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, fundoscopy, 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
“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 2 × 2 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.

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).

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 2 × 2 test. For other variables, both groups were compared by paired 2 tests after the Shapiro–Wilk test showed normal distribution. All data are reported as mean ± 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 \( \chi^2 \) 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 \( \chi^2 \) 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 \( K_{\text{max}} \) in relation to the corneal apex, we found that the majority of \( K_{\text{max}} \) in both groups was located in

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Features</th>
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<tbody>
<tr>
<td><strong>Control Group</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>No. eyes</td>
</tr>
<tr>
<td>KK in both eyes</td>
</tr>
<tr>
<td>KK in 1 eye</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Age range (yr)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>Sc (logMAR)</td>
</tr>
<tr>
<td>Cc (logMAR)</td>
</tr>
<tr>
<td>Allergic asthma</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
</tr>
</tbody>
</table>

logMAR, logarithm of the minimum angle of resolution; sc, without correction; cc, with correction.
K
KI 1.22
AC volume 187.59
AC depth 3.20
ARTmax 180.28
Pachymin 469.04
D value 7.96
RPImin 1.36

Apex.
Pachymin, pachymetry minimum.

Keratoconus has been postulated for many years, and there is
with the control group (Table 3)
comparing the anterior 120
m
of the cornea (Fig. 1). Distance of
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 \( K_{\text{max}} \) 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
to the corneal center, minimum relative pachymetric
progression (RPI\text{min}), mean refraction, keratoconus index,
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 accepted1,18–21
suggesting that keratoconus patients need a genetic predispo-
sition and an environmental factor for clinical manifestation of
the disease. Our study shows that patients with an atopic

\[ \text{DISCUSSION} \]

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
keratoconic 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 \( K_{\text{max}} \) and thinnest point in
pachymetry are provided. We decided to use \( K_{\text{max}} \) 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, \( K_{\text{max}} \)
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 keratoco-
nus in patients with atopic syndrome might justify more frequent
follow-up examinations and potentially earlier intervention.

\[ \text{TABLE 2. Various Pentacam Parameters for Keratoconus Patients With and Without Atopic Traits and Their Significance Level for Comparison} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group</th>
<th>Atopic Group</th>
<th>( P ) for Control Versus Atopic</th>
</tr>
</thead>
<tbody>
<tr>
<td>( RPI_{\text{min}} )</td>
<td>1.36 ± 0.68</td>
<td>1.37 ± 0.59</td>
<td>0.874</td>
</tr>
<tr>
<td>( ART_{\text{max}} )</td>
<td>180.28 ± 74.16</td>
<td>184.50 ± 78.99</td>
<td>0.606</td>
</tr>
<tr>
<td>Pachy\text{min}</td>
<td>469.04 ± 44.81</td>
<td>467.24 ± 43.84</td>
<td>0.695</td>
</tr>
<tr>
<td>D value</td>
<td>7.96 ± 4.20</td>
<td>7.89 ± 3.70</td>
<td>0.854</td>
</tr>
<tr>
<td>AC depth</td>
<td>3.20 ± 0.36</td>
<td>3.24 ± 0.36</td>
<td>0.232</td>
</tr>
<tr>
<td>AC volume</td>
<td>187.59 ± 40.42</td>
<td>189.85 ± 31.77</td>
<td>0.515</td>
</tr>
<tr>
<td>KI</td>
<td>1.22 ± 0.13</td>
<td>1.20 ± 0.12</td>
<td>0.163</td>
</tr>
<tr>
<td>( K_{\text{max}} )</td>
<td>54.59 ± 6.85</td>
<td>54.41 ± 6.05</td>
<td>0.791</td>
</tr>
</tbody>
</table>

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

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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 μm 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. Breaks in the Bowman layer and thickened subbasal nerve plexus have also been described. 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 other 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 μm. 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.

**ACKNOWLEDGMENTS**

We are very grateful to Mrs. Alison McEwan for her comments on an earlier version of the manuscript and for revision suggestions.

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

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

* Diameter from corneal center.

Some studies imply that mechanical trauma caused by eye rubbing may be one of the main reasons for keratoconus manifestation. Bawazeer et al 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, 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. 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. Interestingly, high densitometry levels can even be observed in clinically clear corneas.
REFERENCES