

Keratoconus epidemiology: A review

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Abstract

Keratoconus is an ectatic corneal disease that affects both men and women, usually at a young age. Risk factors such as eye rubbing, environmental and genetic factors contribute to its pathogenesis. Keratoconus presents a variable prevalence, being as high as 5% of the population in the Middle East. In this review, an English-language search for keratoconus epidemiology was undertaken using the PubMed database. We present and discuss the findings of the most relevant epidemiological studies on keratoconus and describe its characteristics and risk factors, correlating them with its pathogenesis.

Keywords:

Corneal ectasia, epidemiology, keratoconus, prevalence, risk factors

INTRODUCTION

Over the last years, researchers have found that the prevalence and incidence of keratoconus cases in the population presented a high variability.^[1-3] There are different explanations for this variability, including the heterogeneity of epidemiological studies and the lack of well-defined criteria for the definition and classification of keratoconus.^[4] These criteria have been mainly affected using new diagnostic imaging devices to assess different cornea parameters and by artificial intelligence algorithms.^[1,3]

A great majority of the prevalence studies are performed with patients in hospitals or medical clinics - when it is easier to collect data, leading to an underestimated prevalence as patients are commonly symptomatic, and the early and more subtle forms can be missed.^[4-15] One of the first publications on keratoconus epidemiology is the study performed by Kennedy *et al.*^[5] in Minnesota, USA, who found a prevalence of 0.054% based on the clinical findings of scissors movement in retinoscopy and keratometry. This number was similar to those reported in Finland^[6] or in Denmark^[7] but higher than those reported in Russia, 0.0004%,^[8] or 0.0068% in

Macedonia.^[4] More recently, a large-scale study from the Netherlands showed a much higher prevalence of keratoconus, 0.27%.^[9]

The true prevalence of the disease can be determined more accurately by population-based screening studies. Cross-sectional surveys enroll people who volunteer to participate in the investigation, creating selection bias.^[4,16] The first population-based screening study for keratoconus was published in the USA in 1959^[17] when 0.6% of examined eyes had the ectasia diagnosis confirmed by finding the typical oval pattern images on a Placido disc.^[17]

Another study in India using keratometry values of more than 48D as a cutoff found a prevalence of 2.3% of keratoconus.^[18] A similar study conducted in China found a prevalence of 1% of corneas with more than 48D^[19] using optical low coherence reflectometry biometry. An investigation of French army recruits using corneal topography reported a prevalence of keratoconus of 1.2%.^[4] Using corneal topographic and tomographic values, other population-based surveys from Asia, the Middle East, and Oceania found a higher prevalence of keratoconus ranging from 0.9% to 3.3% [Table 1].^[4] In 2018, Torres-Netto *et al.* used the Scheimpflug corneal tomography to determine the prevalence of keratoconus in a pediatric population in Saudi Arabia: 4.79% or 1:21, the highest reported so far.^[24] A recent

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Table 1: Population-based epidemiological studies of keratoconus*^{††}

Author	Location	Age (years), mean	Sample size	Prevalence/ 100,000	Method	Sampling method
Hofstetter ^[17]	Indianapolis, USA	1-79	13,345	120	Placido disc*	Rural volunteers
Santiago <i>et al.</i> (1995) ^[11]	France	18-22	670	1190	Topography	Army recruits
Jonas <i>et al.</i> ^[18]	Maharashtra, India	>30 (49.4±13.4)	4667	2300	Keratometry*	Rural volunteers (8 villages)
Millodot <i>et al.</i> ^[16]	Jerusalem, Israel	18-54 (24.4±5.7)	981	2340	Topography	Urban volunteers (1 college)
Waked <i>et al.</i> ^[20]	Beirut, Lebanon	22-26	92	3300	Topography	Urban volunteers (1 college)
Xu <i>et al.</i> ^[19]	Beijing, China	50-93 (64.2±9.8)	3166	900	Optical low coherence reflectometry*	Rural+urban volunteers
Hashemi <i>et al.</i> ^[21]	Shahrud, Iran	50.83±0.12	4592	760	Topography	Urban volunteers from random cluster
Hashemi <i>et al.</i> ^[22]	Tehran, Iran	14-81 (40.8±17.1)	426	3300	Topography	Urban volunteers (stratified cluster)
Shneur <i>et al.</i> (2014) ^[12]	Haifa, Israel	18-60 (25.05±8.83)	314	3180	Topography	Urban volunteers (1 college)
Hashemi <i>et al.</i> ^[23]	Mashhad, Iran	20-34 (26.1±2.3)	1073	2500	Topography	Urban volunteers (stratified cluster in 1 university)
Torres Netto <i>et al.</i> ^[24]	Riyadh, Saudi Arabia	6-21 (16.8±4.2)	1044	4790	Rotational Scheimpflug corneal tomography system	Patients who were seen at emergency rooms for nonophthalmic appointments at four locations in Saudi Arabia

*The methods for detecting keratoconus used in these studies have limitations and results should be interpreted with caution, **[Table 1] was modified from original

meta-analysis that included more than 50 million individuals from 15 countries determined that the global prevalence of keratoconus was 138/100,000.^[25]

Characteristics and risk factors for keratoconus

Age

Keratoconus has its most significant incidence in the age of 20 and 30 years, and progression occurs up to 35 years of age.^[26,27] New imaging technology, including corneal tomography, has provided an early diagnosis of keratoconus, even before the decrease of visual quality.^[4] Corneal tomography has allowed an early therapeutic intervention and more efficient control of the ectasia progression. It is postulated that the rate of progression of keratoconus in children is higher than in adults.^[28,29] The most likely reason is the association of young patients with ocular allergy and eye friction.

The prevalence of keratoconus in patients older than 50 years is not very significant, ranging from 7.4% to 15%.^[30-32] There is an inverse relationship between the severity of keratoconus and age. The corneal collagen interfibrillar space decreases with age, and the collagen bundles' fibers thicken, which increases the corneal rigidity. This change might explain the decrease in keratoconus incidence with increasing age.

Sex

Some authors reported a higher prevalence of keratoconus in men, with values ranging from 53% to 62%.^[15,32-35] Others found a preponderance of women, with rates ranging from 53% to 66%.^[15,33,36] The Collaborative Longitudinal Assessment of Keratoconus (CLEK) study showed the most significant functional discomfort in women, not evidenced in the clinical examination.^[37]

A possible relationship between sex hormones and corneal biomechanical properties at different stages of life was raised after discovering that there are estrogen, progesterone, and androgen receptors on corneal epithelial cells and

keratocytes.^[38] High estrogen levels during pregnancy impair corneal biomechanics and thickness.^[39,40] Several studies have shown that serum levels of MMPs increase and serum levels of TIMPs decrease during pregnancy.^[41,42] The increase in proteolytic enzymes and the decrease in their inhibitors during pregnancy must be correlated with the progression of keratoconus. Another example of this correlation is the report of rapid progression of keratoconus in a 49-year-old woman on selective tissue estrogen regulator (STEAR) therapy for endometriosis.^[30,43]

Genetics

The pathogenesis of keratoconus seems to have the contribution of genetics and heredity. Familial keratoconus is primarily autosomal dominant.^[44] Furthermore, monozygotic twins show a greater concordance in the topography of keratoconus than dizygotic twins.^[44] On the other hand, family-based linkage studies have identified 19 likely genetic loci with mutations for keratoconus, indicating genetic heterogeneity. Keratoconus can show itself in different degrees of involvement, even in the same individual.^[45,46] These characteristics reveal the influence of cofactors in the phenotypic presentation of this corneal ectasia.

Keratoconus association with predisposing family history has also been investigated, presenting a wide variability.^[15,29,46,47] The CLEK study found a positive family history of keratoconus in 13.5% of the patients.^[37] The Dundee University Scottish Keratoconus Study^[48] reported a keratoconus rate of 5% for Caucasians and 25% for the Asian subgroup. This difference confirms a higher level of positive family history in populations with a higher prevalence of keratoconus. Similar results were observed in studies involving patients with keratoconus in families with many children.^[6] Lapeyre *et al.* collected data from 94 unrelated patients already diagnosed with keratoconus and at least 2 of their first-degree relatives. Among the 221 relatives, 20 (9.05%) were diagnosed with keratoconus and

31 (14.03%) with subclinical keratoconus. The prevalence was estimated to be 0.14 among their parents, 0.03 among their children, and 0.10 among their siblings.^[35] In the Iranian rural study, there was a higher odds ratio for the sibling pairs than parent-offspring pairs.^[32] In communities with consanguineous relationships, the genetic influence for keratoconus is also strongly present.^[49]

Environment

Keratoconus prevalence is not the same throughout the different parts of the world. Northern Europe, the Urals, northern USA, and Japan have low numbers,^[5,6,8,13,42,50] whereas in countries of the Middle East,^[14-16,18,22,23] India,^[18] and China,^[19] keratoconus is relatively common. A characteristic shared by the Middle East countries and some areas in India is the hot and dry climate, where oxidative damage due to excessive ultraviolet light exposure and ethnic background and nutrition seem to facilitate the manifestation of keratoconus^[51] [Table 1]. Rabinowitz analyzed the main environmental factors associated with 218 patients with keratoconus were allergy in 44%, joint hypermobility in 34%, eye rubbing in 80%, and positive family history 10% compared with 183 regular patients (35%, 12%, 58%, and 0.05%, respectively).^[47]

Eye rubbing and atopy

Allergy and syndromic conditions, such as Down's,^[52] stimulate eye rubbing.^[31] This action induces biomechanical alterations and inflammation of the cornea. Approximately 70% of keratoconus patients report rubbing their eyes. There are some variations in this association, whether the eye rubbing is gentle or vigorous^[48] and the rubbing length. The CLEK study reported that 48% of keratoconus patients rubbed both eyes vigorously, and 2.2% rubbed only one eye.^[37] Asymmetric keratoconus has also been correlated with eye rubbing. The mechanism behind this association includes the trauma on the ocular surface^[53] that induces epithelial and stromal cells to secrete matrix metalloproteinases, which together with the release of inflammatory mediators lead to apoptosis of keratocytes and progressive loss of the stromal collagen and corneal thinning.^[53]

There are some conflicting reports in the literature regarding the association between keratoconus and atopy.^[53] A positive association has been reported,^[35,54-56] but many reports did not find a significant association when compared to a control group.^[57-59] A multivariate logistic regression analysis confirmed that atopy was not truly associated with keratoconus but with eye rubbing.^[6,31,35,48,52,54,55,60]

Other factors

The association between diabetes and keratoconus has been reported.^[61] Diabetes can exert a protective against keratoconus by enhancing nonenzymatic glycosylation, which increases protein crosslink.^[62,63]

Other genetic conditions have been linked to keratoconus such as mitral valve prolapse,^[64] floppy eyelid syndrome,^[65] obstructive sleep apnea,^[30,66] and connective tissue disorders

as Ehlers-Danlos, Marfan syndrome, and Osteogenesis Imperfecta.^[67]

CONCLUSION

The prevalence of keratoconus is variable and affects up to 5% of the population in some regions of the world, as the Middle East. Both sexes are affected, reaching different ethnic groups. Environmental factors such as sunlight exposure and dry weather, eye rubbing, and genetic factors contribute to its pathogenesis. The combination of new imaging technologies and artificial intelligence algorithms has allowed earlier diagnosis and more efficient therapy, improving the visual prognosis and quality of life of patients with keratoconus.

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Conflicts of interest

There are no conflicts of interest.

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