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ORIGINAL PAPER

Mapping the Future: Anterior Segment OCT for Corneal Epithelial Thickness in Vernal Keratoconjunctivitis

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ABSTRACT

Objective: *To compare corneal epithelium parameters in between children with vernal keratoconjunctivitis (VKC) and healthy controls with the help of anterior segment optical coherence tomography (OCT).*

Materials and methods: *Children aged 5 to 18 years with a diagnosis of VKC were included in this study. A total of 216 eyes were included in the study, which were divided into two groups: the case group comprising 108 eyes of VKC patients and the control one comprising 108 eyes of healthy subjects. Central 5 mm cornea was taken into consideration for evaluation of different epithelial thickness parameters using anterior segment OCT.*

Results: *On analysis of the corneal epithelium parameters, the superior quadrant in VKC patients as compared to controls was found to be significantly thinner (38.69 ± 5.91 μm vs 40.98 ± 3.86 μm). Other noteworthy findings were a reduced minimum (MIN) epithelial thickness and a greater negative (MIN–MAX) value in VKC patients as compared to controls. In a detailed study specifically in patients*

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with mixed VKC, they had epithelial thinning in the superior quadrant and markedly reduced MIN epithelial thickness than the controls.

Conclusions: *This study demonstrates that children with VKC exhibit notable changes in corneal epithelial thickness parameters, particularly a significant reduction in superior and minimum epithelial thickness compared to healthy controls. Additionally, the significant correlation between epithelial thickness and disease duration suggests that prolonged duration of VKC may exacerbate epithelial thinning. The results underscore the significance of using anterior segment optical coherence tomography as a useful technique for tracking corneal alterations in children with VKC.*

Keywords: corneal epithelial thickness, anterior segment OCT, vernal keratoconjunctivitis, keratoconus.

INTRODUCTION

Allergic conjunctivitis is classified into many varieties, with vernal keratoconjunctivitis (VKC) being one of them. It is a chronic allergic disorder causing type I and type IV hypersensitivity reactions in the conjunctiva and cornea. Vernal keratoconjunctivitis typically affects children and younger ages. It manifests clinically as visual disturbances, persistent discomfort in the eyes, and, if not treated promptly, it can lead to serious complications such as gradual loss of vision, shield ulcer, glaucoma and cataract (1, 2).

Vernal keratoconjunctivitis is divided into palpebral, limbal and mixed forms, according to the location of ocular involvement (3). In palpebral VKC, early indicators include conjunctival redness and a velvety papillary swelling of the upper tarsal plate. As it advances, small flat macro papillae may enlarge into giant papillae over 1 mm in size, often with mucoid deposits. By contrast, bulbar VKC, which is more common in tropical areas, manifests as congestion in the bulbar conjunctiva, with gelatinous papillae and the presence of Horner-Tranta spots around the limbus.

Corneal involvement is frequently seen in palpebral VKC, leading to superficial punctate erosions and potentially serious shield ulcers that hinder vision and are challenging to heal. Complications may include pseudogerontoxon, marked by superficial scarring near the limbus, and associations with corneal ectasias like keratoconus, often linked to repeated eye rubbing. Additionally, lid involvement, such as blepharitis and scarring, can be observed in VKC patients.

Vernal keratoconjunctivitis was initially believed to result solely from an IgE-mediated response involving the release of mast cells (4). Now we are aware that the complicated inflammatory response seen in VKC cannot be explained by IgE alone. Conjunctival scrapings in VKC consist mainly of active eosinophils, although mononuclear cells and neutrophils are present in a lower quantity.

The CD4 T-helper-2-driven type IV hypersensitivity, which involves immunomodulators like IL-4, IL-5, and bFGF, has received more attention (5). Consideration has also been given to a potential hormone influenced mechanism, as symptoms and prevalence of VKC tend to decrease after puberty (4).

The corneal epithelium in a healthy person has relatively constant thickness and a fixed rate of turnover. In order to maintain a healthy ocular surface, this layer, which is in continuous touch with the precorneal tear film, provides vital protective and optical qualities (6). Unlike the relative stability seen in healthy eyes, the corneal epithelium exhibits significant plasticity, allowing it to adapt and mask changes in the underlying stroma (7).

Variable rates of correlation between the onset of keratoconus (KC) and VKC have been documented in published research. Incidences of KC in patients with VKC have been observed at 26.8%, 8.5% and 18.3% as evaluated by keratometry, slit lamp biomicroscopy and quantitative video keratography maps, respectively. Male gender, chronic illness, types of VKC and lesions in cornea have all been associated with an increased prevalence of keratoconus. Conversely, other studies have reported much lower incidences, ranging from 0.77% to 1.33% (8, 9).

As a useful non-invasive imaging method, anterior segment OCT produces high-resolution cross-sectional images of the anterior segment, facilitating precise measurement of corneal epithelial thickness. This method presents signifi-

cant advantages for monitoring VKC, as it allows clinicians to identify subtle changes in corneal architecture that may be undetectable through traditional examination methods.

Keratoconus screening can be improved by the use of corneal epithelium thickness mapping, which has been documented in previous studies. Keratoconus is diagnosed in early stages by the presence of cone on corneal topography, which can be masked by the alterations in the corneal epithelium occurring physiologically. This can lead to further delay in diagnosis, thereby delaying treatment (10).

In a study by Albadawi MA *et al*, corneal epithelial thickness mapping in children with VKC was assessed using anterior segment OCT. In this research, significant epithelium changes were found, which varied with disease phenotype and duration. This was the only study that was carried out and opened the path for the use of anterior segment OCT in VKC patients (11).

The present study is aimed at finding the importance of epithelial thickness parameters in VKC patients with the help of anterior segment OCT.

By correlating epithelial thickness with disease severity, we hope to enhance our understanding of VKC's impact on corneal integrity and provide insights that could inform more effective management strategies. Ultimately, this research seeks to improve the care provided to paediatric patients affected by this debilitating condition, leading the way in paediatric ophthalmology toward improved diagnostic and treatment methods.

In our study we are analysing the corneal epithelial thickness parameters to look for early changes in the cornea in children with VKC. ❑

MATERIALS AND METHODS

We carried out a case-control study on a total of 216 eyes (108 VKC eyes and 108 controls) in patients aged 5-18 years with a confirmed diagnosis of VKC attending OPD of the Department of Ophthalmology, AIIMS Raebareli, India, from July 2023 to July 2024. The 108 VKC eyes were further classified into having mixed VKC (46 eyes: 42.59%), palpebral type VKC (38 eyes; 35.18%) and those with limbal type (24 eyes; 22.22%).

Data from VKC patients were compared to those from an age-matched normal control group of 108 eyes. Participants had to be aged between 5–18 years and VKC was diagnosed clinically on the basis of symptoms and signs. Patients with any other corneal pathology, limbal stem cell deficiency, or dry eye were excluded from the study. Other notable exclusions in this study were patients using long term topical corticosteroids, as this could have a confounding effect on the corneal epithelium. These patients were included in the study after weaning of corticosteroids for a minimum duration of four weeks.

Although there were no problematic cases during the research, a multidisciplinary team of paediatricians and ophthalmologists was prepared to handle any potential consequences.

A complete history, including each patient's allergy and previous treatment, was taken.

A Snellen chart was used to test best corrected visual acuity (BCVA) and the results were converted to the logarithm of the minimum angle of resolution. Each patient underwent a slit lamp examination and VKC was further divided into mixed, palpebral and limbal varieties according to clinical signs. Intraocular pressure (IOP) measurement was done by the Goldmann applanation tonometer.

For all patients meeting the inclusion criteria, they underwent anterior segment OCT scans with the Cirrus HD OCT (5000-24512) version 11.5.2.54532 (CARL ZEISS MEDITEC, Inc). A single scan was acquired for every patient's eye and every examination was thoroughly examined for alignment, measurement coverage and picture quality. Lack of cooperation, resulting in poor-quality imaging, led to patient's exclusion.

A central 5 mm-diameter map is utilised to compute variables based on pachymetry; thickness profiles from each meridian are interpolated to create a 9 mm-diameter epithelial thickness map. On the basis of diameter, the epithelium map was divided into four zones: 2–5 mm, 5-7 mm, 7-9 mm and centre 2 mm. The mean epithelium thickness was evaluated in three zones (superior, inferior and central). The epithelial focal thinning was calculated by finding the difference between the minimum and maximum thickness (MIN-MAX). The mean epithelial thickness in superior and inferior zones

was also evaluated and their difference was used to calculate (S-I) asymmetry.

Analytical statistics

Epi InfoTM for Windows was used to code and enter the data (Version 7.2). The mean, standard deviation, frequencies (number of cases) and relative frequencies (percentages) for categorical variables were calculated and tabulated. Data normality was assessed using the Kolmogorov-Smirnov test.

Unpaired t-tests were used to compare groups in quantitative variables that were normally distributed. Quantitative variables that were not normally distributed were subjected to the Mann-Whitney test. A comparison of categorical data was done using the Chi-square (χ^2) test. Analysis of the correlation of variables with the duration of the disease was done by the Spearman correlation coefficient. P values less than 0.05 were declared statistically significant.

RESULTS

The study involved 216 eyes of patients aged between 5 and 18 years, of which 108 eyes were diagnosed with VKC and 108 eyes belonged to age- and gender- matched healthy controls. Table 1 shows the demographic profile in which the mean age was 12.07 ± 4.25 years in VKC patients and 11.31 ± 3.80 years in healthy controls (p = 0.094). The gender distribution indicated a higher prevalence of VKC in males (70.40%) compared to females (29.63%) in VKC patients.

The VKC group's BCVA was substantially worse than the controls (0.08 ± 0.173 *versus* 0.03 ± 0.125). The IOP in the VKC group was also significantly higher (14.98 ± 2.73 mm Hg) compared to the control group (13.60 ± 2.24 mm Hg), with a p-value of 0.000 (Table 2).

The central epithelial thickness did not significantly differ between the two groups; however, the VKC group had substantially less superior epithelial thickness (44.71 ± 4.39 µm) than controls (46.22 ± 4.90 µm; p = 0.003). The minimum corneal epithelial thickness was substantially lower in the VKC group *vs* the control one (38.69 ± 5.91 µm *vs* 40.98 ± 3.86 µm; p = 0.007). The VKC group showed a significant decrease in thickness (-13.23 ± 8.62 µm) as compared to the controls (-10.97 ± 8.05 µm; p = 0.047) according to the difference between minimum and maximum thickness (MIN-MAX) (Table 2).

TABLE 1. Table depicting the demographic information

Variables	Category	Cases (n=108)	Controls (n=108)	p value
		mean ± SD		
Age (years)		12.07 ± 4.25	11.31 ± 3.80	0.094
		Number of eyes (%)		
Sex	Male	76 (70.40)	65 (60.20)	0.16
	Female	32 (29.63)	43 (39.80)	

TABLE 2. Comparison between cases and controls on clinical examination, epithelial thickness map parameters and pachymetry map parameters

Variable	Cases (n=108)	Controls (n=108)	p-value
	Mean ± SD		
Clinical examination			
BCVA (in Log MAR)	0.08 + 0.173	0.03 + 0.125	**0.002***
IOP (mm Hg)	14.98 ± 2.73	13.60 ± 2.24	**0.000***
Epithelial thickness map parameters			
Central epithelial thickness	48.09 ± 5.67	48.63 ± 4.96	0.169
Superior (SUP)	44.71 ± 4.39	46.22 ± 4.90	**0.003***
Inferior (INF)	47.49 ± 4.51	47.56 ± 4.45	0.668
Minimum (MIN)	38.69 ± 5.91	40.98 ± 3.86	**0.007***
Maximum (MAX)	52.15 ± 6.31	52.71 ± 11.05	0.699
MIN-MAX	-13.23 ± 8.62	-10.97 ± 8.05	**0.047***
SUP-INF	-2.84 ± 5.24	-1.315 ± 6.34	#0.055
Pachymetry map parameters			
Central corneal thickness	502.71 ± 43.64	509.32 ± 48.24	0.179
Minimum (total thickness)	490.97 ± 63.77	495.99 ± 69.36	0.158

#unpaired t test; @Mann–Whitney U test; *p-value <0.05;
BCVA=best corrected visual acuity; IOP=intraocular pressure;
Log MAR=logarithm of minimum angle of resolution;
MIN-MAX=minimum-maximum;
SUP-INF=superior- inferior.

Among the VKC subtypes, children with mixed VKC had a significantly lower superior epithelium thickness (44.41 ± 3.66 µm; p = 0.039) and minimum epithelium thickness (38.17 ± 4.68 µm; p = 0.014) compared to controls (Table 3). On assessing how various forms of VKC affect epithelial metrics, the values were lower in the mixed variety, but there was no statistically significant difference in any of the metrics between the two groups (Table 4).

Correlation analysis was performed between multiple epithelial parameters and duration of VKC but only a significant positive connection between inferior epithelial thickness and disease duration was found by correlation analysis (r = 0.233; p = 0.015) (Table 5). This suggests that as disease duration increased, the epithelial thickness in the inferior quadrant statistically significantly decreased. ❑

Variable	Mixed type (n=46)	Controls (n=108)	@P-value
	Mean ± SD		
Central epithelial thickness	48.09 ± 5.67	49.78 ± 4.21	**0.036***
Superior (SUP)	44.41 ± 3.66	46.22 ± 4.90	**0.039***
Inferior (INF)	47.56+ 4.45	48.39 ± 4.41	0.998
Minimum (MIN)	38.17 ± 4.68	40.98 ± 3.86	**0.014***
Maximum (MAX)	52.80 ± 6.08	52.71 ± 11.05	0.978
MIN-MAX	-14.58 ± 6.91	-10.97 ± 8.05	**0.025***
SUP-INF	-4.04 ± 5.21	-1.315 ± 6.34	#**0.049***

TABLE 3. Characteristics of the epithelial map in the mixed vernal keratoconjunctivitis (VKC) and control groups

#unpaired t test; @Mann–Whitney U test; *p-value <0.05;
MIN-MAX=minimum-maximum; SUP-INF=superior-inferior.

Variable	Mixed type (n=46)	Palpebral (n=38)	p-value
	Mean ± SD		
Central Epithelial Thickness	49.78 ± 4.21	48.09 ± 5.67	0.263
Superior (SUP)	44.41 ± 3.66	45.32 ± 5.49	0.926
Inferior (INF)	48.39 ± 4.41	47.13 ± 4.85	0.965
Minimum (MIN)	38.17 ± 4.68	39.63 ± 6.58	0.393
Maximum (MAX)	52.80 ± 6.08	53.00 ± 7.21	0.956
MIN-MAX	-14.58 ± 6.91	-12.84 ± 10.12	0.969
SUP-INF	-4.04 ± 5.21	-1.89 ± 5.16	0.551

TABLE 4. Characteristics of the epithelial map in the mixed vernal keratoconjunctivitis (VKC) and palpebral VKC groups

MIN-MAX=minimum-maximum; SUP-INF=superior-inferior.

Variables	#Correlation coefficient	P-value
Central epithelial thickness	0.106	0.27
Superior (SUP)	0.139	0.15
Inferior (INF)	0.233	**0.015**
Minimum (MIN)	0.033	0.737
Maximum (MAX)	0.063	0.512
MIN-MAX	-0.036	0.714
SUP-INF	-0.073	0.453
Central corneal thickness	0.041	0.672
Minimum (total thickness)	-0.023	0.811

TABLE 5. Characteristics of the epithelial map in the mixed vernal keratoconjunctivitis (VKC) and palpebral VKC groups

#Spearman correlation coefficient;
MIN-MAX=minimum-maximum; SUP-INF=superior-inferior.

DISCUSSION

Vernal keratoconjunctivitis is a chronic allergic response of conjunctiva characterised by both conjunctival and corneal inflammation as its defining feature and it is more common in areas with warmer temperatures and younger age groups (12).

The examination of corneal epithelial remodelling linked to VKC, a chronic ocular surface condition, is made possible by anterior segment OCT, a non-invasive and accurate method.

To identify the early stages of keratoconus, focal epithelial thinning on corneal pachymetry mapping detection may be a more sensitive method (13).

In this study, the age distribution was 5–18 years old, with the VKC group having a mean age of 12.07±4.25. There are numerous published studies on VKC patients that focus on the same age range (14, 15).

In our sample, which comprised 76 (70.40%) male subjects and 32 (29.63%) female participants, VKC was more than twice as common in males as in females. This male-predilection trend aligns with earlier research that showed that the ratio of males to females ranged from 4:1 to 2:1 (16, 17).

The higher intraocular pressure observed in VKC patients compared to controls may reflect a combination of steroid use and chronic inflammation, as previously reported in a study by Ang M *et al*. Careful monitoring of IOP is essential, particularly given the potential for steroid-induced ocular hypertension in this population (17).

As far as we are aware, there has been only one prior study that used anterior segment OCT to evaluate variations in corneal epithelial thickness in VKC patients.

According to our findings, there are differences in the corneal epithelial thickness parameters between children with VKC and controls. Superior epithelial thinning was observed, and there was a statistically significant difference in VKC patients, although central epithelial thickness was less but not statistically significant in the VKC group. This result is consistent with previous research, conducted by Albadawi MA *et al*, which revealed that kids with VKC had both superior and central corneal epithelial thinning (11).

MIN-MAX values in the VKC group were more negative than those in the controls. The difference between both groups was statistically significant; this denotes that in VKC patients there is an occurrence of focal thinning. The decrease in superior epithelial thickness and other measurements, including MIN-MAX variability and the superior-inferior asymmetry (SUP-INF) ratio, indicates that localised epithelium remodelling is influenced by mechanical forces, such as frequent eye rubbing, and chronic inflammation. Since T-helper cell pathways and inflammatory mediators produced by eosinophils are known to be important in the pathophysiology of VKC, the epithelial thinning may be the result of cytokine-driven damage.

On analysis of the pachymetry maps, central corneal thickness and minimum corneal thickness were both not statistically significant in comparing cases and controls. However, both were lower in the case group. Assessing these total corneal parameters demonstrates that VKC primarily affects the corneal epithelium and has little impact on the total corneal pachymetry.

On assessing the correlation between epithelial mapping parameters and disease duration, as disease duration increased, the epithelial thickness in the inferior quadrant statistically significantly decreased. This correlation suggests that disease duration in VKC has an impact on changing the corneal epithelium thickness.

When assessing the effect of VKC on corneal integrity, phenotypic classification is crucial, as evidenced by the variations in epithelial thickness patterns, especially in the mixed and palpebral VKC subtypes. On comparison of the mixed VKC group with controls, the superior and minimum epithelial thickness had a statistically significant difference. The mixed VKC group had higher SUP-INF and MIN-MAX values, suggesting an asymmetric corneal epithelium in the mixed VKC group.

There was no discernible difference between the mixed VKC and palpebral VKC groups in terms of several epithelial metrics. Nonetheless, the mixed variety had a lower minimum epithelial thickness. This suggests that the variations in the clinical presentation of VKC can have an effect on the epithelial parameters as well as total corneal parameters.

These differences could affect the likelihood of developing secondary issues like keratoconus in a mixed variety of VKC more than the palpebral one. Studies have reported varying prevalence rates of KC among patients with VKC, identifying KC in 26.8% of cases (18). Epithelial mapping has been suggested as a complementary tool to traditional keratoconus screening, enhancing the early detection of subtle topographical changes that may be obscured by epithelial compensation. The mapping of epithelial thickness can be used in situations where the topography appears to be normal.

A recent study divided the diagnosis of keratoconus into five stages based on changes in the corneal structures. One significant disturbance in the first stage is the thinning of the epithelium pachymetry at the conus.

To further understand epithelial thickness mapping in various ocular surface conditions, more research is needed because the epithelium is a dynamic layer that is quickly altered by many circumstances, eyelid pressures and diseases of the ocular surface can cause epithelial redistribution.

By identifying particular patterns of epithelium thinning linked to inflammation and mechanical stress, anterior segment OCT-based epithelial mapping provides important insights into corneal remodelling in paediatric VKC. In order to avoid complications like keratoconus, these findings highlight the necessity of customised monitoring and care of VKC.

Ophthalmologists can enhance diagnostic precision and customise treatment plans to reduce long-term visual morbidity in kids with VKC by implementing epithelial mapping into clinical practice. ❑

CONCLUSIONS

This study demonstrates that children with vernal keratoconjunctivitis exhibit notable changes in corneal epithelial thickness parameters, particularly a significant reduction in superior and minimum epithelial thickness compared to healthy controls. Patients with VKC may have visual impairment as a result of these changes in epithelial integrity. Additionally, the significant correlation between epithelial thickness and disease duration suggests that prolonged duration of VKC may exacerbate epithelial thinning. The findings of our study underscore the importance of using optical coherence tomography of the anterior segment as a useful monitoring tool for corneal changes in paediatric VKC, which can aid in enhancing management strategies and improving patient outcomes in this demographic. ❑

Conflicts of interest: none declared.

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Informed consent: Informed consent was obtained from all subjects involved in the present study.

Institutional review board: The present study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "All India Institute of Medical Sciences Raebareli, Uttar Pradesh, India" (approval number: F. 3/BIOETHICS/AIIMS-RBL/APPRO/IM/2024 - 6/6, approval date: 11 March 2024).

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