

Effects of Atopic Syndrome on Keratoconus

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Purpose: To evaluate the effects of atopic syndrome on manifestations of keratoconus.

Methods: In this retrospective study, we reviewed patient files and data generated by Scheimpflug imaging of 670 eyes of 434 keratoconus patients. Patients were divided into a study group consisting of patients suffering from atopic syndrome (110 eyes of 75 patients), namely allergic asthma, atopic dermatitis, and/or allergic rhinitis, and a control group of patients without known atopic syndrome (560 eyes of 359 patients).

Results: We found a significant difference with the mean age being 36.1 ± 11.7 for the control group, 32.8 ± 9.6 for the atopic group ($P = 0.002$) with 1 atopic trait, and 30.4 ± 7.5 for patients with 2 or more atopic traits ($P = 0.002$). No statistically significant differences were found in the mean corrected distance visual acuity, corneal pachymetry, minimum relative pachymetric progression (RPI_{min}), mean refraction, keratoconus index, anterior chamber depth and volume, K_{max} , and location of K_{max} in relation to the corneal apex. However, we found a significantly higher corneal density for the anterior 120 μm of the cornea in the atopic group (control: 20.74 ± 4.68 , atopic group: 21.92 ± 4.65 $P = 0.016$).

Conclusions: Keratoconus patients suffering from atopic syndrome were significantly younger but showed no topographical changes except in corneal densitometry compared with keratoconus patients without an atopic disease. This suggests atopic syndrome is a factor, which can trigger earlier manifestation of keratoconus.

Key Words: Keratoconus, atopic syndrome, Scheimpflug imaging (*Cornea* 2016;35:1416–1420)

Keratoconus is often a bilateral noninflammatory disorder of the eyes that mainly occurs around the second and third decades of life and causes progressive degeneration of the corneal layers, with stromal changes being the most prominent

finding. Although the etiology still remains unclear, several risk factors, such as chromosomal disorder, environmental exposure, and atopic history, are discussed as risk and progression factors.^{1,2}

The high incidence of atopy in keratoconus patients has been documented in the literature,^{3,4} and it has been postulated that one cause of keratoconus may be eye rubbing, stimulated by ocular itching or discomfort, resulting from atopic diseases.⁵

However, the studies that examined this association used a relatively small sample size or found a relatively weak association.^{6–8} Nevertheless, atopy seems to be an important factor in the occurrence of keratoconus, and it is not unreasonable to assume that this atopic tendency is accompanied by specific changes in the cornea of these patients.

In this study, our aim was to compare the topographical changes in keratoconus patients with and without atopic syndrome, defined as allergic rhinitis, allergic asthma, and atopic dermatitis.

MATERIALS AND METHODS

We retrospectively analyzed 670 eyes of 434 patients with a known history of keratoconus who underwent Scheimpflug imaging (Pentacam HR; Oculus, Wetzlar, Germany) from April 2010 till February 2015 in the Department of Ophthalmology at the Goethe University Frankfurt, Germany. The study protocol was reviewed and approved by our institution's ethical body, the Frankfurt Ethical Commission, and the tenets of the Declaration of Helsinki were followed throughout the study.

All participants had a complete ophthalmological examination before anterior segment tomography, including slit-lamp biomicroscopy, tonometry, funduscopy, and measurement of uncorrected and best-corrected distance visual acuity. Inclusion criteria were age of over 13 and confirmed diagnosis of keratoconus by Scheimpflug tomography and/or clinical examination. We excluded patients with previous ophthalmic surgery or history of corneal scarring caused by trauma, infection, or chemical injury. We also excluded patients with any ectatic conditions that were not keratoconus, such as pellucid marginal degeneration or post-laser-assisted in situ keratomileusis (LASIK) ectasia. Furthermore, we screened patient files for reported atopic syndrome, namely allergic asthma, atopic dermatitis, and allergic rhinitis. Based on these findings, 2 groups of patients were established.

In the “atopic group,” we included keratoconus patients suffering from atopic syndrome (110 eyes of 75 patients). We also subdivided this group into one cohort with exactly 1 atopic trait and one cohort with 2 or more atopic traits. The

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“control group” consisted of 560 eyes of 359 patients, with keratoconus who showed no signs of atopic history or allergies.

Because one of the main changes in keratoconus is the decrease in corneal thickness, we decided to use it as the basis for our sample size calculation. Similar to a previous study, we used a standard deviation of 42 μm for corneal thickness at the thinnest point in eyes with keratoconus. We set the minimum relevant difference at 20 μm between atopic and control group. With alpha 0.05 and beta 0.2, the required sample size for a *t* test was 71 per group.

Data for corneal tomography, pachymetry, and densitometry were recorded using the Pentacam Scheimpflug device (Oculus), which generated a series of 25 Scheimpflug images during the 2 seconds of measuring using 2 cameras. A static camera is placed in the center to detect the pupil's contours and to correct eye movements, and a second rotating Scheimpflug camera performs a corneal scan from 0 to 180 degrees around the optical axis to obtain the slit images. A 3-dimensional model of the anterior eye segment is calculated from 25,000 true elevation points.⁹

Based on Scheimpflug imaging, we examined the thinnest and central pachymetry readings, astigmatic power, irregularity indices, distance of the thinnest point to the corneal center, anterior and posterior elevation values, distance of the anterior and posterior elevation points from the corneal center, corneal density, and mean keratometry readings (K).

Corneal densitometry can be analyzed separately for the anterior (first 120 μm), central, and posterior (posterior 60 μm) layers of the cornea and in 4 annular zones around the corneal apex. These zones stretch from 0 to 2 mm, 2 to 6 mm, 6 to 10 mm, and 10 to 12 mm, respectively. Depending on the degree of light scatter, density is expressed in gray scale units from 0 to 100. This is calibrated and calculated automatically by proprietary software within the Scheimpflug device, with 0 indicating no light scatter (maximum transparency) and 100 being a totally opaque cornea (minimum transparency).^{10–12}

We only included Scheimpflug examinations that were labeled with “OK” by the device's internal quality checking system.

To make a statement about the differences in cone location of the 2 groups, atopic and nonatopic, we computed the Euclidean distance of maximal corneal curvature reading (K_{max}) to the corneal apex for each eye in the 2 groups as follows:

$$\text{distance to apex} = \sqrt{x^2 + y^2}$$

We then compared the mean distance of observations from the atopic and nonatopic groups using a *t* test. For other variables, both groups were compared by paired *t* test after the Shapiro–Wilk test showed normal distribution. All data are reported as mean $\pm$ standard deviation. Data management was performed with Microsoft Excel 2013 for Windows, and Stata for Windows was used for statistical analysis. The level of significance was set at $P < 0.05$.

RESULTS

Of the 434 patients (670 eyes) who were examined, 75 (110 eyes) had at least 1 atopic trait and 14 patients at least 2 atopic traits. Five hundred sixty eyes of the remaining 359 patients formed the control group (Table 1). A χ^2 test showed that in patients with atopic syndrome, keratoconus was present in both eyes significantly more often ($P = 0.01$). Keratoconus patients were more frequently male; however, the χ^2 test showed no statistically significant difference comparing sex ($P = 0.59$) between atopic and control groups. The age, however, diverged significantly between the 2 groups with the mean age being 32.8 ± 9.6 for the atopic group and 36.1 ± 11.7 for the control group ($P = 0.002$). This age gap increased to almost 6 years when inspecting patients with more than 1 atopic trait (mean age of patients with 2 or more atopic traits 30.4 ± 7.5 years $P = 0.002$).

On comparing K_{max} in relation to the corneal apex, we found that the majority of K_{max} in both groups was located in

TABLE 1. Demographic Features

	Control Group	Total	Atopic Group	
			Patients With 1 Atopic Trait	Patients With 2 or More Atopic Traits
No. eyes	560	110	87	23
KK in both eyes	201 patients	55 patients	46 patients	9 patients
KK in 1 eye	158 patients	20 patients	15 patients	5 patients
Age (yr)	36.1 ± 11.7	32.8 ± 9.6	33.4 ± 10.0	30.3 ± 7.5
Age range (yr)	13–67	14–56	14–56	18–47
Sex (M/F)	406/154	77/33	66/21	11/12
Sc (logMAR)	0.64 ± 0.48	0.67 ± 0.48	0.71 ± 0.50	0.50 ± 0.33
Cc (logMAR)	0.23 ± 0.27	0.22 ± 0.23	0.23 ± 0.25	0.18 ± 0.16
Allergic asthma		29 eyes	13 eyes	16 eyes
Atopic dermatitis		37 eyes	20 eyes	17 eyes
Allergic rhinitis		67 eyes	54 eyes	13 eyes

logMAR, logarithm of the minimum angle of resolution; sc, without correction; cc, with correction.

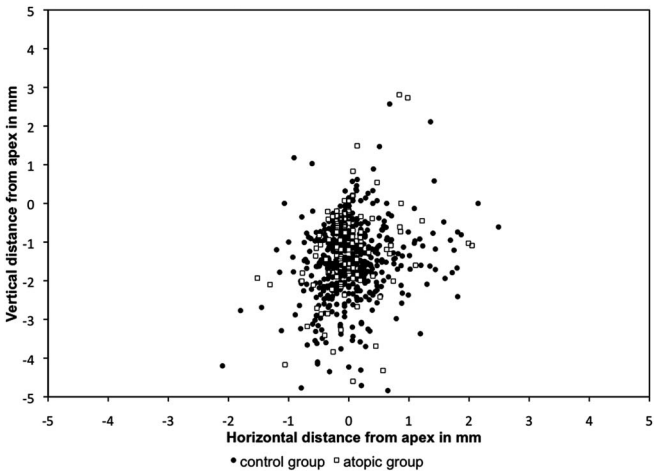


FIGURE 1. Position of $K_{\max}$ in millimeters from the corneal apex.

the 2 inferior quadrants but that there was no significant difference in location between the 2 groups with $P = 0.174$ (Fig. 1). Distance of $K_{\max}$ from the apex was on average 1.56 mm for the nonatopic group 1.44 mm for the atopic group.

Also, further variables used for keratoconus staging, such as the anterior and posterior elevation values, minimum and maximum pachymetric readings, distance of the thinnest point to the corneal center, minimum relative pachymetric progression ($RPI_{\min}$), mean refraction, keratoconus index, anterior chamber depth, and volume, showed no statistical difference between the 2 groups (Table 2).

When comparing the corneal density there was an underlying trend for a higher total corneal density in the atopic group ($P = 0.055$) that became significant when comparing the anterior 120 μm of the cornea ($P = 0.016$) with the control group (Table 3)

DISCUSSION

An association between atopy, allergy, eye rubbing, and keratoconus has been postulated for many years, and there is

strong evidence that atopic traits are more common in patients with keratoconus than in the general population.¹³

Although this is widely accepted, there are very few reports that have investigated topographical features of keratoconus patients with and without atopy using modern imaging techniques such as slit-scan topography and none using Scheimpflug imaging.^{14,15}

A study by Kaya et al¹⁵ described lower central and thinnest corneal thicknesses in keratoconus eyes with atopy than in eyes without atopy. Furthermore, their study showed that the thinnest point of the cornea was more peripheral in eyes with atopy. Therefore, their group suggested that atopic keratoconus patients could be evaluated as a separate entity in keratoconus disease. We also analyzed the cone localization in our study. For exact cone localization, the highest elevation point needs to be considered. By the Scheimpflug system, only exact localization of $K_{\max}$ and thinnest point in pachymetry are provided. We decided to use $K_{\max}$ as the closest approximation for the cone localization and found no significant difference between both groups.

Also, we found no significant difference in any parameter used for topographical staging of the disease between both groups. Our study showed very similar corneal characteristics when comparing both groups with very little difference regarding minimum pachymetric readings, K -index, $K_{\max}$ and minimum corneal thickness. Our data thus support the idea of one underlying pathomechanism that may be amplified by atopic traits, such as allergic asthma, atopic dermatitis, or allergic rhinitis. Nevertheless, the fast progression of keratoconus in patients with atopic syndrome might justify more frequent follow-up examinations and potentially earlier intervention.

There is substantial evidence of a genetic component to keratoconus as computerized corneal topography reveals much about variations in the expression of the keratoconic phenotype, specifically that apparently “unaffected” family members are more likely to have astigmatism or other corneal anomalies than normal eyes.^{16,17}

A “2-hit” hypothesis is increasingly accepted^{1,18–21} suggesting that keratoconus patients need a genetic predisposition and an environmental factor for clinical manifestation of the disease. Our study shows that patients with an atopic

TABLE 2. Various Pentacam Parameters for Keratoconus Patients With and Without Atopic Traits and Their Significance Level for Comparison

Parameter	Control Group		Atopic Group		<i>P</i> for Control Versus Atopic
	Mean ± SD	Range	Mean ± SD	Range	
$RPI_{\min}$	1.36 ± 0.68	0.24–7.23	1.37 ± 0.59	0.32–3.17	0.874
$ART_{\max}$	180.28 ± 74.16	21.0–456.0	184.50 ± 78.99	53.0–436.0	0.606
$Pachy_{\min}$	469.04 ± 44.81	305.0–598.0	467.24 ± 43.84	386.0–587.0	0.695
D value	7.96 ± 4.20	2.11–28.66	7.89 ± 3.70	2.10–19.63	0.854
AC depth	3.20 ± 0.36	2.10–5.11	3.24 ± 0.36	2.54–4.80	0.232
AC volume	187.59 ± 40.42	82.0–302.0	189.85 ± 31.77	128.0–273.0	0.515
KI	1.22 ± 0.13	0.86–1.83	1.20 ± 0.12	0.97–1.63	0.163
$K_{\max}$	54.59 ± 6.85	43.20–84.00	54.41 ± 6.05	43.60–75.60	0.791

AC depth, anterior chamber depth; AC volume, anterior chamber volume; $ART_{\max}$, maximum Ambrosio relational thickness; KI, keratoconus index; $K_{\max}$, maximum keratometry; $Pachy_{\min}$, pachymetry minimum.

TABLE 3. Corneal Light Backscatter in Grayscale Units for Keratoconus Patients With and Without Atopic Traits

	0.0–2.0 mm*	2.0–6.0 mm*	6.0–10.0 mm*	10.0–12.0 mm*	Total Diameter (0.0–12.0 mm*)
Anterior 120 μ m					
Control group	22.24 $\pm$ 6.04	18.96 $\pm$ 4.16	17.91 $\pm$ 5.64	29.43 $\pm$ 11.06	20.74 $\pm$ 4.68
Atopic group	23.62 $\pm$ 6.84	19.95 $\pm$ 4.35	18.73 $\pm$ 5.10	31.55 $\pm$ 11.88	21.92 $\pm$ 4.65
<i>P</i> control versus atopic	0.050	0.030	0.132	0.086	0.016
Center					
Control group	13.53 $\pm$ 2.67	11.97 $\pm$ 2.12	12.79 $\pm$ 3.82	19.48 $\pm$ 6.53	13.63 $\pm$ 2.85
Atopic group	13.88 $\pm$ 2.66	12.29 $\pm$ 2.08	13.05 $\pm$ 3.23	20.49 $\pm$ 6.11	14.05 $\pm$ 2.54
<i>P</i> control versus atopic	0.213	0.142	0.450	0.119	0.127
Posterior 60 μ m					
Control group	9.92 $\pm$ 1.94	10.00 $\pm$ 1.81	11.61 $\pm$ 3.37	16.70 $\pm$ 5.16	11.54 $\pm$ 2.49
Atopic group	10.08 $\pm$ 1.92	10.21 $\pm$ 1.70	11.73 $\pm$ 2.62	17.38 $\pm$ 4.35	11.79 $\pm$ 2.04
<i>P</i> control versus atopic	0.422	0.251	0.678	0.149	0.270
Total thickness					
Control group	15.23 $\pm$ 3.35	13.64 $\pm$ 2.60	14.10 $\pm$ 4.19	21.87 $\pm$ 7.13	15.30 $\pm$ 3.24
Atopic group	15.86 $\pm$ 3.54	14.15 $\pm$ 2.61	14.51 $\pm$ 3.56	23.14 $\pm$ 6.98	15.91 $\pm$ 2.97
<i>P</i> control versus atopic	0.089	0.065	0.295	0.083	0.055

*Diameter from corneal center.

tendency were on average 3 years younger than the control group and almost 6 years younger when suffering from 2 or more atopic traits. Because the corneal phenotype of our patients was very similar, it supports the idea of one underlying pathomechanism; this finding emphasizes that atopic traits are an influential factor affecting the progression of keratoconus or leading to an earlier onset and clinical manifestation of the disease via linked external factors.

Some studies imply that mechanical trauma caused by eye rubbing may be one of the main reasons for keratoconus manifestation.^{5,20–23} Bawazeer et al⁵ stated that ocular discomfort and itching caused by atopy might lead to increased eye rubbing. A logistic regression analysis they performed, which included family history of keratoconus and atopy, found that eye rubbing was the only significant factor associated with keratoconus. Coyle reported the case of a young patient who discovered that he could neutralize a cardiac arrhythmia by vigorously massaging his left eye. In the following years, he developed keratoconus without the presence of other risk factors.

Although the authors of this article acknowledge that keratoconic deformation of the cornea may be caused in some cases solely by mechanical trauma through extreme forms of eye rubbing, we think that the majority of keratoconus cases are not induced by mechanical trauma alone. Because recent studies also suggest that low-level inflammatory components may be present in keratoconus development,^{24–26} we rather think that a genetic preposition is needed, which is amplified by atopic tendencies.

The analysis of corneal densitometry has gained increasing interest over the past few years.^{11,27–33} The disarrangement in corneal histology found in keratoconus patients can lead to alterations in densitometry readings caused by complex mechanisms with size regularity and arrangement of collagen fibrils playing an important role.^{31,34} Interestingly, high densitometry levels can even be observed in clinically clear corneas.³⁵

In our study, we found a trend for increased density when comparing the whole cornea of the atopic group with the control group. The highest densitometry readings in both groups could be found in the anterior 120 μ m of the cornea. The anterior cornea is the most affected layer with alterations in the basal epithelial cell layer, leading to its disappearance and thinning of epithelial layer in keratoconus.³⁶ Breaks in the Bowman layer and thickened subbasal nerve plexus have also been described.^{37,38} However, although we showed that the densitometry of the anterior layer was significantly higher in the atopic group, the nature of this finding is not clear. It might be because of eye rubbing and subsequent disturbances in the anterior corneal segment. There might be also different reasons behind the difference in corneal densitometry. Further prospective investigations with the use of confocal microscopy might be helpful to find an explanation for this.

We found no significant differences in corneal topography comparing keratoconus patients with and without atopic traits except in the corneal densitometry of the anterior 120 μ m. Taking into consideration that the only other significant difference was that the age of patients with atopic diseases was less, we assume that keratoconus also requires predisposing factors in atopic patients and has a similar underlying pathophysiology in these patients. However, atopy seems to be an important factor triggering an earlier manifestation of keratoconus and might justify more frequent patient examination or earlier intervention and should be evaluated in future studies.

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REFERENCES

- Basu S, Vazirani J. Keratoconus: current perspectives. *Clin Ophthalmol*. 2013;7:2019–2030.
- Pearson AR, Soneji B, Sarvananthan N, et al. Does ethnic origin influence the incidence or severity of keratoconus? *Eye (Lond)*. 2000;14:625–628.
- Wachtmeister L, Ingemansson SO, Möller E. Atopy and HLA antigens in patients with keratoconus. *Acta Ophthalmol (Copenh)*. 1982;60:113–122.
- Harrison RJ, Klouda PT, Easty DL, et al. Association between keratoconus and atopy. *Br J Ophthalmol*. 1989;73:816–822.
- Bawazeer A, Hodge W, Lorimer B. Atopy and keratoconus: a multivariate analysis. *Br J Ophthalmol*. 2000;84:834–836.
- Cingu AK, Cinar Y, Turkcu FM, et al. Effects of vernal and allergic conjunctivitis on severity of keratoconus. *Int J Ophthalmol*. 2013;6:370–374.
- Gokhale NS. Epidemiology of keratoconus. *Indian J Ophthalmol*. 2013;61:382–383.
- Yeniad B, Alparslan N, Akarçay K. Eye rubbing as an apparent cause of recurrent keratoconus. *Cornea*. 2009;28:477–479.
- Oliveira CM, Ribeiro C, Franco S. Corneal imaging with slit-scanning and Scheimpflug imaging techniques: corneal imaging techniques. *Clin Exp Optom*. 2011;94:33–42.
- Cho YK, Chang HS, La TY, et al. Anterior segment parameters using Pentacam and prediction of corneal Endothelial cell loss after Cataract surgery. *Korean J Ophthalmol*. 2010;24:284–290.
- Lopes B, Ramos I, Ambrósio R. Corneal Densitometry in Keratoconus. *Cornea*. 2014;33:1282–1286.
- Ní Dhubghaill S, Rozema JJ, Jongenelen S, et al. Normative values for corneal densitometry analysis by Scheimpflug optical Assessment. *Invest Ophthalmol Vis Sci*. 2014;55:162–168.
- Rahi A, Davies P, Ruben M, et al. Keratoconus and coexisting atopic disease. *Br J Ophthalmol*. 1977;61:761–764.
- Taneja M, Ashar JN, Mathur A, et al. Measure of keratoconus progression in patients with vernal keratoconjunctivitis using scanning slit topography. *Cont Lens Anterior Eye*. 2013;36:41–44.
- Kaya V, Karakaya M, Utine CA, et al. Evaluation of the corneal topographic characteristics of keratoconus with orbscan II in patients with and without atopy. *Cornea*. 2007;26:945–948.
- Rabinowitz YS, Garbus J, McDonnell PJ. Computer-assisted corneal topography in family members of patients with keratoconus. *Arch Ophthalmol*. 1990;108:365–371.
- Levy D, Hutchings H, Rouland JF, et al. Videokeratographic anomalies in familial keratoconus. *Ophthalmology*. 2004;111:867–874.
- The Genetic and Environmental Factors for Keratoconus. Available at: <http://www.ncbi.nlm.nih.gov.proxy.ub.uni-frankfurt.de/pmc/articles/PMC4449900/>. Accessed November 13, 2015.
- McGhee CNJ, Kim BZ, Wilson PJ. Contemporary Treatment Paradigms in Keratoconus. *Cornea*. 2015;34:S16–S23.
- McGhee CN. 2008 Sir Norman McAlister Gregg Lecture: 150 years of practical observations on the conical cornea—what have we learned? *Clin Experiment Ophthalmol*. 2009;37:160–176.
- McMonnies CW. Behaviour modification in the management of chronic habits of abnormal eye rubbing. *Cont Lens Anterior Eye*. 2009;32:55–63.
- Coyle JT. Keratoconus and eye rubbing. *Am J Ophthalmol*. 1984;97:527–528.
- Ioannidis AS, Speedwell L, Nischal KK. Unilateral keratoconus in a child with chronic and persistent eye rubbing. *Am J Ophthalmol*. 2005;139:356–357.
- Galvis V, Sherwin T, Tello A, et al. Keratoconus: an inflammatory disorder? *Eye (Lond)*. 2015;29:843–859.
- McMonnies CW. Inflammation and keratoconus. *Optom Vis Sci*. 2015;92:e35–e41.
- Shetty R, Ghosh A, Lim RR, et al. Elevated expression of Matrix Metalloproteinase-9 and inflammatory Cytokines in keratoconus patients is Inhibited by Cyclosporine A. *Invest Ophthalmol Vis Sci*. 2015;56:738–750.
- Otri AM, Fares U, Al-Aqaba MA, et al. Corneal densitometry as an indicator of corneal Health. *Ophthalmology*. 2012;119:501–508.
- Elfleim HM, Hofherr T, Berisha-Ramadani F, et al. Measuring corneal clouding in patients suffering from mucopolysaccharidosis with the Pentacam densitometry programme. *Br J Ophthalmol*. 2013;97:829–833.
- Bhatt UK, Fares U, Rahman I, et al. Outcomes of deep anterior lamellar keratoplasty following successful and failed “big bubble”. *Br J Ophthalmol*. 2012;96:564–569.
- Koh S, Maeda N, Nakagawa T, et al. Quality of vision in eyes after selective lamellar keratoplasty. *Cornea*. 2012;31:S45–S49.
- Rozema JJ, Trau R, Verbruggen KHM, et al. Backscattered light from the cornea before and after laser-assisted subepithelial keratectomy for myopia. *J Cataract Refract Surg*. 2011;37:1648–1654.
- Greenstein SA, Fry KL, Bhatt J, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. *J Cataract Refract Surg*. 2010;36:2105–2114.
- Alnawaiseh M, Rosentreter A, Böhm MR, et al. Accelerated (18 mW/cm²) corneal collagen Cross-Linking for progressive keratoconus. *Cornea*. 2015;34:1427–1431.
- Freegard TJ. The physical basis of transparency of the normal cornea. *Eye (Lond)*. 1997;11:465–471.
- Patel SV, McLaren JW, Hodge DO, et al. The effect of corneal light scatter on vision after penetrating keratoplasty. *Am J Ophthalmol*. 2008;146:913–919.
- Mathew JH, Goosey JD, Bergmanson JPG. Quantified Histopathology of the Keratoconic Cornea. *Optom Vis Sci*. 2011;88:988–997.
- Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42:297–319.
- Uçakhan OO, Kanpolat A, Yılmaz N, et al. In vivo confocal microscopy findings in keratoconus. *Eye Contact Lens*. 2006;32:183–191.