0.213	**0.239**	**0.047**
Control group	0.314	0.066	**0.432**	**0.010**
Dystrophy group	0.060	0.733	0.106	0.545

r: Pearson correlation coefficient.

anterior scleral thickness values ($p>0.05$). There was also no correlation between nasal, temporal, and mean anterior sclera thicknesses and corneal and anterior segment parameters ($p>0.05$).

Discussion

Despite the fundamentally different optical properties of the cornea and the sclera, both tissues embryonically originate from the mesenchyme and have similar collagen content [3]. Granular and lattice dystrophies are characterized by the age-dependent progressive accumulation of mutant protein between the collagen lamellae of the corneal stroma, while the hallmark of macular dystrophies is accumulation of glycosaminoglycans [11-14]. In our study, we found that anterior scleral thickness did not differ between lattice, granular, and macular corneal dystrophies.

Macular corneal dystrophy is thought to occur due to dysregulation of keratan sulfate proteoglycan synthesis or catabolism [15,16]. In a study evaluating the serum assays of patients with macular corneal dystrophies, Klintworth et al. noted the absence of keratan sulfate, indicating defects in the synthesis of keratan sulfate in macular corneal dystrophies [17]. In another study, Thonar et al. reported low serum keratan sulfate levels in patients with macular corneal dystrophy, pointing to the potential of systemic manifestations [18]. In contrast, we did not detect any changes in the scleral thickness of patients with macular dystrophies in our study. Corneas with macular corneal dystrophy show diffuse thinning involving the entire cornea, unlike the localized thinning in keratoconus [19]. This has also been confirmed in histopathological examinations of corneas with macular corneal dystrophy [20]. We could not evaluate the central corneal thickness in macular dystrophy due to the insufficient quality of corneal topography images and the low number of patients.

While many different subtypes of lattice corneal dystrophy have been reported, the majority of patients encountered in clinical practice present with the characteristic phenotype of lattice corneal dystrophy, referred to as classic lattice corneal dystrophy. The myriad of other phenotypes of lattice corneal dystrophy that differ from classical lattice corneal dystrophy in terms of age of presentation, morphology of stromal deposits, and location of stromal deposits are known as variant lattice corneal dystrophies. Another form of lattice corneal dystrophy, associated with mutations in the gelsolin gene, has been defined as lattice corneal dystrophy type 2. However, in contrast to other corneal dystrophies, corneal amyloid deposition does not represent primarily localized protein deposition; rather, it occurs secondary to systemic amyloid deposition; therefore, it is not a true corneal dystrophy. Scleral thickness has not been previously evaluated in classical lattice corneal dystrophy, but in a histopathological study conducted with patients with familial amyloidosis, diffuse amyloid deposits were found in the anterior sclera using Congo red stain. The authors suggested that scleral fibroblasts might also produce scleral deposits [21]. In addition, Haraoka et al. reported amyloid deposition in four (44.4%) of nine cases of familial amyloidosis [22]. Amyloids appeared as spotty deposits within the sclera, especially in the anterior regions of the globe.

Granular corneal dystrophy is identified by the tiny, distinct, well-demarcated, whitish opacities in the anterior stroma. Immunohistochemical staining with antibodies to the TGFBI protein demonstrates that stromal deposits characterizing granular corneal dystrophy consist of a mutated TGFBI protein [23]. In our study, scleral thickness and corneal and anterior segment parameters, except for IOP, were found to be similar in the subgroup analyses of patients with dystrophies.

In the literature, corneal biomechanical alterations have been observed in stromal corneal dystrophies [24,25]. IOP may be underestimated in corneal stromal dystrophies. Although no significant difference has been previously reported in IOP between dystrophy subgroups, we found that the IOP measured by Goldman applanation tonometry was significantly higher in lattice corneal dystrophy. This finding needs to be verified by Corvis ST or an ocular response analyzer.

In the literature, the steep keratometry value is found to be higher in corneal stromal dystrophies. Kocluk et al. determined that the maximum keratometry value was higher in macular corneal dystrophy than in granular and lattice dystrophies, and similar between granular and macular dystrophies. Still, the authors did not have a control group to compare these findings [10]. In the same study, moreover, they reported that corneal volume was smaller in the macular corneal dystrophy group. In contrast, in the current study, we found that corneal volume was similar in all dystrophy subgroups.

The sclera can be affected by factors such as age, refractive error, and glaucoma [26]. It has been reported that sclera changes as age increases [26,27]. Our study found that nasal scleral thickness increased with age only in the healthy group. In the dystrophy group, there was no change in scleral thickness with age. We did not find any correlation between nasal, temporal, and mean anterior scleral thickness, anterior segment, and corneal parameters.

The small number of patients in the subgroups is one of the limitations of this study. Another limitation is that scleral thickness measurement was performed manually. Finally, we collected measurements between 9:00 and 12:00, so we could not evaluate the effect of diurnal variation.

We found that scleral thickness did not change in corneal dystrophies. Studies with a larger number of patients are required to exclude structural changes in scleral thickness in patients with corneal stromal dystrophy.

Ethical approval

Approval was received for this study from the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Decision no: HNEAH-KAEK 2023/109 HNEAH-KAEK 2023/KK/109).

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