Original research

A contralateral eye study comparing characteristics of corneal endothelial cells in bilateral keratoconus patients with unilateral corneal Vogt's striae

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Abstract

Purpose: The aim of this study was to analyze and compare corneal endothelial cell morphology and characteristics in bilateral keratoconus (KCN) patients with unilateral Vogt's striae.

Methods: Fifty patients aged 20–38 years were recruited in this cross-sectional contralateral eye study. In this study, corneal endothelial cell parameters were evaluated in patients with bilateral KCN and unilateral Vogt's striae using the Topcon SP2000P specular microscope (Topcon, Tokyo, Japan).

Results: In the current study, there were no significant differences in corneal endothelial cell parameters including endothelial cell density (ECD), hexagonal cell ratio (HEX), and coefficient of variance of cell size (CV) between the KCN groups with and without Vogt's striae, [(2968.34 ± 276.65 vs. 2980.05 ± 253.30, $P = 0.618$), (51.88 ± 13.57 vs. 53.24 ± 9.31, $P = 0.658$), and (32.50 ± 5.40 vs. 32.97 ± 4.07, $P = 0.467$), respectively]. Also, among study groups with and without Vogt's striae, ECD did not correlate with anterior chamber depth (ACD) [($P = 0.564$, r = 0.09), ($P = 0.219$, r = −0.18), respectively], maximum keratometry (Kmax) [($P = 0.215$, r = 0.18), ($P = 0.898$, r = 0.02), respectively], and central corneal thickness (CCT) [($P = 0.989$, r = −0.02), ($P = 0.643$, r = −0.07), respectively].

Our results showed significant differences in corrected and uncorrected distance visual acuity (UDVA), cycloplegic refractive error components (calculated by vectorial analysis), CCT, and Kmax between two study groups (all $P < 0.05$) except for J_{45} (Jackson cross cylinder, axes at 45 and 135°) ($P = 0.131$).

Conclusions: We were not able to find the statistically significant differences in ECD, HEX, and CV between KCN eyes with and without Vogt's striae. Despite clinical and tomographic results, it seems that Vogt's striae cannot cause deterioration in the corneal endothelial morphology.
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Keywords: Keratoconus; Corneal endothelial cell; Vogt's striae; Endothelial cell density; Contralateral eye study

Introduction

Keratoconus (KCN) is a corneal ectatic disorder with a non-inflammatory and progressive nature.[1–4] This ectatic disorder can be characterized by several clinical and subclinical manifestations that have been described in a large body of literature.[2,5–7]

For evaluation and detection of clinical cases of KCN, corneal Vogt's striae have been considered one of the classic signs of KCN.[7,8] Vogt's striae in the corneal stroma are mostly parallel to the anterior corneal steep axis of the KCN cone and are presented as fine vertical and uncommonly horizontal lines in the stroma.[2,8,9] These fine vertical or horizontal lines are also known as stress lines.[8,10] Vogt's striae are visible in moderate to severe stages of KCN using high magnification biomicroscopy.[1,2,11] The Collaborative Longitudinal Evaluation of KCN (CLEK) study showed that 34% and 30% of KCN patients have unilateral and bilateral Vogt's striae, respectively.[11]

Some studies have assessed numerous corneal characteristics associated with Vogt's striae.[8,12] Hollingsworth and Efron pointed out the appearance of stromal banding patterns in KCN patients using in vivo confocal microscopy (IVCM). They stated that these alternating dark and light bands correspond to the Vogt's striae.[8] In another study, Mocan et al. using IVCM found no difference in endothelial cell density (ECD) between keratoconic corneas with and without IVCM evidence of Vogt's striae.[12]

The significance of the corneal endothelial morphology in different ocular conditions is the main focus of many studies.[13–16] On the other hand, abnormal alterations of the corneal microstructure in KCN patients may lead to changes in the corneal endothelial layer.[17–19] Due to the association of the Vogt's striae with different subclinical changes in the cornea,[8,12] some questions have arisen about a probable association between the Vogt's striae and changes in the corneal endothelial cells in clinical KCN.

There are different devices for in vivo assessment of corneal endothelial cells.[20,21] One of the available and common devices for in vivo assessment of the corneal endothelial cells is the TOPCON SP-2000P (Topcon, Tokyo, Japan), a specular microscope that can measure corneal endothelial properties in terms of ECD, hexagonal cell ratio (HEX), and coefficient of variance of cell size (CV).[22] The mechanism of this instrument has been described earlier.[23]

Many articles have evaluated the corneal endothelial cell layer in KCN eyes,[24–26] but no study has assessed the corneal ECD and morphology in Vogt's striae using the specular microscopy. The aim of this contralateral eye study was to compare corneal endothelial cell properties measured with the Topcon SP2000P non-contact specular microscope in patients with bilateral KCN with unilateral Vogt's striae.

Methods

Fifty consecutive patients with bilateral KCN but unilateral Vogt's striae participated in this cross-sectional contralateral eye study conducted from February to June 2017. The study was performed at Sedaghat Eye Clinic, Mashhad, Iran. All participants were residents of Mashhad with the same ethnicity.

The Institutional Review Board/Ethics Committee of Mashhad University of Medical Sciences approved the study and registered it under the number 950806. This study followed the tenets of the Declaration of Helsinki. The sample size was calculated based on a pilot study. The participants received necessary information about the study, and written informed consent was obtained from each one.

All the participants underwent a comprehensive ophthalmic examination, including a full patient history, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), evaluation of the retinoscopic reflex, manifest and cycloplegic refraction (Topcon KR-1, Tokyo, Japan), ophthalmoscopy, noncontact computerized tonometry (Topcon CT-1/CT-1P, Tokyo, Japan), slit-lamp biomicroscopy, and Scheimpflug-based tomography (Pentacam HR, Oculus, Optikgerate GmbH, Wetzlar, Germany). The inclusion criterion in this study was a precise diagnosis of bilateral KCN patient with unilateral Vogt's striae established by an experienced corneal refractive surgeon based on slit-lamp biomicroscopic signs (Vogt's striae, Fleischer's ring, apical thinning) as well as corneal topographic/tomographic evaluation (skewed asymmetric bow-tie, inferior steepening, abnormal elevation and pachymetry maps, and KCN screening by Belin/Ambrosio Enhanced Ectasia Display III), irregular and scissoring retinoscopic reflex. Slit-lamp biomicroscopy using 40× magnification was done to assess unilateral Vogt's striae.

The exclusion criteria of this study were age below 18 and over 40 years, history of previous eye surgery as well as corneal scarring, vascularization, inflammation, and opacity. In addition, history of severe keratitis, severe dry eye, glaucoma or glaucoma suspect, treatment with intraocular pressure lowering drugs, and underlying autoimmune or systemic diseases were considered other exclusion criteria. It should be noted that patients with a history of corneal cross-linking for KCN or patients who used the contact lens for less than four weeks before the commencement of this study were not involved in the study group. Furthermore, women who were on their menstrual period, pregnant and lactating women, and patients with forme fruste KCN or KCN suspect were excluded from this study.

The corneal endothelial layer was evaluated in vivo using the Topcon SP2000P non-contact specular microscope (Topcon, Tokyo, Japan). All corneal endothelial measurements were done consistently based on the manufacturers' instructions. The calibration of Topcon SP2000P was checked by the manufacturer's representative before the beginning of the study.

The Topcon SP2000P has the ability to measure ECD, HEX, and CV. The mechanism of the Topcon SP2000P has already been described in other studies,[23] and the repeatability[27] and validity[28] of the Topcon SP2000P have previously been reported. As for the results of the Topcon SP2000P, the system monitors the entire process automatically and then presents acceptable measurements. We only measured the central corneal endothelium in this study because a great proportion of the Vogt's striae in keratoconic corneas can be visualized in the central cornea.[12]

All measurements were done between 3:00 pm and 5:00 pm by one experienced optometrist. Three effective measurements were taken at 1-min intervals using the Topcon SP2000P, and the average of the values was used for analyses.

Power vector analysis was applied to compare refractive error components between keratoconic eyes with and without

Vogt's striae. The data of spherocylindrical refraction were transformed to vectors expressed by 3 dioptric powers: M, J_0 (Jackson cross cylinder, axes at 0 and 90°), and J_{45} (Jackson cross cylinder, axes at 45 and 135°) [M = S + (C/2), J_0 = −C/2cos (2α), J_{45} = −C/2sin (2α)], where M was matched to the spherical equivalent (SE) of the measured refractive error, and J_0 and J_{45} were the 2 Jackson cross cylinder equivalents to the conventional cylinder. It is also noteworthy that cycloplegic refraction was noted in the usual manner (sphere, cylinder, and axis); then these documented data were converted to power vector coordinates as described by Thibos and Horner.[29]

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software version 22 (SPSS Inc., Chicago, IL, USA) and MedCalc Software version 15.8.X86 (MedCalc Software bvba, Ostend, Belgium). The normal distribution of the parameters was assessed using Kolmogorov−Smirnov test. Paired sample t-test was used to compare the parameters with a normal distribution, and the Wilcoxon signed rank test was used to compare non-parametric parameters. Pearson correlation coefficients were used for correlative analyses. To study the agreement between the measurements made by devices, the method described by Bland and Altman was used.[30] The 95% limits of agreement (LoA) [mean difference ± 1.96 standard deviation (SD)], which define the range within which most differences between measurements by the two methods will lie, were calculated. A *P* value less than 0.05 was considered significant.

Results

The present study was conducted on 50 bilateral KCN patients [28 males (56%) and 22 females (44%)] to compare endothelial cell parameters between eyes with and without Vogt's striae using a specular microscope. The mean age of the participants was 27.54 ± 6.78 years (range, 20−38 years). The participants were assigned into two groups: KCN patients with Vogt's striae comprised Group 1, and KCN patients without Vogt's striae formed Group 2.

As shown in Table 1, there were significant differences in the sphere, cylinder, SE, J_0, UDVA, CDVA, and maximum keratometry (Kmax) between the two groups (all *P* < 0.001). Moreover, the KCN eyes with Vogt's striae had deeper anterior chamber depth (ACD) (*P* < 0.001) and thinner corneas [measured by the Pentacam (*P* < 0.001)] than those without Vogt's striae.

As shown in Table 2, although we were not able to find statistically significant differences in CV, ECD, HEX (all *P* > 0.05), the eyes with Vogt's striae had thinner corneas [measured by specular microscopy (*P* < 0.001)] than those without Vogt's striae.

According to Table 3, in KCN eyes with and without Vogt's striae, ECD did not correlate with ACD [(*P* = 0.564, r = 0.09), (*P* = 0.219, r = −0.18), respectively], Kmax [(*P* = 0.215, r = 0.18), (*P* = 0.898, r = 0.02), respectively] and central

corneal thickness (CCT) [(*P* = 0.989, r = −0.02), (*P* = 0.643, r = −0.07), respectively].

As shown in Table 4, no correlation was observed in CCT (*P* > 0.05) between the two imaging devices (Pentacam and Topcon SP2000P specular microscope). The 95% LoA was determined for better comparison of the degree of agreement between the two methods. According to Table 4 and Fig. 1, although there was a higher agreement between measurements of the Pentacam and specular microscope in KCN eyes with Vogt's striae than those without Vogt's striae, we were not able to find a reasonable agreement between CCT measurements by the Pentacam and specular microscope in KCN eyes with and without Vogt's striae.

Discussion

Previous studies have found that the corneal ECD and morphology are important factors affecting different stages of KCN.[24,25] We designed this study in order to evaluate and compare the morphology and characteristics of corneal endothelial cell in bilateral KCN patients with and without Vogt's striae using the Topcon SP2000P non-contact specular microscope.

According to the present study, we were not able to find a statistically significant difference between bilateral KCN patients with and without Vogt's striae in terms of ECD, HEX, and CV. Furthermore, KCN eyes with Vogt's striae had worse visual acuity (corrected and uncorrected), refractive errors (SE and J_0), and corneal tomographic parameters (Kmax, CCT, and ACD) compared with the KCN eyes without Vogt's striae. Also, we calculated the correlation between the ECD and corneal tomographic parameters in the present study. Findings of this study indicated that the ECD did not have any correlation with ACD, Kmax, and CCT in KCN eyes with and without Vogt's striae.

Mocan et al. reported an association between the presence of the Vogt's striae and other microstructural corneal changes in the KCN patients using the IVCM. They reported that there is no significant difference in terms of ECD between KCN eyes whose corneas had IVCM evidence of Vogt's striae and those that did not.[12] Despite the similar clinical findings (SE, astigmatic errors, and corneal power) of the present study with the study conducted by Mocan et al., there is a significant difference between the two studies. They did not investigate various characteristics of corneal endothelial cell by means of specular microscopy.

A large body of literature has described the ECD in eyes with KCN. Weed et al. argued that the presence of KCN did not affect the ECD,[18] while Goebels and colleagues emphasizes that as the severity of KCN increase, ECD decreases and CV increases.[24] Also, Timocin et al. conducted a research study to assess the ECD in keratoconic eyes and indicated that the change in ECD did not depend on the CCT and different stages of KCN.[26] Results of Timocin et al. on the correlation between ECD and CCT were consistent with the results of our study. Notably, all of the above-mentioned studies did not investigate any association of the presence of

Table 1

Contralateral comparison of basic and tomographical parameters between keratoconus (KCN) eyes with and without Vogt's striae.

Parameter	With Vogt's striae		Without Vogt's striae		Mean difference	P-value
	Mean ± SD	Range	Mean ± SD	Range		
Sph (D)	−3.14 ± 2.62	−13.00 to +1.00	−1.40 ± 2.13	−8.75 to +1.50	−1.74 ± 3.49	**<0.001**[b]
Cyl (D)	−5.83 ± 3.09	−10.50 to −1.75	−2.84 ± 2.17	−9.25 to 0.00	−2.99 ± 3.82	**<0.001**[b]
SE (D)	−6.06 ± 3.26	−15.00 to −1.12	−2.82 ± 2.86	−12.37 to +0.75	−3.24 ± 4.51	**<0.001**[b]
J_0 (D)	1.23 ± 2.42	−3.70 to +8.93	0.49 ± 1.24	−2.07 to +4.09	0.74 ± 2.70	**0.001**[b]
J_{45} (D)	0.10 ± 1.92	−3.94 to +3.09	0.25 ± 1.18	−3.25 to +3.64	−0.16 ± 2.17	0.131[b]
UDVA (logMAR)	0.76 ± 0.44	0.1 to 1.60	0.34 ± 0.36	0.00 to 1.60	0.42 ± 0.53	**<0.001**[b]
CDVA (logMAR)	0.43 ± 0.32	0.00 to 1.00	0.13 ± 0.16	0.00 to 0.40	0.31 ± 0.31	**<0.001**[b]
Kmax[a] (D)	58.16 ± 5.62	44.10 to 69.60	50.37 ± 4.64	44.10 to 63.50	7.79 ± 5.59	**<0.001**[c]
CCT[a] (μm)	463.20 ± 34.35	376.00 to 542.00	489.64 ± 35.99	390.00 to 553.00	−26.44 ± 21.47	**<0.001**[c]
ACD[a] (mm)	3.55 ± 0.36	2.79 to 4.47	3.41 ± 0.36	2.28 to 4.24	0.14 ± 0.26	**<0.001**[c]

Sph: Sphere, Cyl: Cylinder, SE: Spherical equivalent, J_0: Jackson cross cylinder, axes at 0 and 90°, J_{45}: Jackson cross cylinder, axes at 45 and 135°, UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, Kmax: Maximum keratometry, CCT: Central corneal thickness, ACD: Anterior chamber depth, D: Diopter, logMAR: Logarithm of the minimum angle of resolution, SD: Standard deviation. There were no missing data. P-value <0.05 is statistically significant.

[a] Measured by Pentacam.
[b] Wilcoxon signed ranks test.
[c] Paired-samples T test, bold values are significant.

Table 2

Contralateral comparison of endothelial cell parameters was measured by specular microscope between keratoconus (KCN) eyes with Vogt's striae and those without Vogt's striae.

Parameter	With Vogt's striae		Without Vogt's striae		Mean difference	P-value
	Mean ± SD	Range	Mean ± SD	Range		
CCT (μm)	459.28 ± 35.49	378.00 to 540.00	481.38 ± 34.14	397.00 to 548.00	−22.10 ± 30.32	**<0.001**[b]
ECD (cell/mm^2)	2968.34 ± 276.65	2166.00 to 3507.00	2980.05 ± 253.30	2345.00 to 3520	−11.72 ± 165.01	0.618[b]
CV (%)	32.50 ± 5.40	18.00 to 51.00	32.97 ± 4.07	24.00 to 43.00	−0.47 ± 4.51	0.467[a]
HEX (%)	51.88 ± 13.57	17.00 to 75.00	53.24 ± 9.31	31.00 to 74.00	−1.36 ± 14.22	0.658[a]

CCT: Central corneal thickness, ECD: Endothelial cell density, CV: Coefficient of variation, HEX: Hexagonal cells, SD: Standard deviation. There were no missing data. P-value <0.05 is statistically significant.

[a] Wilcoxon signed ranks test.
[b] Paired-samples T test, bold values are significant.

Table 3

Correlative coefficient of corneal endothelial cell density (ECD) with anterior chamber depth (ACD), maximum keratometry (Kmax), and central corneal thickness (CCT) in keratoconus (KCN) eyes with Vogt's striae and those without Vogt's striae.

Parameter		ACD (mm)		Kmax (D)		CCT[a] (μm)	
		P-value	r	P-value	r	P-value	r
ECD (cell/mm^2)	With Vogt's striae	0.564	0.09	0.215	0.18	0.989	−0.02
	Without Vogt's striae	0.219	−0.18	0.898	0.02	0.643	−0.07

ACD: Anterior chamber depth, Kmax: Maximum keratometry, CCT: Central corneal thickness, ECD: Endothelial cell density, r: Pearson correlation coefficient. There were no missing data. P-value <0.05 is statistically significant.

[a] Measured by specular microscope.

Vogt's striae with ECD, HEX, and CV values in keratoconic corneas.

In brief, the evaluation of endothelial cell parameters in the keratoconic corneas through different devices has indicated contradicting results in different studies. Diversity of the results may be due to the methods and materials of the studies.

Considering the significance of CCT in the keratoconic eyes, several studies compared the CCT measurements through different devices.[31−34] The results of the present study did not able to indicate any reasonable agreement between measurements of Pentacam and Topcon SP2000P for CCT in the KCN eyes with and without Vogt's striae. The present study is the first research to compare the CCT measurements between Scheimpflug-based tomography and specular microscope in keratoconic eyes with and without Vogt's striae.

Few studies have investigated the agreement among CCT measurements in keratoconic eyes using different devices, and all the published studies concluded that these devices should not be used interchangeably in KCN eyes.[31−34] Results of our study were consistent with the literature showing that one

Table 4
Pentacam and specular microscope measurements for central corneal thickness (CCT).

Parameter		Pentacam	Specular microscope	Difference		Correlation		95% LOA	
		Mean ± SD	Mean ± SD	Δ	P	r	P	Lower	Upper
CCT (μm)	With Vogt's striae	463.20 ± 34.35	459.28 ± 35.49	−3.92 ± 41.03	0.502	0.31	0.208	−76.50	84.30
	Without Vogt's striae	489.64 ± 35.99	481.38 ± 34.14	−8.26 ± 42.50	0.176	0.27	0.620	−75.00	91.60

CCT: Central corneal thickness, r: Pearson correlation coefficient, LoA: Limits of agreement, SD: Standard deviation. There were no missing data. *P*-value <0.05 is statistically significant.
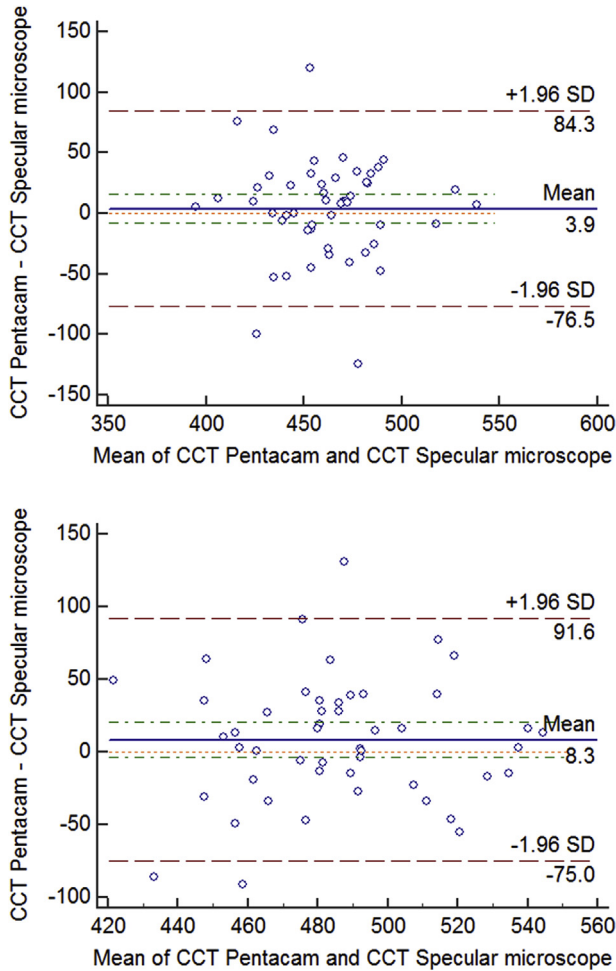

Fig. 1. Bland−Altman plots of the central corneal thickness (CCT) as measured by Pentacam against specular microscope in keratoconus (KCN) eyes with Vogt's striae (Top), without Vogt's striae (Bottom). The middle line in each figure is the mean difference of values, and the lines on the sides represent the upper and lower 95% limits of agreement (LoA) [mean difference ± 1.96 standard deviation (SD)].

should be cautious interpreting CCT measurements obtained from different devices in eyes with KCN. Also, findings of the present study may be of interest for researchers deliberating the agreement between Pentacam and Topcon SP2000P measurements for CCT in keratoconic eyes with and without Vogt's striae.

In summary, this study investigated the morphology and characteristics of the corneal endothelial cell through Topcon SP2000P specular microscope. We are not able to indicate any significant difference between KCN eyes with and without Vogt's striae in terms of ECD, HEX, and CV. Findings of the present study also suggested that there was not any correlation between ECD with ACD, Kmax, and CCT. Meanwhile, we were not able to find reasonable agreement between CCT measurements by Topcon SP2000P and Pentacam in keratoconic corneas with and without Vogt's striae.

Due to the proximity of the deep stromal Vogt's striae to the corneal endothelial cell layer,[8,10–12] it is hypothesized that the endothelial cell morphology is affected by Vogt's striae in keratoconic corneas.

Our findings suggest that in clinical practice, when corneal endothelial cell morphology and characteristics are evaluated in KCN patients, no emphasis needs to be placed on the presence of Vogt's striae in cornea. The results of the present study can be used in clinical evaluation, monitoring, and treatment of KCN patients with and without Vogt's striae. Despite clinical and tomographic results, it seems that Vogt's striae cannot cause deterioration in the corneal endothelial morphology. Our results should allow more KCN patients with Vogt's striae to have deep anterior lamellar keratoplasty instead of penetrating keratoplasty.

Although the current study is valuable for the evaluation and comparison of corneal endothelial cell morphology and characteristics in KCN eyes with and without Vogt's striae, conducting the present study without IVCM as well as its small sample size should be considered limitations. Also, we did not evaluate the repeatability of CCT measurements by Topcon SP2000P and Pentacam in keratoconic corneas with and without Vogt's striae, but this is not the main focus of this study.

Acknowledgment

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