International Journal of Biomedicine 14(3) (2024) 428-434
http://dx.doi.org/10.21103/Article14(3)_OA6

ORIGINAL ARTICLE

Ophthalmology

INTERNATIONAL JOURNAL OF BIOMEDICINE

# Early Findings of Keratoconus, Clinical Management, and the Challenge in Stopping its Progression

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## Abstract

***Background*:**Keratoconus (KCN) is considered a bilateral corneal ectatic disorder characterized by cone-like steepening of the cornea and irregular stromal thinning, which can lead to decreased visual acuity. This study aimed to assess the prevalence and risk factors for the KCN development in Kosovo.

***Methods and Results***: This retrospective study was conducted in the Department of Ophthalmology at the University Clinical Center of Kosovo. The study included 131 respondents, with a total of 262 eyes. Keratometry basis parameters, such as flat keratometry (K1), and steep keratometry (K2), and maximal corneal curvature (Kmax) were determined. Corneal pachymetry was applied to measure the thickness of the cornea. Staging of KCN was done according to the adapted Amsler-Krumeich staging classification system (AK) for anterior data and corneal thickness (CT). Of 262 examined eyes, 240 (91.6%) were KCN eyes, 2 (0.8%) were suspect for KCN, and 20 (7.6%) were normal. KCN Stage 1 on the AK classification was predominant ($P$<0.001). KCN Stage 1 on the AK classification was predominant (52.9%) ($P$<0.001). We did not find a statistically significant difference between the mean age of patients and the KCN stage ($P$=0.235). The level of K1 was significantly lower in the non-KCN group (41.4±0.5 D) compared to KCN, and with increasing KCN stage, the K1 value significantly increased, reaching a maximum level in Stage 4 (53.3±4.3 D) ($P$=0.0000). A similar trend was typical for K2 and Kmax: from 44.7±5.1 D and 44.5±3.1 D, respectively, in the non-KCN group to 55.6±4.9 D and 65.3±8.3 D, respectively, in KCN Stage 4 ($P$=0.0000). Regarding the CT, the highest values were in the non-KCN group (504.0±27.6 µm), gradually decreasing from KCN Stage 1 to Stage 4 (466.2±36.0 µm vs. 378.6±95.0 µm, $P$=0.0000).

***Conclusion***: Screening programs that detect KCN at its earliest grade are the key to enabling early management, halting progression, and preserving the quality of visual acuity.**(International Journal of Biomedicine. 2024;14(3):428-434.)**

**Keywords:** keratoconus • keratometry • corneal thickness • corneal topography

**For citation:** Ismaili M. Early Findings of Keratoconus, Clinical Management, and the Challenge in Stopping its Progression. International Journal of Biomedicine. 2024;14(3):428-434. doi:10.21103/Article14(3)_OA6

## Abbreviations

**AT**, apical thickness; **CT**, corneal thickness; **CXL**, corneal collagen cross-linking; **Km**, mean central keratometry; **Kmax**, maximal corneal curvature.

## Introduction

Keratoconus is a Greek word (kerato: Cornea; konos: Cone), meaning cone-shaped protrusion of the cornea.[1] Keratoconus (KCN) is considered a bilateral corneal ectatic disorder characterized by cone-like steepening of the cornea and irregular stromal thinning, which can lead to decreased visual acuity.[2] Eye rubbing can be evoked by symptoms of allergy and dryness of the eye.[3,4] This disorder has been known in the middle of the 19th century.[5] The disease may begin as unilateral, but finally, the other eye becomes involved.[6] New imaging technology, including corneal tomography, has provided an early diagnosis of keratoconus, even before the decrease in visual quality.[7] Corneal tomography characterizes the elevation of the front and back corneal surfaces and reconstructs the pachymetric mapping, which has significantly enhanced the sensitivity and specificity for detecting corneal ectasia.[8,9] The symptoms and signs of keratoconus vary

depending on severity. In the early stages, it can mimic simple refractive errors with good visual acuity. As it progresses, there is a reduction in best corrected visual acuity (BCVA), distorted vision, and 'ghosting.'[10]

## Materials and Methods

This retrospective study was conducted in the Department of Ophthalmology at the University Clinical Center of Kosovo. The study included 131 respondents, with a total of 262 eyes. Age, gender, visual acuity (VA), and clinical signs and symptoms were recorded. Keratometry basis parameters, such as flat keratometry (K1), and steep keratometry (K2), and maximal corneal curvature (Kmax) were determined. Corneal pachymetry was applied to measure the thickness of the cornea. The diagnosis of KCN was confirmed if both eyes were suspect to KCN signs or if one eye was suspect and the contralateral was normal. Eye rubbing was the most frequent clinical sign of KCN in this study.

Data collection

Of all respondents included in this research, 26 eyes had bilateral KCN, and 26 had unilateral KCN but with different degrees of severity. Furthermore, asymmetric refractive error astigmatism was typical for the mild and moderate KCN forms, while the advanced form was characterized by progressive astigmatism.

Classifications were based on disease evolution, ocular signs, and corneal topography data. Staging of KCN was done according to the adapted Amsler-Krumeich staging classification system (AK) for anterior data and CT: Stage 1 (Km < 48 D), Stage 2 (Km <53 D, CT> 400 µm), Stage 3 (Km >53 D, CT>300 µm), and Stage 4 (Km >55 D, CT<300 µm).

Inclusion criteria: Respondents with evident signs of keratoconus in corneal maps (taken from Scheimpflug tomography), respondents with myopia or myopic astigmatism, respondents without eye disease, and those without eye surgery.

Exclusion criteria: Patients with glaucoma and previous corneal refractive surgery procedures, evidence of other anterior segment pathology including corneal opacities, corneal oedema, the respondents with staphyloma, severe cases of KCN, refusal to give consent.

Procedure

Data collected from respondents with KCN were retrospectively collected for 262 eyes examined over a period of three years. After the informed consent was obtained, the respondents underwent a complete ophthalmic examination, anterior segment evaluation by slit-lamp examination (localized stromal thinning, Fleischer's ring, Vogt's striae, conical protrusion), corneal tomographic by the Pentacam HR system (Oculus, Wetzlar, Germany), and retinoscopy (scissor reflex sign). Objective refraction included autorefraction, and subjective refraction included (Snellen's visual acuity chart). After testing the right eye, the acuity of the left eye was measured. The results were the same when the left eye was analyzed; thus, right-eye data were presented.

Statistical data analysis

Statistical analysis was performed using the statistical software package SPSS version 22.0 (SPSS Inc, Armonk, NY: IBM Corp). For the descriptive analysis, results are presented as mean (M) ± standard deviation (SD). Multiple comparisons were performed with one-way ANOVA and a post-hoc Tukey HSD test. Categorical variables were analyzed using the chi-square test. Spearman's rank correlation coefficient ($r_s$) was calculated to measure the strength and direction of the relationship between two variables. A probability value of $P<0.05$ was considered statistically significant.

## Results

All respondents included in the research were aged 13–37, with a mean age of 23.49±4.9 years. Only 10.7% of patients had a positive family history. Of the 262 examined eyes, 160 (61.1%) underwent surgical intervention: 67(41.9%) with the Epi-off technique and 93 (58.1%) with Epi-on (Table 1).

***Table 1.***

***General characteristics of study patients.***

| | | |
|---|---|---|
| Total patients | 131 | 100.0% |
| Gender | | |
| M | 78 | 59.5% |
| F | 53 | 40.5% |
| Age (year) | | |
| Mean ± SD | 23.4 ± 4.9 | |
| Range | 13 - 37 | |
| Residence | | |
| Urban | 68 | 51.9% |
| Rural | 63 | 48.1% |
| Positive family anamnesis | 14 | 10.7% |
| Total Eyes | 262 | 100.0% |
| Treated | 160 | 61.1% |
| Untreated | 102 | 38.9% |
| Technique | | |
| Epi -off | 67 | 41.9% |
| Epi-on | 93 | 58.1% |

Out of 76 patients with eye rubbing, 71 (93.4%) had keratoconic eyes, while out of 55 patients who did not have eye rubbing, 50 (90.9%) did not have keratoconic eyes. Patients with KCN were 1.174 times more at risk of having eye rubbing RR=1.174 (95% CI, 0.747 - 1.842) without significant difference ($P$=0.486). We did not obtain a substantial correlation between eye rubbing and KCN ($r_s$=0.046, 95% CI: -0.078 to 0.170).

Of 262 examined eyes, 240 (91.6%) were KCN eyes, 2 (0.8%) were suspect for KCN, and 20 (7.6%) were normal. We did not obtain a statistically significant difference in the prevalence of KCN according to gender and KCN stages

($P$>0.05) (Table 2). The right eye was without keratoconic manifestation in 6.9% of patients, without significant difference according to gender ($P$=0.739), while the left eye was without keratoconic manifestation in 8.4% of patients, without significant difference according to gender ($P$=0.999) (Table 2).

***Table 2.***

***KCN eyes according to gender.***

| | M | | F | | Total | | $P$-value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Total | 78 | 100.0 | 53 | 100.0 | 131 | 100.0 | |
| OD | | | | | | | |
| KCN | 71 | 91.0 | 50 | 94.3 | 121 | 92.4 | |
| non-KCN | 6 | 7.7 | 3 | 5.7 | 9 | 6.9 | 0.739 |
| Suspect | 1 | 1.3 | - | - | 1 | 0.8 | |
| OS | | | | | | | |
| KCN | 71 | 91.0 | 48 | 90.6 | 119 | 90.8 | |
| non-KCN | 7 | 9.0 | 4 | 7.5 | 11 | 8.4 | 0.999 |
| Suspect | - | - | 1 | 1.9 | 1 | 0.8 | |

*KCN - keratoconic eyes, non-KCN - non-keratoconic eyes, Suspect - keratoconic eyes*

KCN Stage 1 on the AK classification was predominant (52.9%) ($P$<0.001). We did not find a statistically significant difference between the mean age of patients and the KCN stage ($P$=0.235) (Table 3).

***Table 3.***

***The average age of patients according to the KCN stages.***

| Group | Age (year) | | | | |
|---|---|---|---|---|---|
| | N | Mean | SD | Min | Max |
| Non-keratoconic | 11 | 20.0 | 3.8 | 15 | 26 |
| Suspect | 1 | 23.0 | - | 23 | 23 |
| KCN | | | | | |
| Stage 1 | 63 | 23.3 | 4.1 | 15 | 35 |
| Stage 2 | 38 | 24.0 | 5.6 | 13 | 34 |
| Stage 3 | 8 | 26.8 | 6.7 | 20 | 37 |
| Stage 4 | 10 | 22.4 | 4.8 | 16 | 33 |
| Total | 131 | 23.4 | 4.9 | 13 | 37 |
| Statistics | $P$=0.235 | | | | |

Keratometry readings are presented in Table 4. The level of K1 was significantly lower in the non-KCN group (41.4±0.5 D) compared to KCN, and with increasing KCN stage, the K1 value significantly increased, reaching a maximum level in Stage 4 (53.3±4.3 D). A similar trend was typical for K2 and Kmax: from 44.7±5.1 D and 44.5±3.1 D, respectively, in the non-KCN group to 55.6±4.9 D and 65.3±8.3 D, respectively, in KCN Stage 4. Changes in CT were opposite: the highest values were in the non-KCN group (504.0±27.6 μm), gradually decreasing from KCN Stage 1 to Stage 4 (466.2±36.0 μm vs. 378.6±95.0 μm, $P$=0.0000). However, no significant differences between the non-KCN group and the suspected group were noted for all indicators, possibly due to the small size of the suspected group (Table 4).

***Table 4.***

***Keratometry parameters, VA, and CT among study groups.***

| Variable | Non-KCN n=20 (1) | Suspect n = 2 (2) | Stage 1 n=144 (3) | Stage 2 n = 64 (4) | Stage 3 n=15 (5) | Stage 4 n=17 (6) | Statistics |
|---|---|---|---|---|---|---|---|
| K1, D | 41.4±0.5 | 45.0±3.2 | 47.5±2.0 | 49.3±2.6 | 50.5±5.5 | 53.3±4.3 | F=47.4293 P=0.0000<br>$P_{1-2}$=0.4255, $P_{1-3}$=0.0000, $P_{1-4}$=0.0000, $P_{1-5}$=0.0000, $P_{1-6}$=0.0000, $P_{2-3}$=0.7567, $P_{2-4}$=0.1970, $P_{2-5}$=0.0592, $P_{2-6}$=0.0004, $P_{3-4}$=0.0001, $P_{3-5}$=0.0004, $P_{3-6}$=0.0000, $P_{4-5}$=0.5939, $P_{4-6}$=0.0000, $P_{5-6}$=0.0310 |
| K2, D | 44.7±5.1 | 47.1±2.8 | 45.4±2.3 | 48.8±3.5 | 52.5±5.8 | 55.6±4.9 | F=42.1507 P=0.0000<br>$P_{1-2}$=0.9288, $P_{1-3}$=0.9524, $P_{1-4}$=0.0000, $P_{1-5}$=0.0000, $P_{1-6}$=0.0000, $P_{2-3}$=0.9805, $P_{2-4}$=0.9812, $P_{2-5}$=0.2718, $P_{2-6}$=0.0104, $P_{3-4}$=0.0000, $P_{3-5}$=0.0000, $P_{3-6}$=0.0000, $P_{4-5}$=0.0021, $P_{4-6}$=0.0000, $P_{5-6}$=0.0993 |
| Kmax, D | 44.5±3.1 | 46.9±1.6 | 49.1±4.9 | 53.1±5.2 | 59.5±5.4 | 65.3±8.3 | F=46.5169 P=0.0000<br>$P_{1-2}$=0.9890, $P_{1-3}$=0.0031, $P_{1-4}$=0.0000, $P_{1-5}$=0.0000, $P_{1-6}$=0.0000, $P_{2-3}$=0.9911, $P_{2-4}$=0.5521, $P_{2-5}$=0.0168, $P_{2-6}$=0.0000, $P_{3-4}$=0.0000, $P_{3-5}$=0.0000, $P_{3-6}$=0.0000, $P_{4-5}$=0.0003, $P_{4-6}$=0.0000, $P_{5-6}$=0.0209 |
| VA(sc) | 0.77±0.27 | 0.95±0.07 | 0.47±0.30 | 0.32±0.25 | 0.24±0.26 | 0.19±0.22 | F=13.8236 P=0.0000<br>$P_{1-2}$=0.9533, $P_{1-3}$=0.0001, $P_{1-4}$=0.0000, $P_{1-5}$=0.0000, $P_{1-6}$=0.0000, $P_{2-3}$=0.1542, $P_{2-4}$=0.0225, $P_{2-5}$=0.0106, $P_{2-6}$=0.0043, $P_{3-4}$=0.0054, $P_{3-5}$=0.0310, $P_{3-6}$=0.0016, $P_{4-5}$=0.91773, $P_{4-6}$=0.5277, $P_{5-6}$=0.9959 |
| CT, μm | 504.0±27.6 | 499.0±48.1 | 466.2±36.0 | 446.9±31.7 | 392.4±114.2 | 378.6±95.0 | F=20/9634 P=0.0000<br>$P_{1-2}$=0.9999, $P_{1-3}$=0.0142, $P_{1-4}$=0.0001, $P_{1-5}$=0.0000, $P_{1-6}$=0.0000, $P_{2-3}$=0.9307, $P_{2-4}$=0.6593, $P_{2-5}$=0.0408, $P_{2-6}$=0.0119, $P_{3-4}$=0.0847, $P_{3-5}$=0.0000, $P_{3-6}$=0.0000, $P_{4-5}$=0.0014, $P_{4-6}$=0.0000, $P_{5-6}$=0.9655 |

## Discussion

KCN usually appears at puberty and progresses until the 30s and 40s. Its progression rate varies between individuals but is generally higher in younger patients.[11] In our research, men were significantly more affected than women (59.5% vs. 40.5%, *P*=0.029). Some authors have found a higher prevalence of KCN in men, with values ranging from 53% to 62%,[12-16] similar to our study. Others found a dominance in women, from 53% to 66%.[12,14,17] A study by Hashemi et al. in the Middle East (Tehran, Iran) found that the overall prevalence rate of KCN was 3.3%.[14] Meanwhile, the prevalence rate was 0.8% in the 14–29-year-old group and 7.5% in those over 60.

The KCN incidence is especially high at the age of 20 to 30, but it progresses up to the age of 35. We also found this in our study, where the patients had KCN progression up to 37 years.

Our results found a greater prevalence of KCN in urban areas than in rural ones, given that urban and rural are progressively interconnected. However, according to Hashemi H, a high prevalence of KCN in Iran was found in rural areas.[4] Our results are similar to those found in the urban area of northern Iran, where the prevalence of KCN was 0.76%, but in a higher percentage.[18] According to the study by Mohaghegh et al.,[19] the likelihood of the incidence of KCN in patients with a positive family history was 20 times higher compared to patients who had a negative family history. According to Wang Y et al.,[20] the probability of KCN is 15 to 67 times higher in patients who have a positive family history.

Although the most common type of KCN is sporadic, our research found a positive family history of the illness in 10.7% of cases, similar to other research studies.[21] Of the environmental causes most frequent in the etiology of KCN was rubbing the eyes (93.4% of all respondents). Other studies also showed that eye rubbing is associated with the progress of keratoconus, even assuming whether gentle friction or vigorous knuckle-grinding rubbing impacts the progression of the disease.[22]

Other studies also found that chronic eye rubbing is linked with the development of keratoconus.[5] Some of these studies found a history of eye irritation, but others showed that eye rubbing could be caused by allergy and dry eye symptoms.[23,24] McGhee [25] found that 40% of patients with KCN had constant eye rubbing. According to Rabinowitz's study,[21] eye rubbing was found in 83% of 218 KCN patients, similar to ours. Like our study results, eye rubbing was more often related to other risk factors in Saudi Arabia studies.[26,27] Asymmetric KCN was found in some studies to be associated with the most vigorous eye rubbing.[28] Some research data show that KC develops after 14 months in case of repeated strong eye rubbing.[29] Contrary to our research results, Owens and Gamble[30] and Millodot et al.[31] found no significant association between KCN and eye friction.

There are several treatment methods available. The selection of the appropriate treatment depends on the patient's cornea parameters, the KCN progression, and the decrease in VA. KCN is the most frequent cause of ectasia, and many clinical studies have proven that corneal collagen cross-linking (CXL) is important for halting the progression of KCN.[22,33] Based on the Dresden protocol, successful cornea crosslinking requires a minimal 400 μm corneal thickness.[34-36] CXL was described for the first time by Wollensak et al.[34] in 2003, a corneal transplant was applied until the advent of CXL. KCN surgical treatment does not eliminate the need for specialized contact lenses because although they are more practical after surgery, they do not improve optimal vision.[36] In our study, we used the treatment CXL according to Dresden protocol, epithelial-off and epithelial-on, in patients with KCN in the early stage to prevent further progression since this is a non-invasive surgical treatment.[32,34,37] Although this method does not reverse the thinning that has already occurred, those in an early stage of KCN are potential patients, as it can prevent further progression since the risk of progression is higher at younger ages.[38,39] According to experimental and clinical findings, CXL effectiveness and the number of patients that needed to undergo the procedure have increased significantly in the last 10 years.[40] In our study, based on the clinical course of the disease as well as other risk factors, all respondents with KCN were selected in the surgically treated group (61.1%) and untreated group (38.9%).The CXL epi-on technique is more advantageous than the CXL epi-off technique, as it preserves the CT and VA and eases the postoperative pain and infection risk. However, its disadvantage is that it might fail and require further treatment.[41]

Belin ABCD represents an advanced practical staging system due to recent challenges regarding diagnosing and treating KCN.[41] In our study, KCN Stage 1 on the Amsler-Krumeich (AK) classification was predominant (*P*<0.001).

Our results showed that out of 262 eyes examined, 0.8% were suspected of KCN. The cornea's tomographic assessment revealed that these changes also manifested in the other eye. Knowing that KCN is bilateral but progresses asymmetrically, patients have frequent dioptric changes depending on the stages of the disease, in which case patients experience decreased VA changes that cannot be corrected. For the diagnosis of subclinical KCN, only the topography of the front surface is not enough, and it requires the measurement of the anterior and posterior cornea.

Based on other scientific research, the frequency of suspected KCN eyes was very low since the patients were diagnosed in the early stages of KCN, like in our study.[42-44] All patients included in the study had KCN in one or both eyes. The right eye was without keratoconic manifestation in 9(6.9%) patients, without significant difference according to gender (*P*=0.739), while the left eye was without keratoconic manifestation in 11(8.4%) patients without significant difference according to gender (*P*=0.999).

Regarding the association between the average age of the patients and the KCN stage, it was found that 22.4% of the youngest respondents were in the advanced stage (*P*=0.235). Therefore, this was a challenge for immediate treatment and efficient progression stopping. In our study, we did not obtain a statistically significant difference between the average age of patients and KCN and its stages.

Our keratometry readings found that the values of K1, K2, and the maximal corneal curvature values (Kmax) were

the lowest in the non-keratoconic and suspect eyes compared to all KCN stages ($P$<0.001).

Regarding the CT, the highest values were in the non-KCN group (504.0±27.6 μm), gradually decreasing from KCN Stage 1 to Stage 4 (466.2±36.0 μm vs. 378.6±95.0 μm, $P$=0.0000).

Moreover, progression of KCN can occur with no change of Kmax, as was the case in the study by Rubinfeld and Mahmoud, who found such progression in 29 eyes.[45,46] Kmax is very often used as an indicator of ectatic progression. An increased Kmax was found in several studies but did not show an appropriate cut-off of progression.[47] According to a study by Choi et al.,[48] K1, K2, and Km rates are significantly different in non-progressing and progressing keratoconic eyes, contributing to detecting progression. We must emphasize that early ecstatic alterations are apparent on the anterior surface, usually after having affected the posterior corneal surface.[49] Given that progressive corneal steepening defines KCN, endothelial damage is inevitable due to thin corneas. Therefore, suspect keratoconic eyes can be identified at their early stage [50,51] by measuring the thickness of the cornea. Our results confirm this, too: The thickness of the cornea was significantly lower in Stage 4. In the current study, uncorrected VA was significantly decreased in Stage 4 compared to Stage 1 ($P$<0.001). VA is not a reliable variable that correlates well with KCN progression, particularly if the patient wears contact lenses or spectacles. [51,52]

**In conclusion**, screening programs that detect KCN at its earliest grade are the key to enabling early management, halting progression, and preserving the quality of visual acuity.

## Ethical Considerations

The study was conducted in accordance with ethical principles of the Declaration of Helsinki (2000; revised October 2013, Fortaleza, Brazil) and was approved by the Ethics Committee at the University of Prishtina (Ref. Nr.12072).

## Competing Interests

The author declares that there is no conflict of interest.

## Acknowledgments

The author would like to thank colleagues and hospital staff for their constant support and guidance throughout the study.

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