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Original research

Demographic profile, clinical, and topographic characteristics of keratoconus patients attending at a tertiary eye center

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Abstract

Purpose: To evaluate the demographic profile, clinical, and topographic characteristics of keratoconus (KCN) patients attending at a subspecialty eye hospital in Tehran, Iran.

Methods: In this cross-sectional study, all patients who attended Noor Eye Hospital between March 2011 and March 2017 and had a diagnosis of KCN were identified, and the required number of patients was randomly selected. The following data were extracted from patient's records: age, sex, visual acuity, refraction, keratometry, pachymetry, and treatment procedures. The data of KCN laterality, severity, morphology, and cone location were also extracted by analyzing the corneal imaging maps.

Results: The records of 1080 eyes of 540 patients were evaluated. The mean age of the participants was 31.04 ± 8.54 years (range, 13–63 years), and 69.3% of the patients were male. The highest and lowest frequency of KCN was seen in the age group 20–30 years and above 50 years, respectively. Bilateral KCN was detected in 93.3% [95% confidence interval (CI): 91.68–94.75] of the subjects. 43.7% (95%CI: 32.88–54.48), 55.6% (95%CI: 44.73–66.38), and 0.8% (95%CI: 0.75–0.78) of the cases had nipple, oval, and globus cones, respectively. The cone was central in 52.1% (95%CI: 41.10–63.11), paracentral in 43.6% (95%CI: 36.13–51.04), and peripheral in 4.3% (95%CI: 00.76–7.86) of the cases. The frequency percentage of KCN according to severity was 15.2% (95%CI: 13.09–17.46), 56.4% (95%CI: 53.37–59.37), and 28.4% (95%CI: 25.75–31.21) for mild, moderate, and severe KCN, respectively. Among different parameters, only cone location had a significant association with age as the frequency of paracentral and peripheral cones increased with ageing ($P = 0.002$).

Conclusions: The mean age of KCN patients in our study was higher than similar studies in other Asian countries. KCN was bilateral in most cases with an oval morphology and central cone location. Most of the patients had moderate to severe KCN.

Keywords: Keratoconus; Demographic profile; Clinical characteristics; Subspecialty hospital; Iran

Introduction

Keratoconus (KCN) is an asymmetrical and progressive corneal ectasia that leads to visual impairment via causing irregular astigmatism, myopia, higher order aberrations (HOAs), and corneal scar.[1] Since young people comprise the majority of the patients with KCN, its adverse effects on the visual system has a major impact on the quality of life of the

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patients. Therefore, detection and effective management of this disease are of utmost importance.[2,3] The prevalence of KCN varies in different countries, indicating the possible role of genetics in its etiology.[4,5] The prevalence of KCN in Asian populations is about 4 times higher than other ethnic populations,[6] with the highest prevalence reported in the Mediterranean region and Middle East, including Iran.[7–9]

Knowledge of the demographic profile and clinical and topographic characteristics of KCN patients in different populations is important from different aspects. Knowledge of the relationship between demographic factors (including age and sex) and KCN can provide a clearer picture of the nature of this disease and its etiology.[10] KCN clinical and topographic indices are very important in the process of diagnosis, since this disease is mainly detected through assessment of these indices and their changes compared to the normal status.[11,12] Therefore, awareness of the topographic and clinical characteristics of KCN helps to prepare a standard diagnostic protocol, which not only assists in clinical diagnosis of this disease, but also contributes to organizing a proper screening program for early detection.[13] Clinical and topographic indices are also important in the management of KCN, as the effect of treatment procedures is determined through evaluation of the resulting changes in these indices.[14] On the other hand, the choice and sequence of treatment procedures are a function of these indices, as well.[14] For example, by knowing the severity status of KCN in any population, one can predict the percentage of patients requiring more complex and costly therapeutic measures such as corneal cross-linking, intrastromal corneal ring segments (ISCRS), or corneal transplantation.[15,16] This is important for planning health policy strategies and also for assessing the economic burden of the disease and budget allocation.[17]

Considering the marked relationship between KCN and ethnicity,[7] clinical/topographic indices of KCN in each population are unique to the population, and the clinical characteristics in different ethnic populations cannot be replaced or adapted to each other. Considering the importance of the knowledge of demographic profile and clinical/topographic indices of KCN, different studies have evaluated these parameters in different ethnic populations.[18–24] Some epidemiological studies have also been carried out in this field in Iran,[8,25–27] but the aim of these studies was mainly to determine the prevalence of the KCN. Therefore, the clinical characteristics and their relationships have received less attention. Also, some important topographic features of KCN like cone location have not been evaluated in these studies. Therefore, the aim of the present study was to comprehensively investigate the demographic profile and clinical and topographic characteristics of KCN patients attending a tertiary eye center in Iran.

Methods

Study setting and sampling

In this cross-sectional study, all patients who attended Noor Eye Hospital between March 2011 and March 2017 and had a definite diagnosis of KCN were identified using the computerized hospital record system. After preparing a sampling frame, the required number of patients was randomly selected according to the estimated sample size using the random sample of cases command of the Statistical Package for the Social Sciences (SPSS) software. To calculate the required sample size for this study, the following formula for calculating the sample size of descriptive studies was used:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}}\delta^2}{d^2}$$

To calculate the required sample size according to this formula, the mean keratometry reading was considered the major quantitative diagnostic index of the KCN. By considering 5.91 the standard deviation of this index according to one of the previous studies (which reported the keratometry distribution in a large sample of KCN patients), $\alpha = 0.05$ and $d = 0.50$ diopter (D), the final sample sized was estimated at 540 patients.

Data extraction and definitions

After sampling, the patients' records were investigated. The records contained a comprehensive eye examination, including the measurement of visual acuity and manifest refraction (objective refraction with an auto refractometer and subjective refraction), slit-lamp biomicroscopy, fundus examination, and corneal imaging by the Pentacam rotating Scheimpflug imaging system (Pentacam HR, Oculus; Optikgeräte GmbH, Wetzlar, Germany). In all patients, a diagnosis of KCN was made by an ophthalmologist based on the results of slit-lamp biomicroscopy (including corneal stromal thinning, cone-shaped corneal protrusion in the apical region, Fleischer ring, Vogt striae, and corneal scar) and/or corneal topographic and pachymetric assessments.

The following items were considered in cornel images for a diagnosis of KCN: the presence of a focal steep area as a hot point in the corneal topographic map (corresponding keratometry values > 45.00 D), a central keratometry reading more than 47.2 D, inferior/superior corneal power asymmetry more than 1.4, a slope of more than 21° on asymmetric astigmatic axes, and corneal thickness at the apex of the cone approximately 30 microns thinner than the corresponding distance above the pupil center.[28] A corneal specialist confirmed the diagnosis of KCN in all records.

The exclusion criteria were a history of any ocular surgery (except for KCN), any significant ocular disease except KCN, and any associated systemic disease or syndrome. If a record lacked the required data or had evidence of the exclusion criteria, the subject was excluded from the study and replaced with another individual using the same sampling protocol.

After primary evaluation of patient's records, the following data were extracted in the next stage: age, sex, best corrected distance visual acuity (BCVA), subjective refraction (sphere and cylinder), minimum (min), maximum (max), and mean keratometry readings of the anterior corneal surface according to the Pentacam's axial curvature map, central corneal

thickness (CCT) and thickness of the thinnest point of cornea (TPT) according to the Pentacam's thickness map, and treatment procedures (corneal collagen cross-linking, ISCRS, and keratoplasty). The data of the age, visual acuity, refraction, keratometry, pachymetry, and topographic indices obtained on the first patient's visit were used for analysis.

If a diagnosis of KCN was confirmed in both eyes and recorded in the patient's record, the patient was considered a case of bilateral KCN, and if a diagnosis of KCN was confirmed in one eye, the patient was considered a case of unilateral KCN. Moreover, the criteria proposed by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study[18] was used for categorization of KCN severity according to max keratometry (max-K). According to these criteria, KCN was classified to mild, moderate, and severe as follows; mild: a max-K value less than 45 D, moderate: a max-K value between 45 and 52 D, severe: a max-K value more than 52 D.

The morphologic pattern of KCN was classified to three types of nipple, oval, and globus cones based on the cone size and displacement of the cone apex according to the tangential corneal topography map as follows[29]; the nipple type: cone size $\leq$5 mm with a steep curvature and the apical center usually central or paracentral with an inferior nasal displacement, oval type: the cone size is 5–6 mm with an oval shape usually with an inferior temporal displacement, the globus type: a cone size of more than 6 mm that involves more than 70% of the cornea.

The location of the cone was determined based on the location of the point with the highest elevation on the anterior elevation map using the best-fit sphere as 1) central: highest elevation in the central 3 mm zone, 2) paracentral: highest elevation in the paracentral 3–5 mm zone and 3) peripheral: highest elevation outside the central 5 mm zone.[29]

The study was approved by the Ethics Committee of Iran University of Medical Sciences and the tenets of the Declaration of Helsinki were followed in conducting the study.

Statistical analysis

SPSS software version 20 was used for data analysis. Descriptive statistics are presented as frequency percentage for qualitative variables and mean and standard deviation for quantitative variables. The normality of the data was checked by the Kolmogorov-Smirnov test. According to the normality status of the data, independent Samples T test, Mann-Whitney test, One-Way Analysis of Variance (ANOVA), and Kruskal-Wallis test were used for comparison of quantitative variables between different age and sex groups. Chi square test was applied to compare the ratios of qualitative variables between different age and sex groups. The generalized estimation equation (GEE) method was used to analyze the results of both eyes. A P value of less than 0.05 was considered statistically significant.

Results

In this study, the records of 1080 eyes of 540 KCN patients were evaluated. 16 eyes of 8 patients were excluded during initial sampling, and 16 eyes of 8 other patients were replaced. The mean age of the participants was 31.04 $\pm$ 8.54 years (range, 13–63 years), and 69.3% of the patients were male. Table 1 presents the frequency distribution of KCN according to age and sex. According to Table 1, the highest and lowest frequency of KCN was seen in the age group 20–30 years and above 50 years, respectively. Chi square showed no significant association between age and sex ($P = 0.136$).

Bilateral KCN was detected in 93.3% [95% confidence interval (CI): 91.68–94.75] of the subjects. Regarding KCN morphology, 43.7% (95%CI: 32.88–54.48), 55.6% (95%CI: 44.73–66.38), and 0.8% (95%CI: 0.75–0.78) of the cases had nipple, oval, and globus cones, respectively.

The cone was central in 52.1% (95%CI: 41.10–63.11), paracentral in 43.6% (95%CI: 36.13–51.04), and peripheral in 4.3% (95%CI: 00.76–7.86) of the cases. The frequency percentage of KCN according to severity was 15.2% (95%CI: 13.09–17.46), 56.4% (95%CI: 53.37–59.37), and 28.4% (95%CI: 25.75–31.21) for mild, moderate, and severe KCN, respectively.

As for the management of KCN, 10.4% (95%CI: 2.71–18.13) of the patients underwent collagen cross-linking, 29.1% (95%CI: 16.76–41.47) underwent ISCRS implantation, 5.1% (95%CI: 4.24–5.99) underwent both cross-linking and ring implantation, and 10.1% (95%CI: 1.03–29.63) received keratoplasty.

Table 2 presents the mean of quantitative parameters, including BCVA, sphere, and cylinder of subjective refraction, mean K, min keratometry (min-K), max-K, CCT, and TPT according to age and sex. According to Table 2, only max-K showed statistically significant difference between different age groups ($P = 0.04$). However, this difference does not appear to be clinically significant. There was no statistically significant difference in other parameters between different age and sex groups (P values > 0.05).

Chi square was applied to determine the association of qualitative parameters of KCN, including laterality, morphology, cone location, and severity with age and sex. The results showed a significant difference in the distribution of cone location in different age groups ($P = 0.002$). Table 3 shows the frequency distribution of KCN according to cone location in different age groups. According to Table 3, the

Table 1
The frequency distribution of keratoconus (KCN) eyes according to age and sex.

	Frequency	
	Number	%
Age	1080	100
<=20	74	6.9
20–30	526	48.7
30–40	334	30.9
40–50	108	10.0
>50	38	3.5
Sex	1080	100
Male	748	69.3
Female	332	30.7

Table 2
Clinical characteristics of keratoconus (KCN) patients according to age and sex.

		BCVA (logMAR)	Sphere (diopter)	Cylinder (diopter)	Mean K (diopter)	Max-K (diopter)	Min-K (diopter)	CCT (micron)	TPT (micron)
		Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
Age	<=20	0.34 (0.27–0.42)	−2.04 (−2.58−1.50)	−3.25 (−3.76−2.75)	48.14 (47.15–49.13)	50.03 (48.94–51.12)	46.25 (45.29–47.22)	472.09 (458.27–485.91)	458.16 (443.59–472.73)
	20–30	0.28 (0.25–0.32)	−2.38 (−2.71−2.06)	−2.84 (−3.05−2.63)	47.89 (47.38–48.40)	49.61 (49.03–50.18)	46.18 (45.71–46.64)	476.75 (471.68–481.82)	455.83 (450.36–461.29)
	30–40	0.26 (0.22–0.29)	−2.58 (−3.07−2.08)	−2.85 (−3.11−2.58)	47.43 (46.84–48.02)	49.02 (48.37–49.67)	45.85 (45.29–46.41)	478.72 (472.23–485.20)	456.76 (449.75–463.77)
	40–50	0.37 (0.30–0.44)	−2.92 (−3.88−1.96)	−3.20 (−3.67−2.74)	48.43 (47.37–49.49)	50.26 (49.08–51.44)	46.61 (45.62–47.60)	479.18 (467.71–490.64)	459.23 (447.14–471.31)
	>50	0.41 (0.28–0.55)	−1.74 (−2.75−0.73)	−3.20 (−3.79−2.62)	49.83 (48.11–51.56)	51.80 (49.82–53.78)	47.86 (46.27–49.45)	474.94 (458.31–491.56)	450.09 (434.01–466.17)
	P-value[a]	0.06	0.20	0.18	0.07	0.04	0.15	0.93	0.86
Sex	Male	0.29 (0.27–0.32)	−2.36 (−2.65−2.08)	−2.92 (−3.10−2.74)	47.66 (47.26–48.05)	49.34 (48.9–49.78)	45.97 (45.60–46.33)	479.11 (474.96–483.26)	457.31 (452.9–461.71)
	Female	0.29 (0.26–0.33)	−2.65 (−3.12−2.17)	−2.93 (−3.18−2.67)	48.42 (47.77–49.08)	50.18 (49.44–50.92)	46.67 (46.07–47.27)	472.98 (466.18–479.78)	454.5 (447.05–461.95)
	P -value[b]	0.81	0.18	0.99	0.09	0.08	0.12	0.08	0.73

BCVA: Best corrected distance visual acuity; MAR: Minimum angle of resolution; Max-k: Maximum Keratometry; Min-k: Minimum Keratometry; CCT: Central corneal thickness; TPT: Thinnest point thickness; CI: Confidence interval.

[a] *P*-value for age.

[b] *P*-value for sex.

frequency of the central type was significantly higher than the paracentral type in the age group below 20 years, and there were no peripheral cases in this age group. The frequency of the paracentral and peripheral types increased considerably with an increase in age. Other qualitative variables had no significant association with age and sex (*P* values > 0.05).

Discussion

In the present study, we evaluated the demographic profile and clinical and topographic characteristics of KCN in patients attending a tertiary referral eye care center in Iran. The mean age of the participants was 31 years in our study. According to previous studies, the mean age of the KCN patients (on the first visit) was 23–28 years in European countries,[5,6,21,30–32] 25–39 years in the USA,[33,34] and 18–24 years in Asian countries.[35–39] Therefore, the mean age of the patients in our study was higher than other Asian and even European patients. The frequency distribution of the patients in different age groups showed that the majority of the patients (48.7%) presented to the clinic when they were 20–30 years old, which is consistent with the results of previous studies reporting that KCN is prevalent in the 2nd and 3rd decades of life and is less common in older patients.[4,21,39] An important finding of the present study was the high frequency of patients above 30 years, comprising 44.5% of the whole patients, which can explain the higher mean age of patients in this study compared to other Asian studies. The possible reasons may be different etiologic factors, lack of early detection, and delayed presentation for medical care. Therefore, it should be kept in mind that Iranian KCN patients may present at older ages than expected.

Most of the KCN patients in our study were male (about 70%), which is in line with the results of most studies in this regard.[40] Although there has been a report of lack of gender difference in the distribution of KCN[8,26,34,41] and even a higher prevalence in women,[42] most recent studies have reported higher prevalence of KCN in males.[4,19,30,39,43] However, the reason for the gender difference in the distribution of KCN is not clear, although there are hypotheses involving the role of sex hormones.[21] A higher anatomical or physiological susceptibility or more environmental exposures can also contribute to the higher prevalence of KCN in men.[44,45] The possibility of clinical bias due to higher severity of the disease in men (resulting in more visits) should be also considered. Nonetheless, the gender difference in the distribution of KCN, regardless of its reason, is of clinical importance. It should be mentioned that the higher frequency of male patients in our study cannot be due to the higher severity of the disease because our findings showed no significant association between sex and disease severity.

About 93% of the patients had bilateral KCN, and only 7% had unilateral KCN. The frequency percentage of unilateral KCN in different clinical studies ranges from 4 to 18%, and studies conducted in Asian countries have mostly reported a lower frequency percentage of unilateral KCN (4–12%) compared to studies conducted in other ethnic populations

Table 3
The frequency distribution of keratoconus (KCN) according to cone location in different age groups.

Cone location	Age Number (percent)					Total
	<=20	20–30	30–40	40–50	>50	
Central	49 (9%)	282 (51.8%)	144 (26.50%)	48 (8.8%)	21 (3.9%)	544 (100%)
Paracentral	24 (5.3%)	209 (45.9%)	161 (35.40%)	49 (10.8%)	12 (2.6%)	455 (100%)
Peripheral	0 (0%)	18 (40%)	16 (35.50%)	7 (15.6%)	4 (8.9%)	45 (100%)

(13–18%),[20,33–38] which is consistent with the results of the present study. However, it should be noted that this comparison is based on clinical studies that usually cover more severe and established cases of the disease, while population-based studies have reported a higher percentage of unilateral KCN, even in Asian populations.[25] Another possible reason for the low frequency of unilateral KCN in the present study may be the high mean age of the patients because an increase in age is associated with increased odds of the involvement of both eyes.[39]

Another interesting feature of the present study was evaluation of the morphologic pattern of KCN. According to our findings, the highest morphologic frequency was related to the oval pattern (55.6%), followed by the nipple (43.7%), and globus pattern (less than 1%). In the CLEK study, which is one of the well-known studies in KCN, the frequency percentage of oval, nipple, and globus types was 28.7%, 44.3%, and 6.7%, respectively.[46] A comparison of our results with the results of the CLEK study shows that the dominant morphologic pattern in both studies was the oval type. On the other hand, the frequency of the nipple type was markedly higher and the frequency of the globus type was considerably lower when compared to the CLEK study. Similar to our results, Hashemi et al., also reported a high prevalence of nipple and oval cones in another study in Iran.[25] This finding, apart from its diagnostic importance, can be considered a positive point in terms of KCN management in the Iranian population because management of the nipple and oval types are far easier than management of the globus type.[47]

We also evaluated the severity of KCN in our study. According to the results, 15.2%, 56.4%, and 28.4% of the patients had mild, moderate, and severe KCN, respectively. The frequency of moderate and severe KCN in our study was similar to its frequency in Asian populations but higher than in other ethnic populations, especially European populations,[4–6,18,22,35,37,48] which confirms that patients with a more advanced disease seek management in Asian countries.

We found no significant association between the severity of KCN with age and sex. Most previous studies have reported similar results regarding the association of KCN severity with sex,[22,39,44] but there are controversies regarding its association with age. Some studies have reported a higher frequency of severe KCN in younger age groups[23,39] and have attributed this finding to the slower progression of the disease in older people; therefore, these people seek medical care less than younger patients. Similar to our results, other studies have found no relationship between age and KCN severity.[4,22] According to the results of these studies, severe KCN cases may present at any age.

Regarding the cone location, most cases in our study had a central (52.1%) or paracentral cone (43.6%), and the peripheral type had a low frequency (4.3%). An interesting finding of our study was a marked association between the cone location and age as a significant increase in the frequency of paracentral and peripheral cone types with ageing. We believe that in addition to diagnostic significance, this finding is important in the management of KCN, as the cone location is an important determinant in contact lens management of KCN.[49,50] The fitting of traditional contact lenses in peripheral cones is challenging due to poor centration, and special contact lenses may be required in this setting.[51] The cone location also affects the results of corneal cross-linking.[52] According to a study by Greenstein et al., cross-linking has a lower efficacy in the peripheral cones as compared to the centrally-located cones.[52] Considering therapeutic limitations in peripheral cones, it can be assumed that KCN management in older patients may be more challenging and costly despite the lower frequency of the disease in this age group. This point should receive attention considering the high frequency of KCN patients in older age groups in this study.

We also studied the frequency of different treatment procedures in KCN patients. The frequency of keratoplasty was reported 10–15% in previous studies,[40] which is consistent with our results. An interesting finding was the considerable frequency of the use of ISCRS (more than 35% of the patients), which was much higher than similar studies.[21,22] In developed countries, KCN is mostly managed by contact lenses, which are considered the most common and most successful treatment option for improvement of visual acuity.[40,46] One of the main indications of ISCRS is contact lens intolerance or lack of success.[53] We believe that the high frequency of the use of ISCRS in our study is due to poor contact lens practice. It should be mentioned that contact lens practice in Iran has some serious limitations since many patients are not familiar with this treatment option, practitioners do not have access to various contact lenses and trial sets (due to limitations in availability or high costs), and these lenses are not covered by insurance. As a result, the ophthalmologist has no choice but to implant ISCRS if the patient does not achieve a satisfactory vision with spectacles. Therefore, we recommend that contact lens management should receive more attention and support in Iran.

The study setting was one of the limitations of this study because we only evaluated KCN patients attending one tertiary

eye care center, which increases the odds of selection bias and decreases the generalizability of the results. Therefore, further population-based studies are warranted in this regard. In conclusion, the mean age of KCN patients in our study was higher than similar studies in other Asian countries. Similar to previous studies, most of the patients were male. KCN was bilateral in most cases with an oval morphology and central cone location. Most of the patients had moderate to severe KCN. Among different clinical and topographic parameters, only cone location had a significant association with age as the frequency of paracentral and peripheral cones increased significantly with ageing. Other clinical and topographic parameters showed no significant association with age and sex.

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