Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2020, 122, 3: 112–116
Received: 02.04.2020 Accepted: 17.04.2020

ORIGINAL ARTICLE

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2020.97666

Inter-eye asymmetry in manifest refraction, keratometry and pachymetry in eyes with keratoconus

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ABSTRACT

Aim of the study: To evaluate selected visual system parameters in keratoconus patients and establish criteria which will enable better screening for keratoconus.

Material and methods: 146 eyes of 73 patients diagnosed with keratoconus were included in the study. Each patient underwent optometric and ophthalmological examination with corneal tomography.

Results: We found a statistically significant inter-eye difference between the better and worse eye in median values of uncorrected (0.24 vs. 0.62 LogMAR) and best corrected (0.03 vs. 0.24 LogMAR) distance visual acuity. Our study also showed statistically significant differences in median values of keratometry between the better and worse eye (K1 43.1 vs. 45.4 D, K2 45.2 vs. 49.0 D), mean values of thinnest central cornea (TCC) (488 vs. 458 μm) and median grade 1.5 and 2.5 for the better and worse eye, respectively. The most prevalent refractive error was compound myopic astigmatism, followed by hyperopic compound or mixed astigmatism.

Conclusions: Keratoconus should be suspected in patients with inter-eye differences in manifest refraction, especially when astigmatism exists. Any inter-eye asymmetry in keratometry or pachymetry values should be an indication for full keratoconus screening.

KEY WORDS: keratoconus, inter-eye asymmetry, pachymetry, keratometry, manifest refraction.

INTRODUCTION

Keratoconus (KC) is a progressive corneal, bilateral ectasia characterized by thinning and weakening of the cornea that results in corneal steepening, protrusion, irregular astigmatism, and gradual impairment of vision [1].

Worldwide, KC occurs in approximately 1 in 2000 individuals, as reported by Rabinowitz at the end of the 20th century [1]. However, reported epidemiological data differ between geographical zones and other factors such as age or gender.

Ethnicity has been reported to play a role in keratoconus. Asians have 4.4 times higher risk for developing keratoconus than Caucasians, and Indians have steeper corneas than Chinese patients with keratoconus [2, 3]. Recently reported KC prevalence in the pediatric population in Saudi Arabia is higher than in previous reports: 4790/100,000 (4.79%) [4].

Keratoconus affects both genders, and data about gender predilection are not consistent. Li *et al.* found no difference between genders, whereas Wagner *et al.* found KC more frequently in males [5, 6].

Keratoconus is a multifactorial disease caused by genetic and environmental factors. Genetics of KC are still under study, but multiple genes have been identified as potential disease risk factors [7-9]. There were studies and anecdotal reports published supporting the idea that in development of KC mechanical factors such as eye rubbing are involved [10, 11]. Contact lenses, especially rigid gas permeable (RGP), are also considered as a risk factor by causing microtraumas and increased dryness which provokes eye rubbing [12, 13].

Keratoconus has been classified as a noninflammatory disease; however, recent studies found evidence of inflammatory markers, and cytokines including interleukins (IL-1, IL-6, IL-8) and tumor necrosis factor α (TNF-α) in the tears of patients with keratoconus [14-16].

Coexistence of KC with systemic conditions is widely discussed. Atopy is found in 53% of patients with KC [17]. Kaya *et al.* stated that KC in patients with atopy differs significantly from KC in patients without atopy and could be described as a separate clinical condition [18]. Allergy and atopy are reported as dominant risk factors for the habit of eye rubbing [19].

Refractive status of patients with keratoconus is well described. The most common refractive error in KC is compound myopic astigmatism, with the incidence rate in

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different studies reported from 69.7% to 85.7%. Types of astigmatism (with-the-rule, against-the-rule, oblique) are different depending on stages of KC [20, 21]. Frequency of high astigmatism (> 2 D) is significantly higher in population with KC and subclinical KC (14.1%) than in the normal population (6.86%) [22-24].

Early diagnosis of keratoconus is still a challenge; the most important aspect is to think about this condition as soon as possible.

Keratoconus can be clinically diagnosed on slit-lamp findings, e.g. corneal thinning, Vogt's striae, Fleischer ring, Munson sight, corneal scarring. However, these changes are seen in severe stages of the disease [1].

The gold standard in KC diagnosis and monitoring its progression is corneal tomography. But to diagnose the earliest stages of keratoconus also epithelium thickness mapping should be used [25, 26].

The management of KC is mainly consisted of visual acuity improvement using glasses and contact lenses, especially rigid gaspermeable, intracorneal ring segment implantation for moderate stages and keratoplasty (lamellar or penetrating) for advanced ones [27].

A well-described strategy for slowing the progression of keratoconus is to perform corneal collagen cross-linking (CXL). Wollensak reported in 2006 the results of the first clinical study on CXL with riboflavin and UVA as a procedure for the treatment of progressive keratoconus in adults [28]. CXL has been proven to be successful at stiffening and thus arresting and in many cases even regressing the progression [28-30].

The Global Consensus on Keratoconus and Ectatic Diseases, involving opinions from 45 KC clinical experts from around the world, agreed that CXL can be beneficial upon diagnosis in young patients with keratoconus [31].

The keratoconus patient requires a multi-professional approach in which at different stages (clinical suspicion, diagnosis, management and follow-up) optometrists, contact lens practitioners and ophthalmologists are involved.

AIM OF THE STUDY

The aim of our study was to evaluate and perform a statistical analysis of the selected visual system parameters in keratoconus patients.

MATERIAL AND METHODS

All study participants were recruited and examined in the Optegra Eye Health Care Clinic in Poznań, Poland. Accurate anamnesis was performed with special attention given to coexisting atopic diseases. Each patient underwent optometric examination including uncorrected distance visual acuity (UCVA), best corrected distance visual acuity (BCVA) (visual acuity was assessed with a Snellen chart and then converted to LogMAR visual acuity). We used manifest refraction for further analysis, and not objective refraction (cycloplegic autorefractometry). Then ophthalmological examination was performed, which included anterior and posterior segment evaluation (1% tropicamide (WZF, Polfa S.A.) was used for pupil dilatation), and intraocular pressure measurement. Imaging examination included corneal tomography WaveLight Oculyzer II (Alcon, Texas, US), and the following parameters were used for further analysis – keratometry: K1 (flat), K2 (steep), grade, thinnest central cornea (TCC). Grade is an automatic classification of keratoconus stage based on Oculyzer software version 1.20r20.

Patients were referred to Optegra for enhanced diagnosis with or without clinical suspicion of KC.

The data were collected in an Excel Sheet (Microsoft Corporation) and for statistical analysis Statistica 12.0 (StatSoft Polska) was used. The Shapiro-Wilk test was used for the evaluation of the distribution of continuous variables. Non-normally distributed variables are presented as median and range (minimum-maximum); normally distributed data are shown as mean ± standard deviation. Categorical variables are shown as a percentage of the total number. Nonparametric Spearman correlation between analyzed parameters was calculated.

The study was approved by the ethics committee of Poznan University of Medical Sciences.

RESULTS

In total 73 patients (59 males and 14 females) were enrolled in the study, and data of 146 eyes were analyzed. Data of patients' age and coexisting atopy are presented in Table I.

Median UCVA was 0.2 and 0.6 LogMAR for the better and the worse eye respectively, and BCVA was 0.0 and 0.2 respectively. Further data of visual acuity are presented in Table II. Differences in visual acuity between the better and worse eye are statistically significant. Information about manifested refraction parameters are presented in Table II. Additional information about refractive error and astigmatism are presented in Table III.

The median grade was 1.5 for the better eye and 2.5 for the worse eye. Further corneal parameters – keratometry and TCC – are presented in Table IV. It has to be emphasized that differences in all discussed corneal parameters between the better and worse eye are statistically significant.

We counted the number of patients with BCVA 0.4 LogMAR or worse (≥ 0.4) for the better and worse eye and found 3 patients (4.1%) and 25 (34.2%) respectively.

Numbers of eyes within defined K value ranges are presented in Table V.

Correlation between grade and cylinder (negative value) was calculated and a negative, statistically significant correlation was found: Spearman's $R = -0.327476$, $p = 0.0002$. We also checked whether a correlation exists between grade

Table I. Number of patients by age, gender, and with atopy (% of: all patients/in subgroup)

	Median age (range)	≤ 18 years old	> 18 years old	Atopy
Females	25.3 (16.1-43.5)	1 (1.4/20%)	13 (17.8/19.1%)	3 (4.1/13.0%)
Males	24.9 (12.9-44.5)	4 (5.5/80%)	55 (75.3/80.9%)	20 (27.4/86.9%)

Table II. Visual acuity and refractive error: median value (range)

	All eyes ($N = 146$)	Better eye ($n = 73$)	Worse eye ($n = 73$)	*p* value
UCVA LogMAR	0.39 (–0.2-1.6)	0.24 (–0.2-1.5)	0.62 (0.2-1.6)	< 0.000001
BCVA LogMAR	0.12 (–0.2-1)	0.03 (–0.2-0.4)	0.24 (0-1)	< 0.000001
Sphere $n = 110$	–1.0 (–9-2.5)	–0.9 (–9-2.5)	–1.0 (–8-2.5)	0.887
Cylinder $n = 128$	–2.2 (–6.5-0)	–1.6 (–4.3-0.5)	–2.6 (–6.5-0)	0.00001
Axis $n = 128$	90 (0-175)	95 (12-170)	88 (0-175)	0.350

UCVA – uncorrected distance visual acuity, BCVA – best corrected distance visual acuity, p – Mann-Whitney U test

Table III. Type of refractive error and type of astigmatism by the axis: number of eyes (% of all eyes)

	Number of eyes
Type of refractive error	
Myopic compound astigmatism	66 (45.2%)
Hyperopic compound or mixed astigmatism	40 (27.4%)
Myopic astigmatism	22 (15.1%)
Myopia	3 (2.1%)
Hyperopia	1 (0.7%)
Type of astigmatism by the axis	
Against the rule (axis: 61-119°)	74 (50.7%)
Oblique (axis: 30-60°, 120-150°)	33 (22.6%)
With the rule (axis: 0-29°, 151-180°)	21 (14.4%)

value and age, with gender consideration. No statistically significant correlation was found (Spearman's $R = –0.061977$, $p = 0.457$; Spearman's $R = –0.218153$, $p = 0.265$; Spearman's $R = –0.016695$, $p = 0.858$ for all patients, women and men respectively).

We also found that in 41 patients the left eye was the better eye, and in 32 patients the right eye.

DISCUSSION

As noted above, in recent studies reported KC prevalence is very high. Torres *et al.* found KC in nearly 5% of patients in the examined group, which consisted of pediatric patients from non-ophthalmic emergency departments [4]. In our study 5 (6.9%) patients were ≤ 18 years old. It has to be emphasized that 4 (80.0%) patients in this subgroup were male. Awareness of KC prevalence in pediatric and adolescent patients should be increased, because visual impairment in this group may affect social and educational development. Moshiraf *et al.* recommend topographic screening in elementary schools as a way to provide early detection of KC, due to the severity of the disease in children [32].

In the examined adult subgroup there were 55 (80.9%) males and 13 (19.1%) females. Our data from two age ranges demonstrate that a crucial difference in KC prevalence between genders exists. These results are similar to those published by Millodot *et al.* and Mohd-Ali *et al.* [3, 33]. The examined group of 1093 KC patients in the study of Fink *et al.* included 482 (44%) women and 611 men (56%); mean age of the females was 40.0 years and mean age of males was 38.3 years ($p = 0.01$) [34]. In our study women are older than men, but the difference is not statistically significant. However, we suggest that usually KC patients are younger and male, and KC onset is later in female patients.

The most common refractive error in the examined group was compound myopic astigmatism; it was found in 66 (45.2%) of examined eyes. We also found a high frequency of mixed astigmatism and hyperopic astigmatism (27.4%), followed by myopic astigmatism (15.1%). We found myopia in 2.1% of eyes and hyperopia in one eye. The most prevalent type of astigmatism was against-the-rule (50.7%) and oblique astigmatism (22.6%). Cruz-Becerril *et al.* reported higher prevalence of compound myopic astigmatism and with-the-rule astigmatism as dominant [21]. Using schematic eye models Tan *et al.* stated that cone location is the most important factor in vision distortion. KC cones cause myopia when they are located centrally. Peripherally located KC cones can result in hyperopic shift. The authors proved that one meridian of astigmatism will be aligned with the cone direction [35]. We did not evaluate the cone location. Our study is focused strictly on manifest refraction in KC, which is an important criterion in diagnosis and progression of KC. Refractive error examination in KC is a challenge and is often hampered by slight fluctuation in visual acuity at specific spherical power, cylinder power and axis.

Manifest astigmatism was greater in the worse than in the better eye and the difference between median values equated 1.0 D (absolute value), and was statistically significant. Based

Table IV. Corneal parameters: median value (range)

Parameter	All eyes	Better eye	Worse eye	*p* value
Anterior K1 (D)	44.2 (39.6-56.2)	43.1 (39.6-52)	45.4 (40.2-56.2)	0.000001
Anterior K2 (D)	47.1 (40.4-60.8)	45.2 (40.4-57.5)	49.0 (42.6-60.8)	< 0.000001
TCC (µm)	473 ±40	488 ±39	458 ±34	0.000001*
Grade	2 (0-4)	1.5 (0-3.5)	2.5 (0-4)	< 0.000001

*Thinnest central cornea (TCC) – mean value ±SD, p – Mann-Whitney U test, *Student's t-test*

Table V. Number of eyes within defined K values ranges: number of eyes (% of all eyes)

	Number of eyes
Anterior K2 ≤ 47.2 D	83 (56.8%)
Anterior K1 ≤ 43.0 D	53 (36.3%)
Anterior K2 ≤ 44.0 D	27 (18.5%)

on this result we postulate that 1.0 D (absolute value) inter-eye asymmetry in manifest astigmatism could be considered as a cut-off point for full KC screening with corneal tomography. Moreover, we found a statistically significant correlation between grade and amount of manifest astigmatism, which increases as the disease progresses.

Among various indices, keratometry has an important role in diagnosis, grading the disease and tracking its progression [31].

Yekta *et al*. analyzed K data from 2672 patients in a normal population and obtained the following results: mean flat meridian 42.98 D (95% CI: 42.9-43.06 D) and mean steep meridian 43.98 D (95% CI): 43.91-44.07 D) [36]. Even if K1 (flat) and K2 (steep) keratometry are within the normal range we always have to check inter-eye symmetry. In our group 36.3% of K1 and 18.5% of K2 readings were within the normal range of values. Rabinowitz suggested several topometric criteria for the diagnosis of keratoconus, one of them being central K greater than 47.2 D [37]. In our group 56.8% of eyes do not meet the requirements of this criterion.

Median values of K1 and K2 were higher in the worse eye, the difference between the eyes being statistically significant. Also the range of values was different, with higher values in the worse eye. Galletti *et al*. found that the mean anterior keratometry inter-eye difference ≥ 0.3 D could be considered as a warning sign of KC [38].

We have to analyze pachymetry values similarly. The value of the better eye could be within the normal range, but comparison with the worse eye reveals inter-eye asymmetry [38]. The results of our study show significantly lower values of TCC in the worse eye (458 ±34 μm) than in the better eye (488 ±39 μm).

Galletti *et al*. stated that in nonkeratoconic eyes, the inter-eye asymmetry of thinnest pachymetry should be ≤ 12 μm. In our group it was 30 μm [38].

Normal corneas are mostly symmetric, which is why the possibility of detecting ectatic disease by looking for inter-eye differences is especially valuable [39].

Another factor which is widely reported as coexisting with KC is atopy. Almost 32% of patients in our study reported atopy. It is similar to results published by Kaya *et al*., who found in the examined group of 70 KC patients 33 patients with atopy [18]. Atopy may contribute to keratoconus but probably via eye rubbing associated with itching [40]. A significant relationship between the stronger dominant hand and the eye with more advanced keratoconus was proved in the McMonnies *et al*. study [41]. Although we did not check the dominant hand in our group, we found that the better eye was the left one in 41 cases – the right eye was the worse one in those cases, which correlates with data about hand dominance in the population – about 90% of people are right-handed [42].

Delay in proper diagnosis results in a decrease in the patient's visionrelated quality of life (VRQoL).

Best corrected visual acuity of the better eye is the foremost factor affecting VRQoL in patients with keratoconus [43]. In our study median BCVA of the better eye was 0.00 LogMAR but it has to be emphasized that 3 (4.1%) patients functioned with BCVA 0.4 LogMAR and below. This value was reported as significantly lowering all aspects of the patient's VRQoL, e.g. distance vision, social functioning, and mental health [44]. Similar results, for treshold visual acuity 20/40, were published by Kymes *et al*. [45].

Patients with BCVA 0.4 and below in the worse eye reported significantly lower general health scores [44]. In our study there were 25 (34.2%) patients with BCVA 0.4 and below in the worse eye.

There are limitations of this study. Our examined group is relatively small and we used only one set of diagnostic devices. It could be reasonable to validate our findings with other diagnostic systems.

CONCLUSIONS

We emphasize the importance of inter-eye asymmetry in KC screening and detection. We suggest suspecting KC during daily, routine practice in any case, even with normal BCVA and without pathological signs in basic ophthalmic examination, when: compound or mixed astigmatism is found with different manifest refraction values between eyes. Special vigilance should be exerted when inter-eye asymmetry in the amount of manifest astigmatism ≥ 1.0 D (absolute value) exists. Any inter-eye asymmetry in keratometry or pachymetry values should be interpreted likewise. In these cases keratoconus diagnosis should be considered and full cornea diagnostics performed. Fast diagnosis prevents patients from functioning with lowered quality of life.

We can consider atopy as an additional criterion in screening of KC.

We do not recommend analyzing any single value of any parameter derived from one eye as a cut-off criterion in KC diagnosis, e.g. there was a significant number of eyes with keratometry values within normal limits.

The incidence of keratoconus in patients below 18 years of age indicates that increased awareness of pediatric KC is needed. We postulate performing screening tests among adolescents to estimate the real prevalence of KC, which is probably underestimated.

DISCLOSURE

The authors declare no conflict of interest.

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