• Clinical Research •

Comparison of tear film quantity parameters between keratoconus and normal eyes

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Abstract

● **AIM:** To compare the tear film quantity and stability parameters in keratoconus (KCN) and normal eyes using test breakup time (TBUT), noninvasive TBUT (NITBUT), and Schirmer test.

● **METHODS:** All participants (*n*=166), including patients with KCN and age-matched healthy individuals with normal corneas, were recruited from those referred to Farabi Eye Hospital, Iran, in 2023. To better account for genetic and environmental factors, the control group comprised healthy individuals who were relatives of KCN patients and had normal corneal topography. Tear quantity parameters were evaluated in the following order: NITBUT, TBUT, and Schirmer tests.

● **RESULTS:** The mean age of cases in KCN (61.7% males) and normal (63.5% males) participants was 27.54±5.44y (range 19 to 38) and 27.52±5.63y (range 20 to 38), respectively (*P*=0.976). NIBUT, TBUT, and Schirmer's tests were significantly lower in KCN group compared to normal controls (all *P*<0.001). The mean difference for NIBUT was -7.81s (*P*<0.001), and for TBUT was -7.61s (*P*<0.001). Schirmer test values were also significantly lower in the KCN group, with a mean difference of -5.61 mm compared to normal people (*P*<0.001).

● **CONCLUSION:** Our findings demonstrate significant tear film impairment in KCN. The reductions in NIBUT, TBUT and Schirmer scores highlight an underlying tear film dysfunction in KCN that extends beyond the morphological changes of the cornea.

● **KEYWORDS:** keratoconus; tear breakup time; noninvasive tear breakup time; Schirmer test; tear film
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INTRODUCTION

Keratoconus (KCN) is a progressive corneal ectasia characterized by corneal thinning and irregular astigmatism that typically manifests in adolescence or early adulthood[1-2]. While the etiology remains incompletely understood, genetic predisposition, chronic eye rubbing, and biochemical factors contributing to altered corneal biomechanics are implicated in its pathogenesis[3-5].

Clinically, KCN is characterized by localized corneal steepening and thinning, resulting in irregular astigmatism, myopia, and corneal scarring in advanced disease[6]. Diagnosis is made based on characteristic corneal topography and tomographic patterns, in addition to slit-lamp findings[7]. Although KCN has traditionally been considered a non-inflammatory disorder, recent evidence suggests localized inflammation may play a role[8-9]. Multiple studies have identified elevated levels of cytokines, proteases and other inflammatory mediators in the tears of KCN patients compared to controls[9-11].

Dry eye disease (DED) is a multifactorial chronic condition affecting the ocular surface, with a worldwide prevalence up to 34%[12]. It is characterized by tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities[13]. Symptoms of ocular irritation and visual disturbance are common. DED has been associated with conditions causing inflammation, such as autoimmune disorders, allergy, contact lens wear and ocular surgery[14].

Several studies have reported an increased prevalence of DED signs and symptoms in KCN patients compared to healthy controls or myopes[15-17]. Findings include reduced tear breakup time (TBUT), increased corneal fluorescein staining, reduced Schirmer scores and higher surface disease index (OSDI) symptom scores. The association is hypothesized to arise from

the localized inflammatory state and/or neuropathic changes in KCN corneas[18]. However, the relationship between KCN severity and DED remains unclear. While previous studies have consistently reported an increased prevalence of DED signs and symptoms in patients with KCN, several gaps in the existing literature remain. For instance, the specific relationship between KCN severity and tear film dysfunction has not been thoroughly investigated, particularly when assessed using established grading systems like the Amsler-Krumeich classification. Additionally, the control groups in many prior studies were not specifically designed to account for the potential influence of environmental and genetic factors, which may significantly impact study outcomes. To address this, we selected relatives of KCN patients as controls to minimize these confounding variables. Unlike studies that primarily focus on morphological or biochemical changes in the tear film, our research emphasizes commonly used clinical parameters such as TBUT, noninvasive TBUT (NITBUT), and the Schirmer test, making our findings more directly applicable to clinical practice. Furthermore, some studies have overlooked the role of NITBUT, an essential measure of tear film stability. By addressing these gaps and emphasizing these clinical parameters, this study provides a more robust and clinically relevant evaluation of the interaction between KCN and tear film dysfunction.

This study aimed to compare tear film quantity and stability between KCN patients at different disease stages, categorized using the Amsler-Krumeich classification system and normal controls using TBUT, NITBUT, and Schirmer testing. Understanding the differences in tear parameters may provide insights into the pathophysiological interactions between KCN and DED, particularly in mild to moderate stages of the disease, thereby helping to guide appropriate clinical management.

PARTICIPANTS AND METHODS

Ethical Approval This prospective comparative study enrolled KCN patients and normal healthy subjects examined at the cornea clinic of Farabi Eye Hospital, Tehran, Iran, in 2023. The Ethical Committee of Tehran University of Medical Sciences approved this study (IR.TUMS.FNM.REC.1402.037). This study adhered to the tenets of the Declaration of Helsinki. Written informed consent was provided by all participants.

Participants Patients diagnosed with KCN were included if they were under 40 years old and had KCN severity grades 1-4 based on the Amsler-Krumeich classification system[19]. Exclusion criteria were central corneal scarring, history of herpetic keratitis, prior ocular surgery or corneal collagen crosslinking, corneal ectatic disorders besides KCN, and presence of any systemic disease. In our study, we excluded all patients who had worn contact lenses within the two weeks preceding examinations. This decision was made because contact lens can exacerbate dry eye symptoms through various mechanisms such as increased tear evaporation, disruption of the tear film, hypoxia, triggering an inflammatory response, and potential irritation from contact lens solutions[20].

The control group comprised age-matched healthy individuals who were relatives of KCN patients with normal corneal topography and no history of ocular surgery, ocular surface disease, or continuous contact lens wear. The reason for choosing relatives of KCN patients was to minimize the impact of environmental and genetic factors on the study results. Most of the KCN participants in our study have mild and moderate disease.

Ocular Examinations All participants underwent a complete ophthalmologic evaluation, including slit-lamp biomicroscopy, subjective refraction, and corneal tomography. KCN diagnosis was based on characteristic topographic patterns and slit-lamp findings of corneal thinning and steeping by an experienced ophthalmologist.

Objective refractions were measured using an ARK-510A auto refractometer (Nidek, Japan), which provides spherical, cylindrical, and axis measurements. Patients were instructed to open both eyes and fixate on the internal target during autorefraction. The average of three acceptable measurements was used for the study. Moreover, tomography parameters, such as flat keratometry (flat K), steep keratometry (steep K), and central corneal thickness (CCT), were obtained through Pentacam HR (Oculus, Weltzar, Germany). These examinations were consistently conducted by an experienced optometrist using the same methodology. The best-corrected distance visual acuity (CDVA) was determined using a projected Snellen visual acuity chart at 6 m based on the logarithm of the minimum angle of resolution (logMAR).

Subjective refraction was also performed by the same optometrist starting from the objective refraction endpoint. Sphere, cylinder, and axis readings were refined in 0.25 D steps using a phoropter and trial frame to achieve maximum plus for CDVA. As image quality is poor in irregular astigmatism, especially in severe KCN, it is difficult to get the end point of subjective refraction correctly. To identify the precise endpoint, techniques such as fogging (to eliminate accommodation), pinholes (to refine the spherical component), and stenopic slits (to refine the cylinder axis) were used.

Tear Film Assessment Tear film quantity and stability were assessed in the following sequence: NITBUT, fluorescein TBUT and Schirmer testing without anesthesia. All tear film measurements were done in one room with relatively constant temperature and humidity between 9 *a.m.* to 12 *p.m.* NITBUT was measured using an ARK-510A auto refractometer (Nidek, Japan). Participants were instructed to blink normally and then

Table 1 Comparison of age, CDVA, keratometry, and CCT between patients with KCN and normal participants mean±SD

Parameters	Group		Mean difference	95%CI of the mean difference		P^a
	KCN (*n*=81)	Normal (*n*=85)		Lower	Upper	
Age (y)	27.54±5.44	27.52±5.63	0.03	-1.67	1.72	0.976
CDVA (logMAR)	0.14±0.16	1.00±0.00	-0.86	-0.89	-0.82	<0.001
Sphere (D)	-2.70±2.48	-1.31±1.46	-1.39	-2.01	-0.77	<0.001
Cylinder (D)	-3.61±2.46	-1.09±0.88	-2.51	-3.08	-1.95	<0.001
Flat K (D)	45.77±3.32	43.84±3.08	1.92	0.94	2.90	<0.001
Steep K (D)	49.46±4.38	44.90±3.33	4.56	3.37	5.75	<0.001
CCT (μm)	473.10±37.30	524.76±32.77	-51.67	-62.41	-40.92	<0.001

CDVA: Corrected distance visual acuity; logMAR: Logarithm of minimum angle of resolution; D: Diopter; K: Keratometry; CCT: Central corneal thickness; KCN: Keratoconus; SD: Standard deviation; CI: Confidence interval. [a]Independent samples *t*-test. *P*<0.05 is statistically significant.

Table 2 Comparison of NIBUT, TBUT, and Schirmer test between patients with KCN and normal participants mean±SD

Parameters	Group		Mean difference	95%CI of the mean difference		P^a
	KCN (*n*=81)	Normal (*n*=85)		Lower	Upper	
NIBUT (s)	10.98±2.76	18.79±2.66	-7.81	-8.64	-6.98	<0.001
TBUT (s)	9.94±2.74	17.55±2.72	-7.61	-8.45	-6.78	<0.001
Schirmer (mm)	6.87±1.99	12.47±2.76	-5.61	-6.35	-4.87	<0.001

NIBUT: Noninvasive breakup time; TBUT: Tear breakup time; KCN: Keratoconus; SD: Standard deviation; CI: Confidence interval. [a]Independent samples *t*-test. *P*<0.05 is statistically significant.

keep their eyes open. The time from the last blink until the distortion of keratometry mires was recorded as the NITBUT (seconds).

After NITBUT, fluorescein dye was instilled, and patients were asked to blink several times to ensure even coverage. Using the cobalt blue filter on the slit-lamp, the time from the last blink to the first corneal black spot was noted as the TBUT (seconds). Testing was repeated 3 times and averaged for each eye. Finally, Schirmer strips were inserted in the inferior temporal fornix and left in place for 5min with eyes closed. Wetting of the strips was measured in millimeters (mm).

Statistical Analysis Statistical analyses were administered using SPSS 24 (IBM Inc., Chicago, USA). The mean±standard deviation (SD) and frequency values were reported for every parameter, including TBUT, NIBUT, and the Schirmer test. The normal distribution of all data was first checked by using the Shapiro-Wilk test. In cases of parametric analysis, independent samples *t*-test was administered to compare data of the KCN and normal healthy subjects. Also, we compared the data between two groups using linear regression, considering age and sex as confounders. *P*<0.05 were considered to be statistically significant.

RESULTS

Of the total number of 166 participants, 81 people (48.80%) had KCN. The mean age of cases in KCN (61.7% male) and normal participants (63.5% male) was 27.54±5.44y (range 19 to 38) and 27.52±5.63y (range 20 to 38), respectively (*P*=0.976). In the KCN group, most cases (98.77%) had mild and moderate KCN.

Table 1 compares age, CDVA, keratometry, and CCT between patients with KCN and normal participants. The CDVA in patients with KCN was significantly worse than normal participants (*P*<0.001). Also, both flat K and steep K in the KCN group were significantly higher than the normal participants group (*P*<0.001). In addition, the CCT in the KCN group was significantly thinner than the normal group (*P*<0.001).

According to Table 2, the comparison of NIBUT, TBUT, and Schirmer between patients with KCN and normal participants showed that all these parameters in patients with KCN were significantly worse than normal participants (all *P*<0.001). NIBUT and standard TBUT tests were significantly lower in the KCN group compared to normal controls. The mean difference for NIBUT was -7.81s (*P*<0.001), and for TBUT was -7.61s (*P*<0.001). Schirmer test values were also significantly lower in the KCN group, with a mean difference of -5.61 mm compared to normal people (*P*<0.001).

Linear regression analysis confirmed the above-mentioned comparisons (all *P*<0.05). In all study parameters, there was no significant difference between males and females (all *P*>0.05).

DISCUSSION

It is known that the classical definition of KCN interprets this disease as non-inflammatory. However, in recent years, more studies have proven the inflammatory process's involvement in the pathogenesis of this keratectasia[8,10-11]. Increased levels of inflammatory mediators were found in the tear film even at the initial stages of KCN[10]. The present study revealed significantly reduced tear film stability and volume in KCN

patients compared to normal controls, as evidenced by lower mean NITBUT, TBUT, and Schirmer test values. These differences were highly statistically significant, with $P<0.001$ for all parameters.

The results are consistent with previous reports demonstrating impaired tear function in KCN. Mirza *et al*[15] found significantly reduced TBUT and increased corneal fluorescein staining in KCN patients versus controls, although Schirmer values were not significantly different between groups in their cohort. In a pilot study, Uçakhan and Özcan[16] also noted lower Schirmer scores and increased staining in keratoconic eyes. The prospective study by Mirza *et al*[15] reported significantly lower TBUT and Schirmer measurements in KCN patients, with more severe disease associated with worse parameters.

Several factors may contribute to the tear film instability and volume reduction observed in KCN corneas.

Inflammation While traditionally defined as a non-inflammatory disorder, there is growing evidence that KCN involves localized inflammation of the corneal stroma, epithelium and tear film[10,21]. Elevated levels of inflammatory mediators like interleukins, tumor necrosis factor-alpha, matrix metalloproteinases and cathepsins have been identified in keratoconic tears[11,22-23]. Chronic inflammation of the ocular surface may arise from biochemical stressors or eye rubbing in KCN[24]. This creates a vicious cycle, as inflammatory cytokines perpetuate further tear film instability, hyperosmolarity and surface damage[25].

Neuropathy Corneal nerves play an essential role in trophic maintenance of the ocular surface epithelium and tear production. Studies utilizing *in vivo* confocal microscopy demonstrate reduced sub-basal nerve fiber density and abnormal architecture in KCN, which worsens with disease progression[26-28]. Corneal hypoesthesia is also documented in KCN using esthesiometry[29]. The associated neuropathic changes likely contribute to diminished reflex tearing and lubrication.

Epitheliopathy Structural abnormalities of the corneal epithelium are common in KCN, including basement membrane disruptions, reduced cell-to-cell cohesion and epithelial thinning[30]. Dysfunction of matrix metalloproteinases, which regulate epithelial integrity, is implicated[31]. Focal loss of epithelial barrier function would allow tear fluid to permeate the stroma, reducing pre-corneal tear volume and stability.

Mechanical Factors Rigid contact lens wear, a mainstay of KCN management, may adversely affect the ocular surface. Chronic mechanical interaction between the contact lens and cornea can trigger inflammatory cytokine release, hyperosmolar stress and limbal stem cell deficiency[32-33]. Contact lens hypoxia may also play a role. Such changes likely underlie the reduced contact lens tolerance often accompanying KCN progression.

The clinical implications of these findings are significant. Identifying tear film abnormalities on a cellular and functional level provides objective evidence that KCN involves ocular surface disease beyond corneal changes. This challenges the traditional view of KCN as a purely corneal ectatic disorder. Furthermore, the observed tear film dysfunction appears proportional to disease severity. As KCN advances, tear production and stability progressively decline. This substantiates the merit of including tear film evaluation as part of the KCN diagnostic protocol.

From a management perspective, these results highlight the importance of a holistic approach addressing both corneal factors and ocular surface health in KCN patients. Concurrent dry eye treatment, where indicated, is imperative, particularly before contact lens fitting. Lubricating drops, anti-inflammatory therapy, punctal occlusion and serum eye drops represent suitable options for managing tear deficiency and improving contact lens tolerance in keratoconic eyes[34].

Addressing ocular surface inflammation may also have synergistic benefits in minimizing disease progression. Ultimately, maintaining the health of the tear film and corneal epithelium is paramount for optimizing visual outcomes and quality of life in KCN.

This study provides new quantitative estimates of how KCN impacts tear film parameters relative to normal controls. The differences found in mean NITBUT, TBUT and Schirmer values are clinically relevant, with likely functional effects on visual performance and ocular comfort. Statistical analysis confirms the tear quantity and stability changes are highly significant rather than due to chance. The study population was relatively large and groups were well-matched by age and gender. This lends validity to the conclusions that can be drawn.

Nonetheless, certain limitations should be noted. The cross-sectional design only permits analysis of correlation rather than causation. Longitudinal studies tracking tear parameters and KCN progression over time would provide further insight. Confounding factors like allergy status and environment were not controlled. Evaluations were performed at a single time point and may vary diurnally or seasonally. The study was conducted at a specialty tertiary eye hospital, potentially limiting generalizability. We did not compare the quality and quantity of tear film between different stages of KCN due to the small sample size of patients with severe KCN. Therefore, future studies are recommended to investigate the quality and quantity of tear film across different stages of keratoconus. Finally, KCN severity was not stratified in correlational analyses.

In conclusion, this study demonstrates impaired tear production and stability in KCN patients compared to age-similar healthy subjects. NITBUT, TBUT, and Schirmer test values were significantly reduced in the KCN group. These findings highlight the importance of assessing tear film status and treating dry eye as part of KCN management. Further research is warranted to elucidate the complex interplay between structural corneal changes, inflammation, innervation, and tear dysfunction in KCN pathogenesis. Prospective studies tracking ocular surface parameters in tandem with disease progression will help clarify these relationships. Nonetheless, the current results provide valuable insights and quantified metrics that will assist clinicians in optimizing care for patients with this challenging corneal disorder.

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