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· Clinical Research ·

Topographic factors associated with anterior chamber angle narrowing in patients with keratoconus

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Abstract
● **AIM:** To identify topographic determinants of the anterior chamber angle (ACA) in patients with keratoconus (KCN).
● **METHODS:** Four hundred and ten eyes of 294 patients with KCN were recruited for this study. First, complete ocular examinations were performed for all patients, including visual acuity measurement, refraction, and slit-lamp biomicroscopy. Then, all participants underwent corneal imaging by the Oculus Pentacam HR.
● **RESULTS:** The mean age of the participants was 32.40±8.52y (15-60y) and 69.5% of them were male. The mean ACA was 38.47°±5.75° (range: 14.40° to 56.50°) in the whole sample, 38.24°±6.00° in males, and 38.98°±5.11° in females (P=0.447). The mean ACA was significantly different among different groups of cone morphology, as patients with nipple cones showed the lowest mean ACA. Moreover, there were statistically significant differences in the mean ACA among different groups of cone locations, with patients having central cones exhibiting the lowest mean ACA (P<0.001). Anterior and posterior Q values were significantly, directly correlated with ACA (anterior Q: r=0.122, P=0.014, posterior Q: r=0.192, P<0.001).
● **CONCLUSION:** This study provides critical insights into the risk factors for ACA narrowing in KCN patients, which is essential for planning intraocular surgeries. Patients with nipple and central cones exhibited the most significant ACA narrowing. Additionally, more negative Q-values are associated with increased ACA narrowing, highlighting the need for targeted diagnostic and therapeutic strategies.
● **KEYWORDS:** keratoconus; anterior chamber angle; cone morphology; cone location
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INTRODUCTION

Keratoconus (KCN) is a bilateral and asymmetric corneal ectatic disease characterized by progressive stromal thinning and central and paracentral steepening, leading to myopia, and irregular astigmatism[1-2]. The reported prevalence of KCN can range from as low as 0.3 to as high as 2300 cases per 100 000 individuals, while the annual incidence can vary from 1.3 to 32.3 cases per 100 000 people[3]. This corneal disease exhibits a notably higher prevalence in certain geographic regions, such as South Asia and the Middle East[4]. Although KCN may be initially asymptomatic, it can greatly affect a patient's visual acuity and overall quality of life as the disease progresses[5]. KCN is a significant contributor to visual impairment and is a leading reason for corneal transplantation among younger individuals[6].

Previously, KCN was thought of as a localized corneal disease with only central corneal changes taken into account, while recent *in vivo* and histopathological studies have indicated peripheral structural changes of the cornea in patients with KCN[1,7]. It is now suggested that KCN is a pancorneal pathology that is not solely limited to the cone region[8-9]. Smolek[10] proposed that peripheral corneal flattening in KCN serves as a compensating mechanism for the increase in the central curvature. This peripheral flattening can affect the cornea-uvea relationship and potentially results in the anterior chamber angle (ACA) narrowing.

ACA is a vital anatomical structure, housing the trabecular meshwork that facilitates the drainage of aqueous humor, thereby playing a significant role in regulating intraocular pressure (IOP)[11]. A narrow ACA is identified as a key risk factor for the development of angle-closure glaucoma[12]. The evaluation of the ACA is therefore regarded as a crucial component of the ophthalmic examination for diagnosing individuals with or at risk of elevated IOP or angle-closure glaucoma[11].

Limited studies have investigated the ACA in patients with KCN, and reported conflicting results[13-17]. Moreover, previous studies only presented the average ACA within their samples and conducted comparisons with a normal control group. Therefore, it is unclear which groups of KCN patients are more prone to ACA narrowing and whether ACA narrowing is affected by the pattern of corneal topographic changes in these patients. Corneal topographic characteristics are of special importance in the work-up of KCN patients and are specifically taken into consideration by the clinicians[18]. So, identifying topographic predictors of ACA can help to identify KCN patients who are at an increased risk of ACA closure. This issue is especially important in terms of intraocular surgeries such as phakic intraocular lens implantation, penetrating keratoplasty, and cataract surgery which are commonly performed in KCN patients. Notably, surgeons must be mindful of the increased risk of ACA closure in these vulnerable cases when preparing surgical incisions[19]. This information can also help to better understand the mechanism of peripheral corneal and ACA changes in KCN.

In light of the above, it is evident that previous studies have predominantly taken a comparative approach when examining the ACA in individuals with KCN, while the factors contributing to ACA changes in these patients remain unclear. Therefore, the present study aimed to address this knowledge gap by identifying the individual topographic factors linked to ACA narrowing in patients with KCN.

PARTICIPANTS AND METHODS

Ethical Approval This study was supported by the Iran University of Medical Sciences and followed the tenets of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences (ethical code: IR.IUMS.REC.1401.371). Written informed consent was obtained from all participants.

Study Design and Examinations The sample size was determined using the following formula:

$$n=(Z^{\alpha}/_{2}\times\sigma^{2})/E^{2}$$

In this formula, σ represents the standard deviation (SD), and E indicates the error bound at a 95% confidence level. The SD was derived from comparable research by Emre *et al*[17] which indicated an SD of 0.4 for ACA in patients with KCN. With a 5% margin of error and a 95% confidence interval, the required sample size was determined to be 246. After considering a possible 20% drop in the sample, the final number of cases was revised to 294. Two hundred and ninety-four patients who visited a tertiary eye hospital in Tehran, the capital of Iran, and were diagnosed with KCN were recruited for this study.

Complete ocular examinations were performed for all patients, including measurement of uncorrected distance visual acuity using a digital visual acuity chart (Chart SC 1600 Pola, Nidek Co., Ltd., Gamagori, Japan) at 6 m, objective refraction using an autorefractometer (ARK-1, Nidek Co., LTD., Aichi, Japan), subjective refraction, and slit lamp biomicroscopy (BQ-900, HaagStreit AG, Koeniz, Switzerland).

Pentacam HR rotating Scheimpflug imaging system (Oculus; Optikgeräte GmbH, Wetzlar, Germany) was used for corneal imaging, providing precise measurements of the ACA. Images were obtained using automatic mode and only measurements were considered valid that displayed ‘OK’ in the scan quality specification (QS) box. To evenly distribute tear film on the corneal surface, participants were asked to blink completely once before imaging. The following data were extracted from Pentacam’s maps and recorded: ACA, central corneal thickness (CCT) at the pupil center, corneal thickness at the thinnest point, steepest (Ks), flattest (Kf), and mean central keratometry (mean K) readings, anterior and posterior Q values, maximum elevation of the anterior and posterior corneal surfaces, and corneal volume (CV).

The diagnosis of KCN was established through the observation of distorted keratometric mires, scissoring of the retinoscopic reflex, and abnormal corneal topography, in addition to the identification of at least one biomicroscopic sign indicative of KCN (*e.g.* the Fleischer ring, Vogt striae, stromal thinning at the corneal apex, or corneal apical scarring). In the diagnostic process, several atypical topographic features were considered, including an inferior-superior asymmetry exceeding 1.4, localized or inferior steepening with corresponding keratometry readings greater than 45.00 D, or an asymmetric bow-tie pattern characterized by skewed radial axes greater than 21°[20]. A corneal specialist confirmed the diagnosis of KCN in all cases.

Definitions The severity of KCN was categorized into three specific levels based on the guidelines provided by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. These levels were as follows: mild, which is defined by a maximum keratometry measurement of less than 45 D; moderate, characterized by a maximum keratometry measurement between 45 and 52 D; and severe, which is indicated by a maximum keratometry measurement that surpasses 52 D[21]. The cone morphology was divided into three distinct categories: nipple, oval, and globus, determined by the size of the cone and the position of the cone apex as indicated by the tangential map. The nipple cone is characterized by a size of 5 mm or less, exhibiting a steep curvature, with the apical center typically located centrally or paracentrally and showing inferior nasal displacement. The oval cone, measuring between 5 and 6 mm, presents an oval shape and is generally associated with inferior temporal displacement. Finally, the globus cone, which exceeds 6 mm in size, encompasses more than 70% of the corneal surface[18]. The cone location was determined by analyzing the area of maximum elevation on the anterior elevation map, utilizing a reference best-fit sphere. The classifications were as follows: central, defined as the highest elevation within the central 3 mm region; paracentral, indicating the highest elevation within the paracentral zone of 3-5 mm; and peripheral, representing the highest elevation found beyond the central 5 mm area[18]. According to Shaffer's classification system, an ACA of less than 20° was considered narrow[22].

Exclusion Criteria Exclusion criteria were any ocular pathology other than KCN, corneal scars or opacities, history of ocular surgery, any previous surgical treatment of KCN (*e.g.* intrastromal ring segment implantation, corneal transplant, and collagen cross-linking), history of ocular trauma, and history of contact lens wear within the last 4wk.

Statistical Analysis The analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS) version 25. To check the normality of the data, both the Shapiro-Wilk test and normality plots were employed. Descriptive statistics for sample characteristics were reported as mean±SD for continuous variables and as frequency (%) for categorical variables. The Chi-square test was used to compare the ACA across different sex groups. Analysis of covariance (ANCOVA) was applied to evaluate group differences in ACA in relation to KCN severity, cone location, and cone morphology while adjusting for covariates including age, sex, and the specific eye being analyzed (right or left). The Pearson correlation was utilized to explore the relationship between ACA and continuous variables. The correlation coefficient (r) and the R-squared values were presented to reflect the strength of the correlation and the proportion of variance in the dependent variable (ACA) that can be attributed to the independent variables (topographic factors). A P value of less than 0.05 was considered statistically significant. It is important to acknowledge that in bilateral cases, the analysis took into account both eyes, as KCN is characterized by its asymmetrical nature. As a result, the correlation between the fellow eyes is not a relevant factor in the statistical analysis, unlike in the case of normal eyes.

RESULTS

Four hundred and ten eyes of 294 patients with KCN were analyzed for this report. Baseline characteristics of the study sample are shown in Table 1. As seen in Table 1, the mean age of the participants was 32.40±8.52y with a range of 15 to 60y and 69.5% of the participants were male. The majority of cases exhibited moderate KCN severity (60.9%). The predominant morphological pattern identified in this study was oval (54.1%). Additionally, the central cone location was observed in most patients (51.7%).

Table 1 Baseline characteristics of the study sample mean±SD (range)

Variables	Variables
Age (y)	32.40±8.52 (15 to 60)
Sex (male)	285 (69.5%)
Sphere of manifest refraction (D)	-1.87±3.03 (-8.00 to +5.00)
Cylinder of manifest refraction (D)	-2.39±1.71 (-7.00 to -0.75)
BCVA (logMAR)	0.30±0.29 (0.00 to 2.00)
Keratoconus severity, *n* (%)	
Mild	94 (23)
Moderate	249 (60.9)
Severe	66 (16.1)
Cone morphology, *n* (%)	
Nipple	184 (44.9)
Oval	222 (54.1)
Globus	4 (1.0)
Cone location, *n* (%)	
Central	212 (51.7)
Paracentral	174 (42.4)
Peripheral	24 (5.9)
Maximum keratometry (D)	48.23± 4.53 (40.20 to 76.60)
Mean keratometry (D)	46.71± 3.96 (39.95 to 74.50)
Corneal thickness at the thinnest point (μm)	464.66±45.99 (268.00 to 585.00)
Anterior Q value	-0.58±0.48 (0.83 to -2.90)
Posterior Q value	-0.57±0.69 (0.99 to -2.79)
Anterior maximum elevation (μm)	19.98±13.76 (2.00 to 70.00)
Posterior maximum elevation (μm)	42.69±24.68 (3.00 to 152.00)
Corneal volume (mm^3)	56.21±3.51 (42.50 to 68.80)

BCVA: Best-corrected visual acuity; logMAR: Logarithm of minimum angle of resolution.

The mean ACA was 38.47°±5.75° (range: 14.40° to 56.50°) in the whole sample, 38.24°±6.00° in males, and 38.98°±5.11° in females. The Chi-square test showed no statistically significant difference in the ACA between males and females (P=0.447). There was a statistically significant inverse correlation between ACA and age (r=-0.262, P<0.001). Moreover, 8.2% of study participants (n=24) had a narrow ACA.

Table 2 shows the comparison of the mean ACA among different groups of categorical topographic variables. As seen in Table 2, mean ACA was significantly different among different groups of cone morphology, as patients with nipple cones showed the lowest mean ACA. Moreover, there were statistically significant differences in the mean ACA among different groups of cone locations, with patients having central cones exhibiting the lowest mean ACA (P<0.001). Figure 1 illustrates the comparison of the mean ACA across different

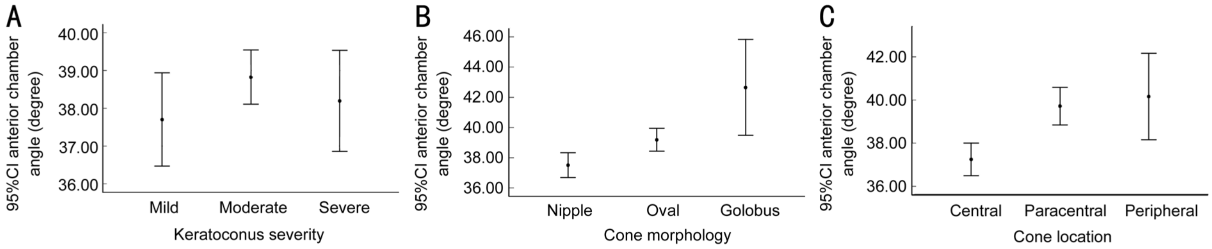

Figure 1 Comparison of the mean anterior chamber angle (°) across different groups of keratoconus severity (A), cone morphology (B), and cone location (C).

groups of KCN severity, cone morphology, and cone location. Table 3 shows the correlation of different continuous topographic variables with ACA. As seen in Table 2, anterior and posterior Q values were significantly, directly correlated with ACA. There was no statistically significant correlation between ACA and other variables (all P>0.05).

Table 2 Comparison of the anterior chamber angle among different groups of categorical topographic variables in patients with keratoconus mean±SD

Variables	Anterior chamber angle (°)	P^b
Keratoconus severity		0.621
Mild	37.70±6.02	
Moderate	38.82±5.73	
Severe	38.19±5.43	
Cone morphology		0.001[a]
Nipple	37.51±5.65	
Oval	39.19±5.75	
Globus	42.65±1.99	
Cone location		<0.001[a]
Central	37.25±5.55	
Paracentral	39.72±5.81	
Peripheral	40.16±4.74	

[a]Statistically significant (P<0.05); [b]Group differences were evaluated using analysis of covariance while controlling for covariates including age, sex, and the eye under analysis (right or left eye).

DISCUSSION

The assessment of ACA is an important diagnostic step to identify patients with narrow ACAs who are at risk for angle-closure glaucoma[23]. The clinical assessment of ACA is conducted through the Van Herrick method, utilizing a slit lamp biomicroscope or gonioscopy; however, the application of these techniques in patients with KCN presents certain limitations[13]. The Van Herrick technique has the potential to produce inaccuracies in KCN patients due to the influence of localized apical protrusion and thinning on anterior chamber depth. This alteration can lead to an overestimation of the measured depth, consequently resulting in a misleading assessment of the ACA[13,24]. Gonioscopy is a more invasive procedure for the ocular surface[11] and its use can be risky in a keratoconic eye. Therefore, it is valuable to recognize the predictive factors associated with ACA narrowing in patients diagnosed with KCN, as this knowledge can facilitate a more precise and safer assessment of the ACA through imaging modalities in cases deemed to be at higher risk for diagnostic or therapeutic interventions.

It is well known that KCN patients have a deeper anterior chamber at the center compared to normal eyes due to the central cone protrusion[9,15,25], but this finding does not reflect the changes of the peripheral cornea and the ACA in these patients. As mentioned earlier, the ACA change in KCN has received little attention and has been associated with inconsistent results. Emre *et al*[17] observed that patients with severe KCN exhibited a significantly reduced mean ACA when compared to those with mild KCN, with measurements of 33.6° and 37.2°, respectively. Their findings led to the conclusion that the ACA diminishes by approximately 10% as the disease progresses. Shariati Moghaddam *et al*[15] observed no statistically significant difference in the mean ACA across varying severities of KCN, aligning with the findings of the present study. Ucakhan *et al*[14] found no statistically significant differences in the ACA among KCN, subclinical KCN, and normal groups. Similarly, Nilsson *et al*[13] reported no statistically significant difference in the ACA between KCN patients and normal controls. Orucoglu and Toker[16] identified a significantly higher mean ACA in the KCN group compared to the control group. These discrepancies can be partially explained by the different technologies used to measure ACA as well as differences in sample size, age distribution, and the KCN grading system. However, it can also be hypothesized that the ACA narrowing in KCN does not occur at a uniform and predictable rate. Instead, it is likely affected by various factors beyond KCN severity, the fluctuations of which across different studies have led to inconsistent findings. Consequently, the assessment of ACA in patients with KCN should be conducted on an individual basis, taking into account potential predictive factors. After analyzing the literature and noting inconsistencies concerning the impact of KCN severity on the ACA, we have chosen to investigate how additional corneal topographic factors, particularly the cone's position and morphology, relate to the ACA.

Table 3 Correlation of continuous topographic variables with the anterior chamber angle in patients with keratoconus

Variables	Correlation coefficient (*r*)	*R*-squared	*P*
Maximum anterior elevation (μm)	0.047	0.002	0.340
Maximum posterior elevation (μm)	-0.012	0.000	0.804
Anterior Q value	0.122	0.014	0.014[a]
Posterior Q value	0.192	0.036	<0.001[a]
Corneal thickness at the thinnest point (μm)	-0.048	0.002	0.338
Corneal volume (mm^3)	-0.033	0.001	0.501

[a]Statistically significant ($P<0.05$).

The present study investigated the relationship between a set of topographic factors and the ACA in patients with KCN. According to the results, KCN patients with nipple and central cones had a significantly narrower ACA. To explain the relationship between the morphology and location of the cone with the ACA, it is essential to examine the potential mechanisms and underlying factors contributing to the peripheral corneal alterations observed in KCN. It has been suggested that KCN is an ectasia that is associated with stromal thinning and stretching[26]. In a cornea affected by KCN, there is a notable increase in peripheral flattening, which occurs alongside localized central steepening and the emergence of the KCN cone[9,15]. This phenomenon serves as a compensatory response facilitated by a mechanism known as biomechanical coupling[10,27]. The peripheral flattening is intended to mitigate the simultaneous expansion of the corneal surface area, thereby enhancing the cornea's ability to withstand stresses associated with stretching[10]. In support of this theory, Smolek[10] reported no apparent increase in the corneal surface area in keratoconic compared to normal corneas. Furthermore, Crahay *et al*[9] observed no significant increase in the corneal surface area with increasing severity of KCN. It is also possible that the peripheral corneal flattening in KCN is intended to provide a smoother transition from the cornea to the flatter scleral surface[28]. The findings of the present study suggest that a more localized and central steepening region in KCN, characterized by a nipple and central cone formation, necessitates a greater degree of peripheral flattening to preserve the total corneal surface area and to facilitate a seamless transition from the cornea to the sclera. This phenomenon may be linked to a more significant ACA narrowing in such instances. Hence, the findings of the present study further support the hypothesis that the peripheral corneal flattening serves as a compensatory mechanism for the increase in the central curvature.

The present study revealed a statistically significant direct relationship between the asphericity values of the anterior and posterior corneal surfaces and the ACA. This indicates that an increase in corneal prolation, characterized by a more negative Q value, corresponds to a reduction in the ACA. This finding aligns with expectations; however, several aspects warrant attention. Initially, the correlations observed were relatively weak, as indicated by the coefficient (r) values. Additionally, the *R*-squared values revealed that merely 1% and 3% of the variations in ACA could be linked to the anterior and posterior asphericity, respectively. Given that the Q value generated by Pentacam HR represents the overall degree of peripheral flattening over an 8-mm chord diameter, it may not accurately represent the specific alterations occurring within the iridocorneal region. Second, the flattening of the posterior corneal surface was a better predictor of the ACA narrowing. An analysis of the sample characteristics indicates that the mean elevation of the posterior cornea was considerably greater than that of the anterior cornea (42.69 microns compared to 19.98 microns). Given the more pronounced central protrusion observed in the posterior corneal surface, it is reasonable to anticipate a corresponding degree of flattening in the peripheral regions, which may elucidate the observed stronger relationship between posterior corneal asphericity and the ACA. Other studies also reported that the posterior corneal surface is affected to a greater extent than the anterior surface especially in the early stages of KCN[3,29].

The results of this study hold clinical relevance for both diagnosis and treatment. In terms of diagnosis, it is crucial to assess the risk of angle closure during procedures that necessitate pupil dilation, such as fundoscopy, particularly in KCN patients exhibiting central and nipple cones or those with pronounced corneal prolation. Furthermore, routine follow-ups should incorporate evaluations for glaucoma, including IOP measurement, careful assessment of the optic nerve head, imaging of the retinal nerve fiber layer in the peripapillary region, and visual field examination, tailored to the individual patient's circumstances. Regarding treatment, heightened caution is warranted during surgical interventions involving the peripheral cornea and the iridocorneal region (*e.g.* intra-stromal ring segment implantation and corneal transplantation) for patients predisposed to ACA narrowing, with careful consideration of potential angle closure and elevated IOP both during and post-surgery.

The present study is limited by its exclusive emphasis on the overall ACA as defined by the capabilities of the measurement device, thereby overlooking the evaluation of sectoral ACA. The distribution of ACA among patients with KCN may systematically vary across different sectors, potentially affecting the interpretation of the overall ACA. Future research should prioritize the measurement of sectoral ACA in KCN patients. Additionally, a notable limitation of this study is the lack of data regarding IOP and the integrity of the optic nerve. It is essential to ascertain the degree to which KCN patients with risk factors for ACA narrowing are susceptible to elevated IOP or the onset of optic neuropathy. Cohort studies are warranted to examine the correlation between corneal topographic characteristics and the risk of glaucoma in individuals with KCN. Moreover, another critical limitation of this research is the omission of axial length measurements. Given the substantial influence of axial length on ACA and the increased risk of angle closure in individuals with significantly short eyes, neglecting to consider axial length may affect the study's findings. Thus, it is imperative to recognize this limitation when interpreting the results.

In conclusion, some corneal topographic characteristics, including the morphology and location of the cone as well as anterior and posterior Q values, were related to ACA changes in KCN patients. Patients with nipple and central cones exhibited the most significant ACA narrowing. Additionally, more negative Q-values were associated with increased ACA narrowing. Identifying KCN patients with an increased risk of ACA narrowing can aid in planning safer intraocular surgeries and improving patient outcomes.

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