

Corneal tomography detection of elevated ectasia risk in atopic dermatitis patients with no prior ophthalmologic diagnosis

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Background. To investigate the association between atopic dermatitis (AD) and keratoconus (KC) in atopic dermatitis patients with no prior ophthalmologic diagnosis.

Methods. Thirty eyes of 30 patients with moderate to severe AD were included in this pilot study and compared to healthy controls (n=20) and patients with forme fruste KC (n=28). In the AD group, diagnosis of KC was based on clinical signs and corneal topography criteria such as inferior steepening (inferior-superior difference >1.45 D) and elevated maximum keratometry values (>47 D). Subclinical KC was defined by the presence of specific sensitive indices from corneal topography, tomography, or biomechanical assessments. Risk factors analyzed for ectasia development were the onset and severity of AD, sensitization to aeroallergens, systemic therapy, concomitant atopic diseases, eyelid eczema, and total IgE.

Results. We identified two manifest KC (6.7%), and six subclinical KC (20%) cases in patients with AD but with no previous diagnosis of KC. No overall differences were found in corneal tomography and biomechanics indices between control and AD patients. However, eye rubbing was not identified as a risk factor for developing ectasia in the AD group.

Conclusion. Dermatologists should be aware that patients with moderate or severe AD may have a higher risk for developing corneal ectasia, particularly when eyelid eczema is present. The estimated prevalence of KC in patients with AD appears to be higher than that in the general population but more studies are needed.

PATIENTS WITH ATOPIC DERMATITIS MAY HAVE A HIGHER RISK FOR DEVELOPPING CORNEAL ECTASIA

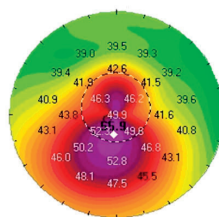
Background.

Keratoconus, an ectatic disorder of the cornea, has been described as a noninflammatory condition, but there is evidence that keratoconic eyes often experience some form of ocular inflammation.



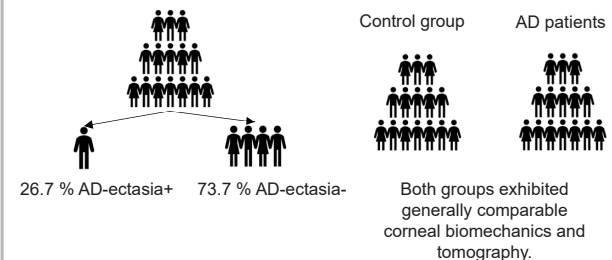
Aim.

To investigate the association between atopic dermatitis (AD) and keratoconus in atopic dermatitis patients without prior ophthalmologic diagnosis.



Main Outcomes.

Patients with Atopic Dermatitis (AD)



Presence of eyelid eczema seemed to be slightly associated with the development of ectasia.

Dermatologists should be aware that patients with moderate-to-severe AD may have a high prevalence of ectasia, considering the overall prevalence of KC in the Caucasian population.

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Graphical Abstract

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Key words: atopic dermatitis, keratoconus, early ectasia

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INTRODUCTION

Keratoconus (KC) is a corneal disease characterized by abnormal corneal protrusion, abnormal distribution of corneal thickness, and clinical progressive corneal thinning (shown in Fig. 1) (ref.¹).

These corneal changes result in irregular corneal astigmatism and myopia, leading to visual impairment¹. KC can begin to develop at puberty and progress until the 3rd or 4th decade of life. Early detection of the disease, which is referred to as early ectasia, is important to alter its progression and to temper its potential for associated morbidity and impairment of quality of life.

Until now, the etiology of KC has been poorly understood¹. There seems to be a complex interaction between genetic, biomechanical, biochemical, and environmental factors. There are well-known risk factors for developing KC, such as Down syndrome, a positive family history of KC, especially with early manifestation, ethnic factors (e.g., people of Asian and Arab descent), and eye rubbing¹. Furthermore, it is well known that atopic diseases (including atopic dermatitis (AD), allergic rhinitis, allergic asthma, and food allergy) may be a trigger for the early manifestation of KC (ref.²). These patients tend to have

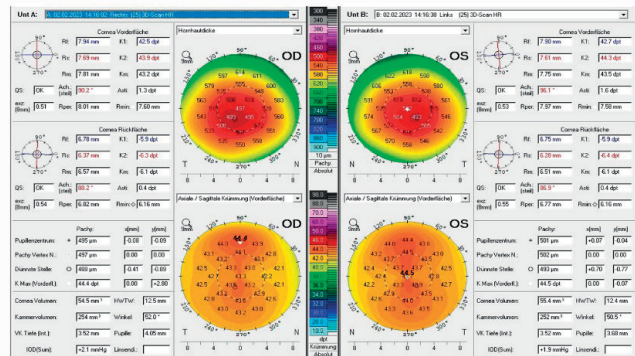
a higher risk of both developing and suffering worsening of a present KC; however, the incidence and risk factors are not yet more precise.

KC has been described as a noninflammatory condition¹, but there is evidence for an association with significant alterations in inflammatory mediators, indicating that keratoconic eyes often experience some form of ocular inflammation^{3,4}.

Atopic dermatitis (AD) is a heterogeneous chronic inflammatory systemic disease characterized by eczematous skin lesions. Eczema occurs in typical skin areas such as the flexures of the neck region but also on the face and eyelids and is accompanied by excruciating pruritus⁵. AD is a multi-faceted disease: the epidermal barrier is disturbed, there is immunological dysregulation as well as an alteration of the microbiome⁶. Cytokines of the type 2 immune response, including IL-4 and IL-13, play a central role in the inflammatory processes that are typical for the development of AD (ref.⁷). The prevalence of AD, especially in adults, ranges from 4.9% to 7.3% in the United States⁸.

Due to pruritus and the resulting scratching, the disease process is maintained⁹. Since it is suspected that keratoconus is triggered by intensive rubbing, the connection with AD would be conceivable.

A



B

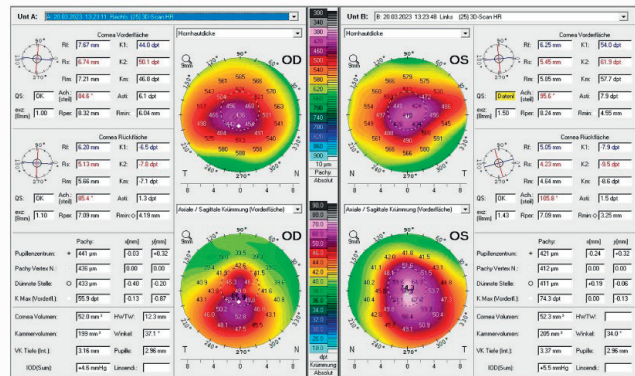


Fig. 1. Slit lamp photography and tomographic records (Pentacam, Oculus®, Wetzlar, Germany) of a normal eye and a KC eye. Notice the significant protrusion in KC in slit lamp photography. Corresponding Pentacam records for a normal eye with regular astigmatism (A) and for KC with typical bow tie shape of the irregular astigmatism (B).

In addition to cyclosporine, biologics such as dupilumab (monoclonal antibody blocking interleukin 4 and interleukin 13) and oral Janus kinase (JAK) inhibitors are now available for systemic therapy of moderate to severe AD (ref.¹⁰). Eyelid eczema and conjunctivitis are described as frequent side effects during therapy with dupilumab in AD (ref.¹¹). Many studies address that AD could contribute to the risk of KC, but just a few address the causality of AD and KC. A recent study showed, that regular ophthalmic examinations are recommended for patients with AD in order to detect KC at an early stage¹², but because of its meta-analysis character it does not focus on an accurate detection of an early ectasia. So, in our pilot study, we aimed to evaluate the prevalence of both KC and early ectasia, using multimodal screening parameters from corneal tomography and biomechanics. We further aimed to investigate associated dermatological risk factors, such as severity of eczema, time of initial manifestation, any systemic therapies, level of total IgE, sensitization to aeroallergens (e.g., house dust mites, pollen, or animal hair), and presence of asthma, for developing corneal ectasia among patients with moderate to severe AD. Since intense eye rubbing is suspected to promote keratoconus, the history of eye rubbing as well as the presence of eczema in the eyelid area at the current time point or in the past was investigated.

PATIENTS AND METHODS

Patients

This cross-sectional pilot study included patients with moderate to severe AD ("objective Scoring for Atopic Dermatitis" (oSCORAD) > 20 and/or currently anti-inflammatory systemic treatment for AD or previous anti-inflammatory systemic treatment for AD within the past 24 months before inclusion, who underwent screening for the presence of both KC and early ectasia at the Department of Ophthalmology at the University Hospital Carl Gustav Carus, TU Dresden, between April 2021 and February 2022. The study participants were recruited from the Department of Dermatology at the University Hospital Carl Gustav Carus, TU Dresden. The diagnosis of AD was determined according to the UK Working Party diagnostic criteria¹³. None of the patients had any known ocular disease.

The study protocol was approved by the Ethics Committee of the University Hospital Carl Gustav Carus, Dresden, TU Dresden, Germany, following the tenets of the Declaration of Helsinki (*EK60022014*).

Before enrolment, all participants were informed about the study purposes, methods, and data analysis, and informed consent was signed.

Our study included 30 eyes of 30 patients with AD. The age-matched control (normal, n=20) group consisted of patients from our clinic for refractive surgery with no abnormalities in corneal tomography, topography, or biomechanics (see criteria for KC and early ectasia below). The age-matched early ectasia group (n=28) included patients from our clinic for ectatic disease, who have very

asymmetric ectasia, with one eye of the patients having normal topography (VAE-NT) and the fellow eye having clinical keratoconus, whereby we focused on the VAE-NT eye. These eyes are considered to represent the early stages of KC, because KC is defined as a bilateral disease¹.

The inclusion criteria were a minimum age of six years, a diagnosis of moderate to severe atopic dermatitis confirmed by a dermatologist with an oSCORAD (objective Scoring Atopic Dermatitis) of at least 20, and/or a recent or former systemic therapy for AD in the last 24 months before inclusion. The inclusion criteria were chosen analogously to those of the TREATGermany registry¹⁴.

Wearing of contact lenses had to be discontinued three days (for soft contact lenses) or two weeks (for rigid gas-permeable lenses) before the examination, and the intraocular pressure (IOP) had to be within the range of 8–21 mmHg.

The exclusion criteria were the presence of corneal or ocular pathology except keratoconus, corneal or ocular surgeries, pregnancy, and diabetes.

Examination methods

To determine the condition of ectasia, corneal tomography was performed using a Scheimpflug tomograph (Pentacam, Oculus®, Wetzlar, Germany). The following parameters were used: maximal keratometry value (Kmax), mean keratometry value (Km), keratoconus probability index (KISA% index), the inferior-superior keratometry value (I-S value), central corneal thickness (CCT), and minimal corneal thickness (MCT). The Belin/Ambrósio total deviation value (BAD-D) was used to describe abnormalities in elevation maps of the anterior and posterior surfaces, as well as corneal thickness distribution, and to predict the presence of ectasia.

The Corvis ST (CVS, software version 1.5r1902, Oculus®, Wetzlar, Germany) records the deformation of the cornea caused by an air pulse with a high-speed Scheimpflug camera to measure corneal biomechanical behavior. In the present study, the following biomechanically related dynamic corneal response (DCR) parameters were analyzed: biomechanically corrected IOP value (bIOP), stiffness parameter at first applanation (SPA1), Corvis Biomechanical Index (CBI), a screening parameter for keratoconus detection, and the Tomographic and Biomechanical Index (TBI), which was obtained with the combined use of Pentacam and Corvis ST.

A clinical KC diagnosis was made based on presence of typical findings in corneal tomography of both eyes. These findings included inferior curvature steepening (Kmax >47 D), skewed asymmetric bowtie, I-S value >1.45, abnormal corneal thickness distribution, abnormal posterior elevation and/or possible secondary manifestations. The VAE-NT group was determined based on normal topography with KISA index <60, I-S value <1.45 D, Kmax <47 D if the fellow eye had clinical KC. For the AD group, clinical KC was diagnosed as described above. Subclinical KC was defined as both eyes showing abnormal topography, tomography, or biomechanics that did not meet the classic KC criteria. Specifically, the evalua-

tion included an assessment of topography pattern, corneal thickness distribution, abnormal anterior and posterior elevation, and/or changes in dynamic corneal response parameters. Except for the VAE-NT group, one eye per patient was randomly selected.

The presence of eye rubbing was determined using a standardized questionnaire for all participants.

Statistical analysis

The primary outcome was the prevalence of clinical KC or early ectasia in atopic dermatitis patients. For secondary outcome we analyzed the differences between control, VAE-NT and study group with abnormal topography. Additionally, we investigated the following dermatologic risk factors for developing ectasia: current quality of life and severity of AD (DLQL index, SCORAD, oSCORAD, EASI score), total IgE level, presence of eyelid eczema, current or former systemic AD therapy, sensitization to aeroallergens (cat, house dust mites, pollen), and presence of allergic asthma.

Statistical analyses were performed using SPSS software (SPSS®, IBM®, Armark, New York, USA; version 27). To compare continuous variables between the

groups, the Kruskal-Wallis test was used with multiple group comparisons and Bonferroni correction as post-hoc analysis because the data were non-normally distributed, as determined by Q-Q plot analysis. We used the Mann-Whitney-U-Test for continuous factors and chi-square test for dichotomous factors.

The sample size for this pilot study was estimated with at least 20 eyes per group providing a power of 80% (ref.¹⁵).

A *P*-value of 0.05 was regarded as the threshold for statistical significance.

RESULTS

Demographics

Thirty eyes of patients with AD (*n*=30), twenty healthy controls (*n*=20) and twenty-eight eyes with VAE-NT (*n*=28) were analyzed in this study. Patient demographics are shown in Table 1.

The tomographic and biomechanical parameters of the groups are presented in Table 2. There was no statistically significant difference in the tomographic and bio-

Table 1. Patients demographics.

Parameter	Normal (<i>n</i> =20) Mean ± SD	VAE-NT (<i>n</i> =28) Mean ± SD	AD (<i>n</i> =30) Mean ± SD	<i>P</i> ¹	<i>P</i> ²	<i>P</i> ³
Age (years)	33.6 ± 11.3	32.9 ± 8.8	40.3 ± 18.8	1.0	0.302	0.145
Sex (m/w)	6/14	21/7	15/15	0.007		
biOP (mmHg)	15.23 ± 1.85	14.87 ± 2.23	15.70 ± 3.09	1.0	1.0	0.639
laterality (R/L)	9/11	17/11	14/16	0.45		

*P*¹, *P* value for comparison between normal vs. VAE-NT; *P*², *P* value for comparison between normal vs. AD; *P*³, *P* value for comparison between VAE-NT vs. AD; *P*<0.05 = statistically significant. Significance is marked in bold.

biOP = biomechanical-corrected intraocular pressure.

Table 2. Corneal tomography and biomechanics.

	Normal (<i>n</i> =20) Mean ± SD	VAE-NT (<i>n</i> =28) Mean ± SD	AD (<i>n</i> =30) Mean ± SD	<i>P</i> ¹	<i>P</i> ²	<i>P</i> ³
Tomography						
Kmax (D)	44.17 ± 1.55	44.55 ± 1.17	45.12 ± 2.56	1.0	0.26	0.79
Km (D)	42.79 ± 1.23	43.30 ± 1.08	43.42 ± 1.58	0.57	0.30	1.0
I-S value	0.02 ± 0.64	0.52 ± 0.51	0.45 ± 1.77	0.45	0.64	1.0
KISA	6.1 ± 7.40	11.6 ± 13.43	83.8 ± 409.01	1.0	0.88	0.85
CCT (μm)	539.55 ± 24.83	527.57 ± 32.40	534.63 ± 38.43	0.67	1.0	1.0
MCT (μm)	536.00 ± 25.13	523.36 ± 32.15	530.97 ± 39.16	0.61	1.0	1.0
BAD-D	1.0 ± 0.57	1.53 ± 0.67	1.25 ± 0.95	0.06	0.80	0.50
Biomechanics						
SPA1	109.71 ± 16.79	100.19 ± 18.61	108.83 ± 21.63	0.30	1.0	0.284
CBI	0.29 ± 0.19	0.53 ± 0.26	0.35 ± 0.31	0.007	1.0	0.03
TBI	0.15 ± 0.17	0.39 ± 0.31	0.25 ± 0.30	0.01	0.67	0.16

*P*¹, *P* value for comparison between normal vs. VAE-NT; *P*², *P* value for comparison between normal vs. AD; *P*³, *P* value for comparison between VAE-NT vs. AD; *P*<0.05 = statistically significant. Significance is marked in bold.

maximal keratometry value (Kmax), mean keratometry value (Kmean), the keratoconus probability index (KISA% index), inferior-superior value (I-S value). Central and minimal corneal thickness (CCT and MCT), Belin/Ambrósio total deviation value (BAD-D), stiffness parameter at first applanation (SPA1), Corvis Biomechanical Index (CBI), Tomographic and Biomechanical Index (TBI).

mechanical parameters among the three groups ($P>0.05$), except for CBI, which was highest in VAE-NT cases compared to normal and AD groups ($P<0.05$). Furthermore, the TBI showed statistically significantly higher values in the VAE-NT group in comparison to the normal group ($P=0.01$). These results suggest that the AD group does not exhibit any general changes in tomography and biomechanics.

Prevalence of early and clinical ectasia in atopic dermatitis patients

According to the above-mentioned diagnostic criteria, we found two patients with clinical KC (6.7%) and six patients (20%) with early ectasia in the sample of atopic dermatitis patients with no prior diagnosis of KC. Two of the eight patients showed progression immediately after the diagnosis of KC and required therapeutic intervention.

Table 3 shows the tomographic and biomechanical parameters of each AD-Patient with early or clinical ectasia (AD+). The table shows the characteristic parameters via which ectatic corneas could be detected in each AD+ patient.

Differences between control, VAE-NT and study group with abnormal topography

We then compared the control group with the VAE-NT group and the AD subgroup, which revealed subclinical or manifest ectasia (AD+; $n=8$). This group had significantly lower SPA1, CCT, and MCT as well as higher CBI, TBI, and I-S values compared to normal eyes (all $P<0.05$, shown in Fig. 2). Similarly, the VAE-NT group had significantly higher I-S, CBI, and TBI values (all $P<0.05$, Fig. 2).

Dermatologic risk factors for development of corneal ectasia

In this study, we further analyzed whether dermatological risk factors predispose patients with AD to the development of corneal ectasia (Table 4). The current severity of eczema, onset and previous course of the disease, and administration of systemic therapy showed no significant correlation. All patients had elevated total IgE, and the median did not differ significantly (no ectasia

2343.0 kU/L (536.00–12697.50) and ectasia 1741.00 kU/L (179.5–9021.5)). The sensitization rates to house dust mites were not different between the two groups (no ectasia sensitization in 72%, patients with ectasia sensitization 50%). The occurrence of eyelid eczema (6/8) was reported in 75% of patients with ectasia compared to 45% of unaffected patients. When inquiries were made concerning eczema of the eyelids during childhood, the distinction was even more apparent; 28% of patients without ectasia reported no eczema of the eyelids, whereas 63% with ectasia could recall eczema of the eyelids during childhood. Both patients with KC reported eyelid eczema during childhood. However, the difference was not statistically significant ($P=0.09$). None of the further investigated risk factors were associated with ectasia development (Table 4). In this small cohort, no association was found for eye rubbing as a risk factor for developing ectasia in the AD group ($P>0.05$).

DISCUSSION

Keratoconus is one of the most common causes of corneal transplant in developing countries¹⁶. Therefore, early detection is important in order to prevent KC progression and, if necessary, to perform less invasive and inexpensive therapies such as corneal crosslinking (CXL) (ref.¹⁷). The prevalence of keratoconus varies according to ethnic and regional factors, ranging from 50 to 600 in 100 000 individuals in the general population. A recent systematic review of over 7 million participants found that KC incidence was 1.38 per 1000 population¹⁶. Ahmed et al. found the overall prevalence of KC was 34% in children with allergic eye disease¹⁸. Risk factors for the development of KC in patients with ocular allergy were age, duration of symptoms -especially eye rubbing-, systemic atopy, and vernal conjunctivitis (VKC). In the present study, we found a very high prevalence of 2 KC in 30 patients. Assuming that this prevalence would persist in a larger population as well, it would result in an extrapolated prevalence of 6700 KC in 100 000 in a group of patients with AD. In addition, six cases of subclinical

Table 3. Ophthalmic characteristics of AD-Patients with Ectasia (AD+).

ID	Gender	Age	Tomographical parameters			Biomechanical parameters			Classification
			Kmax (D)	Pachy min (μm)	BAD D	SPA1 (mmHg/mm)	CBI	TBI	
1	Female	38	<i>47.8</i>	502	<i>1.69</i>	98.4	<i>0.495</i>	0.007	sKK
2	Female	18	<i>47.9</i>	<i>471</i>	<i>2.78</i>	65.6	0.952	1	sKK
3	Female	51	43.1	517	0.97	106.5	0.583	<i>0.297</i>	sKK
4	Female	13	45.8	<i>483</i>	<i>1.73</i>	<i>89.1</i>	0.693	0.163	sKK
5	Female	18	48.4	514	1.51	70.1	0.931	1	KK
6	Male	33	44.7	<i>467</i>	<i>2.12</i>	<i>89.6</i>	0.678	<i>0.379</i>	sKK
7	Male	52	55.2	516	4.83	75.6	0.878	1	KK
8	Male	68	43.5	<i>485</i>	<i>2.2</i>	101.0	0.782	0.503	sKK

Italic, ectasia suspect; **bold**, manifest ectasia; **KK**, manifest Keratoconus; **sKK**, subclinical Ectasia/KK.

Kmax, maximal keratometry value; Pachy, minimal corneal thickness, BAD-D, Belin/Ambrósio total deviation value; SPA1, stiffness parameter at first applanation; CBI, Corvis Biomechanical Index; TBI, Tomographic and Biomechanical Index.

The classification of either early or clinical ectasia was made according to the results of Doctor et al.⁵¹

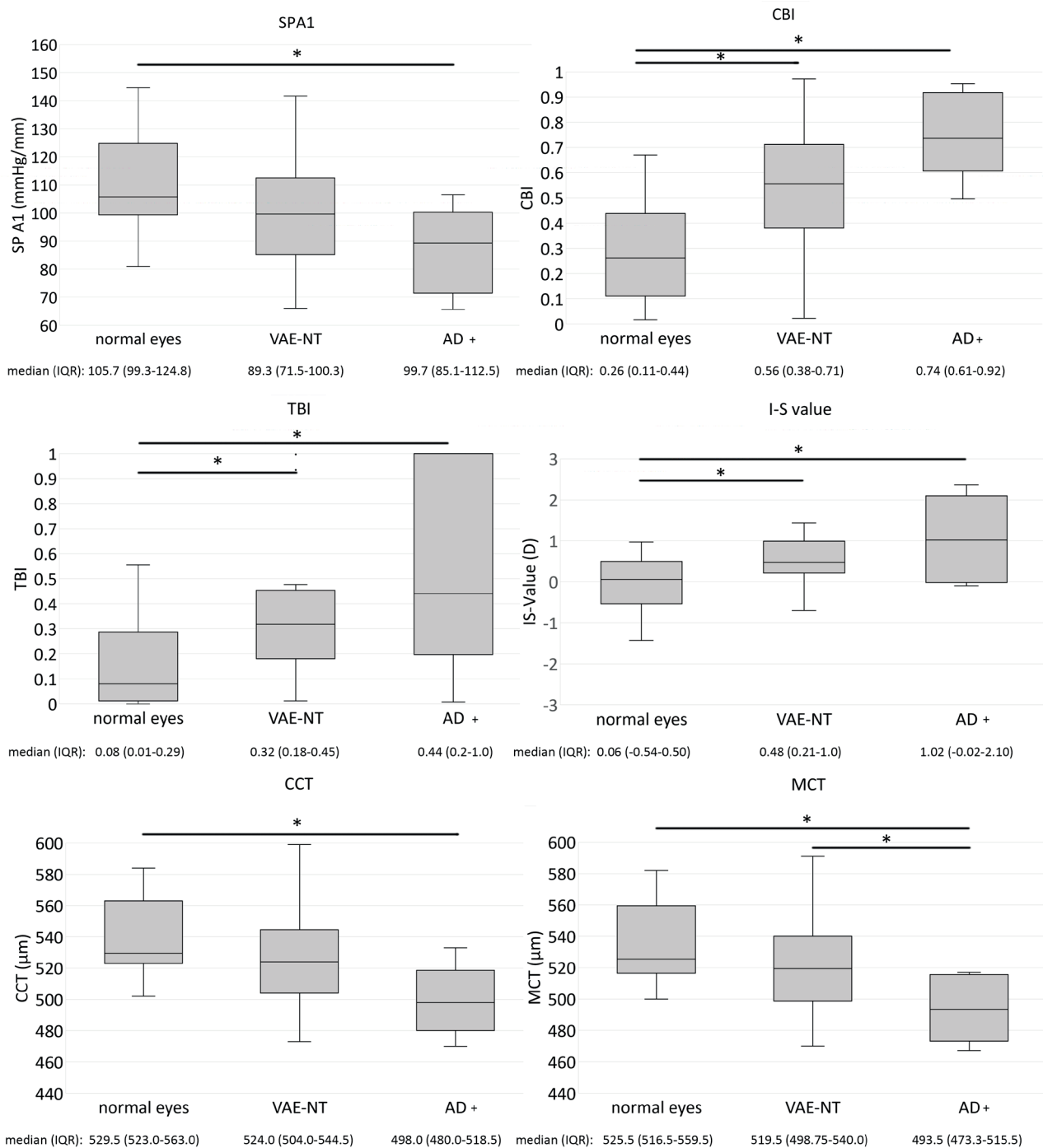


Fig. 2. Box -Plots of relevant tomographic and biomechanical parameters.

SPA1, Corvis stiffness parameter; CBI, Corvis biomechanical index; TBI, tomographic biomechanical index; IS-value, inferior - superior value; CCT, central corneal thickness; MCT, minimum corneal thickness; significance is marked by * = $P < 0.05$.

keratoconus (KC) were identified, which would not have been possible without recent advances in corneal imaging. These advances include corneal tomography, which assesses anterior and posterior surface irregularities and thickness distribution, and corneal biomechanics, which can detect potential cases before they develop into clinical KC (ref.¹⁹).

To date, it is unclear which multifactorial comorbidities predispose to KC, whereas it is known that atopic disorders (including atopic dermatitis, allergic rhinocon-

junctivitis, allergic asthma, and food allergy) are a trigger for an early manifestation of KC (ref.²). Throughout this study, we screened a population of patients with atopic dermatitis for the prevalence of ectasia. Only a few studies have investigated atopy in patients with KC, and most of them only address atopic comorbidities in general, thereby not differentiating between various traits such as AD.

Nevertheless, there is a well-studied association between KC and allergic diseases in the literature²⁰. Antoun et al. found that the presence of allergic conjunctivitis

Table 4. Evaluation of dermatological risk factors in the AD group.

Parameter	Ectasia	Birth/Baby/Childhood/Adolescence/Adulthood	<i>P</i>
Onset of AD	No (n=22)	1 (4) / 7 (32) / 13 (60) / 0 (0) / 1 (4)	0.346
	Yes (n=8)	1 (12) / 2 (25) / 3 (39) / 1 (12) / 1 (12)	
AD severity in the last years	No (n=22)	Mild / moderate / severe 1 (5) / 2 (9) / 19 (86)	0.163
	Yes (n=8)	0 (0) / 3 (37) / 5 (63)	
Current (c)DLQI	Ectasia	Median (IQR)	0.39
	No (n=22)	13.0 (4.0–23.5)	
Current EASI score	Yes (n=8)	5.0 (3.0–21.0)	0.94
	No (n=22)	11.3 (6.8–22.6)	
Current SCORAD	Yes (n=8)	13.7 (7.8–19.2)	0.24
	No (n=22)	50.0 (31.8–65.5)	
oSCORAD	Yes (n=8)	39.0 (30.3–50.6)	0.22
	No (n=22)	41.0 (26.2–51.3)	
Total IgE kU/L	Yes (n=8)	32.4 (25.4–29.9)	0.41
	No (n=22)	2343.0 (536.00–12697.50)	
Eyelid eczema ever	Ectasia	Yes (%) / No (%)	0.15
	No (n=20)	9 (45) / 11 (55)	
	Yes (n=8)	6 (75) / 2 (25)	
	Unknown (n=2)		
Eyelid eczema in childhood	No (n=18)	5 (28) / 13 (72)	0.09
	Yes (n=8)	5 (63) / 3 (37)	
	Unknown (n=4)		
Sens. to house dust mites	No (n=18)	13 (72) / 5 (28)	0.88
	Yes (n=8)	6 (50) / 2 (50)	
	Unknown (n=4)		
Sens. to cat	No (n=17)	13 (76) / 4 (24)	0.93
	Yes (n=8)	6 (75) / 2 (25)	
	Unknown (n=5)		
Allergic Asthma	No (n=22)	10 (45) / 12 (55)	0.41
	Yes (n=8)	5 (63) / 3 (37)	
ARC Pollen	No (n=20)	18 (90) / 2 (10)	0.84
	Yes (n=8)	7 (88) / 1 (12)	
	Unknown (n=2)		
Current syst. therapy	No (n=22)	6 (27) / 16 (73)	0.59
	Yes (n=8)	3 (38) / 5 (62)	
Recent syst. therapy	No (n=22)	7 (47) / 15 (53)	0.129
	Yes (n=8)	5 (63) / 3 (37)	
Eye rubbing	No	9 (41) / 13 (59)	0.657
	Yes	4 (50) / 4 (50)	

DLQI, Daily Quality of life index; EASI, Eczema Area and Severity Index; SCORAD, Scoring Atopic Dermatitis Index; oSCORAD, objective Scoring Atopic Dermatitis Index; ARC, allergic rhinoconjunctivitis.

P<0.05 = statistically significant. Significance is marked in bold.

associated with eye rubbing is a common risk factor for KC progression²¹. Eye rubbing leads to biochemical and biomechanical alterations of the cornea via the release of matrix metalloproteinases and cytokines. Furthermore, it increases hydrostatic intraocular pressure, resulting in the loss of keratocytes, thereby causing a decrease in the collagen matrix that promotes stromal thinning and disease progression²². Wang et al. demonstrated that patients suffering from allergic conjunctivitis are at higher risk of developing KC, which was further correlated with the eye rubbing frequency²³ and seems to be a result of itchy eyes

and allergic reactions. This in turn has been proposed to be a risk factor for developing KC (ref.²⁴). However, previous studies have found that eye rubbing and itchy eyes are independent risk factors and that eye rubbing alone is apparently not sufficient to develop KC (ref.²⁵).

In the current study, eye rubbing could not be identified as a risk factor for the development of manifest KC or early ectasia. It is known, however, that eyelid eczema often causes pruritus, leading to mechanical manipulation of the ocular surface, which in turn is supposed to induce KC (ref.²⁶). In our study, there was a tendency for preex-

isting eyelid eczema as a potential risk factor for ectasia development. This was most evident in a history of eyelid eczema during childhood. However, these results were not statistically significant.

Shajari et al.² also reported that KC is not caused by mechanical forces alone, as recent studies found that low-level inflammatory components may be present in KC development as well^{27,28}. Interestingly, KC was supposed to be a noninflammatory disease since there was no evidence of inflammatory cell infiltration or neovascularization in the cornea^{27,29}. However, there is recent evidence suggesting that proinflammatory factors are involved in its pathogenesis, including an imbalance between inflammatory cytokines, proteases and protease inhibitors, as well as free radicals and oxidants with a pivotal role in KC development³⁰⁻³². The relation of inflammation and KC is reinforced since atopy and ocular surface inflammation have been associated with a higher prevalence of KC (ref.³³). The pathogenesis of AD is complex and seems to result from a combination of genetic and environmental factors inducing dysfunction of the skin barrier and cutaneous and systemic immune dysregulation^{34,35}. The skin barrier abnormalities are supposed to be associated with mutations or impaired expression of the filaggrin, which is also expressed in the cornea epithelium and playing a major role in the corneal epithelial barrier³⁶. It was shown that there was an altered filaggrin pattern in KC, revealing associations of some mutations in the filaggrin gene with KC (ref.³⁷). As AD is a chronic inflammatory skin disease, this inflammation may also affect the eye⁵. KC is more common in men¹⁶ but according to several surveys, AD is more common in women³⁸. Consequently, we found more ectasias in the female sex in our study. An explanation for this finding could be the well-known influence of hormones, such as estrogen, on the development and progression of ectasia. KC has been shown to progress during pregnancy^{39,40}. Similarly, hormonal changes during puberty and pregnancy can lead to flares of AD (ref.⁴¹).

In a study of patients with keratoconus, increased inflammatory mediators were found in tear fluid. Although inflammatory activity appears to be involved in the pathogenesis of KC, disease progression did not correlate with cytokine levels in the longitudinal analysis. In this study, patients with KC, both with and without progression, had more cases of ocular allergy than control subjects⁴².

In addition to the risk of developing KC, patients with AD have been found to have a significantly higher prevalence of ocular complications in large epidemiological studies (blepharitis, keratoconjunctivitis, glaucoma, cataracts, retinal detachment, and ophthalmic herpes simplex virus infections) than the general population. The prevalence of ocular complications is related to AD severity of AD (ref.^{43,44}).

Interestingly, treatment of AD with IL-4 and IL-13 antibodies (dupilumab) can cause ocular side effects, sometimes with severe pruritus⁴⁵. A personal history of asthma and a family history of atopic dermatitis may be associated with a higher risk of developing dupilumab-induced ocular surface disease (DIOSD). The frequency

of occurrence is up to 37%, while dupilumab is discontinued in only 4% of patients because of DIOSD (ref.⁴⁶).

Although dupilumab is approved for the treatment of severe asthma and nasal polyps, the occurrence of DIOSD is observed much less frequently in this setting. This could also indicate that, as in the development of KC, a corresponding predisposition must be present in the eye area.

These findings may suggest that KC and AD have some common pathogenic pathways, explaining the link found between these two entities⁴⁷. This finding is supported by one of our recent studies, which showed that the presence of AD combined with another atopic disease is a risk factor for keratoconus progression and failure of corneal crosslinking⁴⁸.

In addition to 6.7% of AD patients with clinical KC, we also identified six patients (20%) who had suspicious biomechanical parameters and tomography, representing an early form of ectasia. In a recent study⁴⁹, we described very asymmetric eyes that had clinical KC in one eye and an early form of ectasia in the other eye but had normal topography. These eyes (VAE-NT) differed from healthy eyes in terms of corneal biomechanics; more specifically, CBI was significantly higher and SPA1 was significantly lower. Moreover, VAE-NT eyes have a potential risk (14.7% to 35.3% of cases within approximately six years) for the development of clinical keratoconus⁵⁰. Our study demonstrated very similar biomechanical, topographic, and tomographic parameters between the VAE-NT group and the AD-subgroup (AD+), so we hypothesize that the latter also have a higher risk of developing clinical ectasia in the near future. One of our AD patients diagnosed with early ectasia developed manifest KC within a few months after enrolment in our study and even had to be treated with CXL. Furthermore, one patient with AD diagnosed with KC showed immediate progression, requiring CXL. This case also demonstrates the rapid progression of KC in patients with AD, warranting more frequent monitoring and earlier intervention².

Interestingly, sensitization to aeroallergens was not a risk factor for ectasia. Since we only had eight patients with a manifest KC or early ectasia, the sample size may have been too small to obtain significant results. In a follow-up study, we will include a larger sample size in order to be able to better evaluate correlations with influencing factors.

Our preliminary results show that the presence, severity and systemic therapy of AD are not risk factors for the development of ectasia, implying that all patients with moderate to severe AD should be screened for ectasia. In particular, our work provides evidence that patients with eyelid eczema since childhood need rough topical therapy, and that ophthalmologic surveillance should be performed to rule out ectasia, especially in these patients.

Limitations

The limitation of our study is the small sample size, which only allows a cautious statement on the actual prevalence of KC in this population. Nonetheless, when extrapolating our data, a very high prevalence of KC

and ectasia is suggested; especially, we found relatively many patients with early ectasia due to our accurate ectasia screening procedure. However, to detect risk factors for KC and early ectasia development, larger sample sizes are needed and will be investigated in the future. Furthermore, we did not quantify the frequency of eye rubbing. Additionally, since we used a questionnaire with “yes” and “no” responses, there might be a significant response bias.

Further, information on eczema in the eyelid region, onset of AD, or symptoms of allergic rhinoconjunctivitis was also obtained from the patient's medical history, which may be incorrect as some of this dates back a long time in the past.

CONCLUSION

Patients with moderate-to-severe AD appear to have a high prevalence of ectasia, considering the overall prevalence of KC in the Caucasian population. Larger studies are needed to prove these findings of this pilot study and to state screening recommendations in this special population for both dermatologists and ophthalmologists.

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RK is or recently was a speaker and/or advisor for Ocucus and Heidelberg Engineering.

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