Evaluating the Influence of Eye Rubbing and Genetic Predisposition on Keratoconus in Bucaramanga (Colombia): A Case-control Study

Duarte-Bueno Laura María[1,2], Tello Alejandro[1–4], Diaz-Martínez Luis Alfonso[1], Escobar Sergio[2,3], Galvis Virgilio[2–4]

[1]Universidad Industrial de Santander UIS, Bucaramanga, Colombia
[2]Fundación Oftalmológica de Santander FOSCAL, Floridablanca, Colombia
[3]Centro Oftalmológico Virgilio Galvis, FOSCAL, Floridablanca, Colombia
[4]Universidad Autónoma de Bucaramanga (UNAB), Bucaramanga, Colombia

Laura María Duarte-Bueno, MD.

Correspondence address:
Faculty of Health, Department of Surgery, Universidad Industrial de Santander UIS
Bucaramanga, Street. 32 #29–31
Postal code 680002, Colombia
E-mail: lauramariadb95@gmail.com

Submitted to the editorial board: August 8, 2024
Accepted for publication: October 9, 2024
Available on-line: January 20, 2025

The authors of the study declare that no conflict of interest exists in the compilation, theme and subsequent publication of this professional communication, and that it is not supported by any pharmaceutical company.

SUMMARY

Aim: To determine risk factors associated with keratoconus in Bucaramanga, Colombia.
Material and Methods: A paired case-control study was conducted at Bucaramanga, Colombia, between November 2022 and December 2023. The controls were age- and sex-matched. Patients answered a questionnaire designed for this study regarding their family history of keratoconus, eye rubbing, atopy, sun exposure, and sleeping habits. Information from medical records was also obtained. Univariate and multivariate conditional analyses were used to test the significance of associations.
Results: One hundred fifty-six patients with a diagnosis of keratoconus and 312 controls were included. Univariate analyses revealed significant differences between cases and controls in the following factors: very frequent eye rubbing (OR = 20.9, 95% CI 6.2–70.1), a positive family history of keratoconus (OR = 13.0, 95% CI 5.5–30.8), a personal history of atopy (OR = 2.2), and nocturnal eye compression (OR = 1.7, 95% CI 1.0–2.7). Multivariate analysis showed a statistical significance for eye rubbing (OR = 6.9, 95% CI 3.8–12.5), and family history of keratoconus (OR = 10.3, 95% CI 2.3–44.9). There was a significant mild interaction between both, since when the two coincided the OR increased up to 74.1 times.
Conclusion: Eye rubbing and family history of keratoconus were the most important risk factors for keratoconus in our population. Although it is impossible to establish causal relationships, our results suggest that controlling eye rubbing could be a potentially useful preventive measure, particularly in individuals with a family history of keratoconus. Other factors, such as sun exposure, sleeping position, and atopy, may play a role in the pathophysiology of the disease.
Key words: keratoconus, risk factors, case-control studies, Latin America

Čes. a slov. Oftal., 81, 2025, No. 3, p. 129–138

INTRODUCTION

Keratoconus is the most common primary corneal ectasia [1]. Patients present irregular astigmatism and poor vision, which affect their quality of life [2–4]. Its prevalence is variable in different parts of the world. Rates have been reported as low as 0.3 per 100 000 population (Russia) [5] and as high as 47.9 cases per 1 000 population in children (Saudi Arabia) [6,7]. In our country, Galvis et al. found a prevalence of keratoconus or suspected keratoconus of 3.9% in patients seeking refractive surgery in Floridablanca, Colombia [8]. Barraquer et al. reported that 2.8% of patients who consulted an ophthalmological institute in Bogotá, Colombia, had keratoconus or pellucid marginal degeneration [9]. Recently, Mejía-Salgado et al., analyzing the country's diagnostic code reports, reported an incidence of keratoconus of 10.4 (95% CI 10.1–10.6) per 100 000 habitants [10]. Considering these values, this disease is relatively common in our region.

For a long time, keratoconus was considered a non-inflammatory disease. However, with the findings of increased proinflammatory cytokines and collagenases in

the tears and tissues of patients with keratoconus, it is not possible to assert that inflammation does not play a role in the disease [11]. Both genetic and environmental factors have been considered to play a role in the etiology of the disease [1]. Eye rubbing and a family history of keratoconus are the most studied risk factors [12]. Other keratoconus-related factors include genetic conditions [13], atopy, sun exposure, and certain sleeping positions [2,14–17]. Recently, researchers in France showed that stopping the habit of eye rubbing was related to the stabilization of the progression of the disease [18]. This suggests that controlling this environmental risk factor could become an effective preventive measure.

Based on our current understanding, no case-control studies have yet conclusively established the association of these or other potential factors with keratoconus in Latin America. Given the ongoing uncertainties surrounding the disease's origins, there is a compelling rationale for conducting such investigations within our regional context.

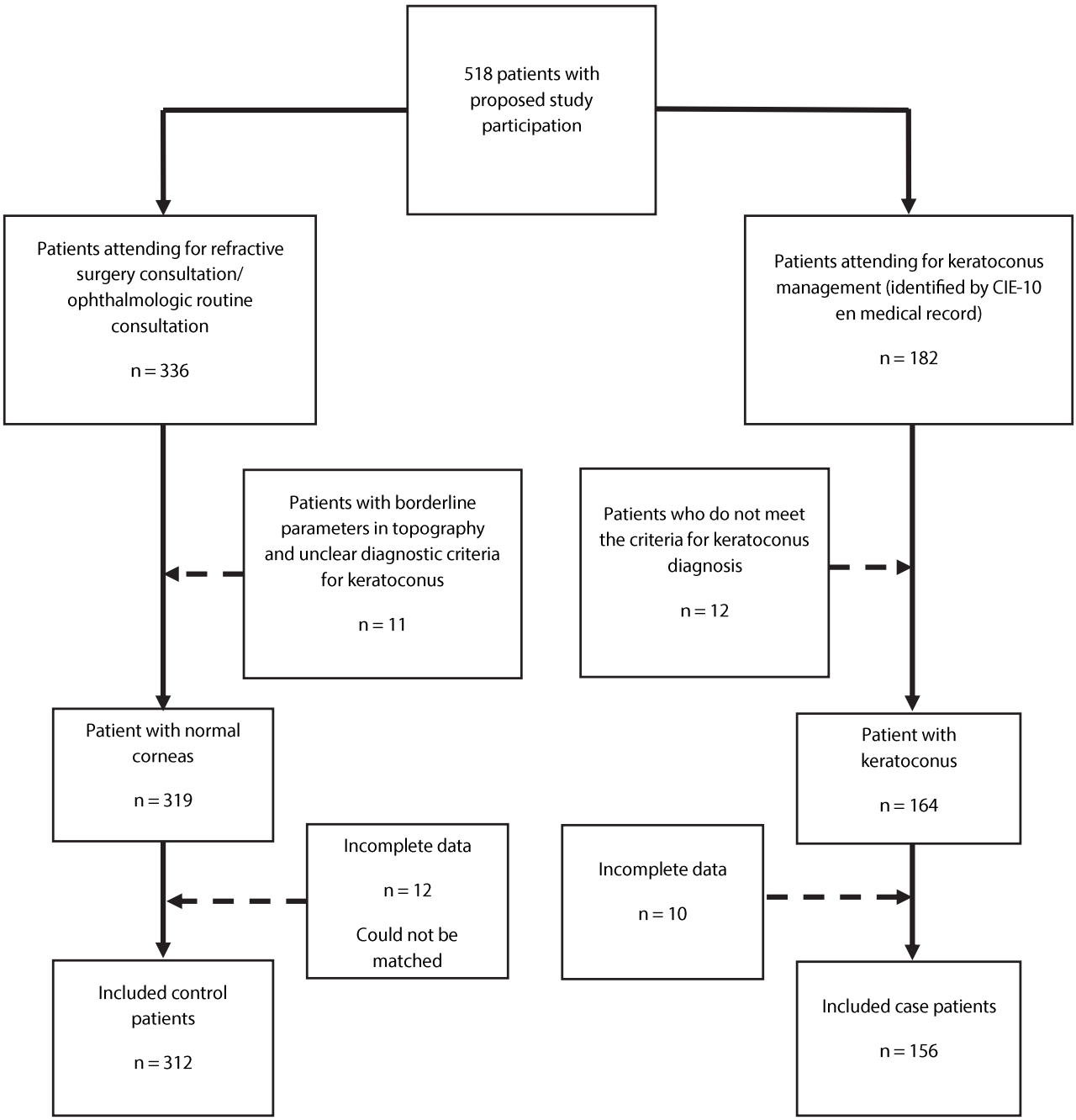

Figure. 1. Patients attending for keratoconus management (identified by ICD-10 in medical records)
ICD -10 - International Classification of Diseases
CIE – 10 is in Spanish, ICD -10 is in English which refers to the 10th revision of the International Classification of Diseases (ICD), a medical classification list by the World Health Organization (WHO)

MATERIALS AND METHODS

Ethical approval. Verbal informed consent was obtained from each patient following the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the Universidad Industrial de Santander (Minute no. 10 of 06/17/2022) and the Ethics Committee of the FOSCAL clinic (Minute no. 07047/2022 of 10/14/2022).

Design. Case-control study matched by age and sex, with a maximum difference of two years. The case-to-control ratio was 1:2. The research was carried out at the Virgilio Galvis Ophthalmological Center of the FOSCAL Clinic, in Bucaramanga, Colombia, between November 2022 and December 2023.

Study population. Patients aged 18 years or older who met the definitions of cases or controls were included.

Case definition: Patients diagnosed with unilateral or bilateral keratoconus confirmed by corneal topography based on specific parameters according to the device used. (19):

- Galilei (Ziemer Ophthalmic Systems, Port, Switzerland): Keratoconus Probability Index > 18.6% and Keratoconus Probability > 25.6%
- Sirius (CSO, Florence, Italy): the result of the artificial intelligence neural network included in the device, indicating "Keratoconus"
- MS-39 (CSO, Florence, Italy): the result of the artificial intelligence neural network included in the device, indicating "Keratoconus"

Control definition: Patients seeking refractive surgery in whom keratoconus was ruled out by corneal tomography (Galilei, Sirius, or MS-39) considering the same parameters.

Exclusion criteria were common to both cases and controls: posterior keratoconus (congenital or acquired), inability to accurately recall events related to the study questionnaire, presence of severe ocular surface disease that could interfere with the accurate diagnosis of keratoconus, and history of corneal surgery before the diagnosis of keratoconus.

The questionnaire designed for this research was based on the surveys conducted by various authors [16,20,21]. Initially, subjects with keratoconus were contacted by telephone, and those who agreed to participate answered the questionnaire. The data were filled out in REDCap [22] in real-time. The controls were identified in the database of patients undergoing refractive surgery,

Table 1. Demographic Characteristics of the population, topographic findings, and Amsler-Krumeich

Parameters	Cases (n = 156)		Controls (n = 312)		p-value
Age (years)*	29.5 (25.5 to 37.0)		31.0 (26.0 to 37.0)		0.226
Keratometry (diopters)*					
Eye	Right	Left	Right	Left	
Minimum K	44.5 (43.1–47.4)	44.8 (43.0–47.5)	42.7 (41.8–43.8)	42.7 (41.7–43.6)	< 0.001
Maximum K	49.0 (46.5–52.8)	49.4 (45.8–53.1)	44.2 (43.2–45.2)	44.2 (43.2–45.2)	< 0.001
Average K	46.8 (44.7–50.4)	46.9 (44.7–50.4)	43.4 (42.5–44.4)	43.3 (42.6–44.5)	< 0.001
Thinnest pachymetry (microns)*					
Right eye	464 (433–486)		544 (523–566)		< 0.001
Left eye	459 (429–187)		543 (523–565)		< 0.001
Amsler-Krumeich classification					
Right eye					
1	74 (47.4%)		n/a		
2	37 (23.7%)		n/a		
3	18 (11.5%)		n/a		
4	27 (17.3%)		n/a		
Left eye					
1	74 (47.4%)		n/a		
2	41 (26.3%)		n/a		
3	17 (10.9%)		n/a		
4	24 (15.4%)		n/a		

Classification of the eyes included in the study.
**Median (interquartile range)*
K – keratometry, n/a – not applicable

in whom the same process was performed. Subsequently, one of the authors completed the remaining information from the medical record.

The variables analyzed were diagnosis of keratoconus, eye rubbing, family history of keratoconus, type of relationship with the family member diagnosed with keratoconus, consanguinity of parents, type of consanguinity relationship between parents, sleeping position, ocular compression when sleeping, atopy, socioeconomic status, sun exposure, patient age, sex, eye diagnosed with keratoconus, topographic classification (Amsler-Krumeich scale), hand dominance, and preferred eye for rubbing.

Statistical analysis. Sample size calculation was performed for two main outcomes of interest, to estimate the likelihood ratio (*odds ratio* – OR –) considering **α of 0.05, β of 0.2**, and a case-control ratio of 1:2. It was assumed that the expected prevalence of family history of keratoconus among controls would be 1%. At the same time, that of eye rubbing would be 28%, as estimated by the studies by Bawazeer [23] and Gordon-Shaag [20], with a potential OR for the first factor of 6.3 and 3.4 for the second. The estimated sample size was 124 cases and 248 controls for family history, and 28 cases and 56 controls for eye rubbing. Finally, the sample size calculated for family history was chosen, as it ensured the necessary power for all primary outcomes.

The analysis was performed with Stata/IC 16.1 (StataCorp LLC, College Station, Texas, United States of America), beginning with the descriptive univariate analysis of each group separately (cases and controls). The normality of the quantitative variables was evaluated using the Shapiro-Francia test. If they had a normal distribution, they were described as mean and standard deviation, and if not, median and interquartile range (IQR) were used. Subsequently, to establish differences between cases and controls, conditional logistic regression was performed for each variable, and the raw OR of each was estimated. Finally, conditional multivariate modeling was conducted to calculate the adjusted OR for the two main variables of interest, while accounting for other potential confounding factors.

RESULTS

Characteristics of the population. As shown in Figure 1, we included 156 patients with a diagnosis of keratoconus and 312 controls matched by age and sex; 59.0% of both groups were men. Table 1 shows the general characteristics of the population studied.

In neither of the two groups (cases and controls) were significant differences detected in keratometry between the right eye (OD) and the left eye (OS). On the other hand, there were statistically significant differences between cases and controls in the values of minimum, maximum, and average keratometry (K). The minimum K in the OD was 1.9 (95% CI 1.3–2.5) diopters and in the OS 2.1 (95% CI 1.3–2.8) diopters, steeper in cases than in controls. The maximum K in the OD was 4.8 (95% CI 4.0–5.5) diopters and in the OS 5.2 (95% CI 4.3–6.2) diopters, steeper in cases than in controls. The average K in the OD was 3.4 diopters (95% CI 2.4–4.3) and in the OS was 4.8 diopters (95% CI 4.0–5.5), steeper in cases than in controls. (Table 1).

Characteristics of patients with keratoconus. The median age of diagnosis of keratoconus was 18 (IQR 15–23) years. According to the Amsler-Krumeich scale, the keratoconus severity of the OD (111 eyes, 71.1%) in stages 1 and 2, was similar to the distribution of the OS (74 eyes, 73.2%) (Table 1).

The 42.6% of subjects with a dominant right hand and the 50% with a dominant left hand, in the keratoconus group, reported having rubbed both eyes equally. Among those who reported a preference for rubbing one eye, 21.3% of individuals diagnosed with keratoconus and with a dominant right hand reported

Table 2. Relationship between preferred eye for eye rubbing, dominant hand, and asymmetry assessed by the Amsler-Krumeich classification in cases with keratoconus

Preferred eye for rubbing	Dominant hand		
	Right (n = 136)	Left (n = 18)	Ambidextrous (n = 2)
Both equally	58 (42.6%)	9 (50.0%)	0 (0%)
Right	29 (21.3%)	2 (11.1%)	2 (100.0%)
Left	22 (16.2%)	7 (38.9%)	0 (0.0%)
Not sure	27 (19.9%)	0 (0.0%)	0 (0.0%)
Preferred eye for rubbing	Most affected eye (Amsler-Krumeich classification)		
	Right (n = 37)	Left (n = 32)	No asymmetry (n = 87)
Both equally	15 (40.5%)	17 (53.1%)	35 (40.2%)
Right	14 (37.8%)	0 (0.0%)	19 (21.8%)
Left	3 (8.1%)	11 (34.4%)	15 (17.2%)
Not sure	5 (13.5%)	4 (12.5%)	18 (20.7%)

a preference for rubbing the OD, only 16.2% reported a preference for rubbing the OS. In the group of subjects with keratoconus, with the left hand dominant, 38.9% reported having rubbed the OS more versus 11.1% who reported rubbing the OD more (p = 0.004) (Table 2).

In patients with asymmetric keratoconus (Amsler-Krumeich classification), with greater involvement in the OD, the highest percentage (40.5%) reported having rubbed both eyes equally. Conversely, 37.8% reported having rubbed the OD more, while 8.1% reported rubbing the OS more. Among patients with more severe involvement in the OS, 53.1% reported having rubbed both eyes equally, none (0.0%) reported having rubbed the OD more, and 34.4% reported having rubbed the OS more (p < 0.001). (Table 2).

Risk factors. In the univariate analysis, it was found that the OR was statistically significant for the frequent (2 to 9 times/day) or very frequent (> 10 times/day) eye-rubbing groups and a gradient effect was evident (the OR was much higher for the very frequently eye-rubbing group than for the frequently eye-rubbing group). Combining these two groups (frequent or very frequent eye rubbing), they were 7.9 times (95% CI 4.7–13.1) more likely to present keratoconus than the controls (Table 3).

Table 3. Univariate analysis of studied risk factors for keratoconus

Parameters	Cases (n)	Controls (n)	Crude OR (95% CI)
Eye rubbing			
Never	5 (3.2%)	34 (10.9%)	Reference
Rarely (NOT every day)	10 (6.4%)	61 (10.6%)	1.20 (0.3–4.2)
Moderately (once/day)	15 (9.6%)	110 (35.3%)	1.02 (0.3–3.0)
Frequently (2 to 9 times/day)	87 (55.8%)	95 (30.5%)	6.67 (2.3–19.3)
Very frequently (> 10 times/day)	39 (25.0%)	12 (3.9%)	20.91 (6.2–70.1)
Preferred eye for rubbing			
Both eyes equally	67(43.0%)	183 (58.7%)	Reference
Right	33(21.2%)	34 (10.9%)	2.60 (1.5–4.6)
Left	29 (18.6%)	15 (4.8%)	4.95 (2.5–9.9)
Not sure	27 (17.3%)	80 (25.6%)	0.87 (0.5–1.5)
Family history of keratoconus			
Negative	114 (73.1%)	302 (97.8%)	Reference
Positive	42 (26.9%)	10 (3.2%)	13.04 (5.5–30.8)
Relationship with family member diagnosed with keratoconus			
No family history	114 (73.1%)	302 (97.8%)	Reference
First grade	8 (5.1%)	3 (0.9%)	8.94 (2.0–40.4)
Second grade	16 (10.3%)	6 (1.9%)	8.18 (2.7–24.4)
More distant than second–degree	18 (11.5%)	1 (0.3%)	48.63 (6.2–381.9)
Parental consanguinity			
Negative	155 (99.4%)	311 (99.7%)	Reference
Positive	1 (0.6%)	1 (0.3%)	2.00 (0.1–32.0)
Sleeping position			
Supine position	27 (17.3%)	62 (19.9%)	Reference
Lateral decubitus	62 (39.7%)	142 (45.5%)	1.04 (0.6–1.8)
Prone position	31 (19.9%)	51 (16.4%)	1.45 (0.8–2.8)
Not sure	36 (23.1%)	57 (18.3%)	1.50 (0.8–2.9)
Nocturnal eye compression			
No	104 (66.7%)	239 (76.6%)	Reference
Yes	39 (25.0%)	55 (17.6%)	1.65 (1.0 –2.7)
Not sure	13 (8.3%)	18 (5.8%)	1.64 (0.4–2.4)

Table 3. Univariate analysis of studied risk factors for keratoconus – continuation

Same position when getting up			
Yes	43 (27.6%)	108 (34.6%)	Reference
No	78 (50.0%)	139 (44.6%)	1.37 (0.9–2.1)
Not sure	35 (22.4%)	65 (20.8%)	1.33 (0.8–2.3)
Personal history of atopy			
Negative	76 (48.7%)	212 (68.0%)	Reference
Positive	80 (51.3%)	99 (31.7%)	2.19 (1.5–3.2)
Not sure	0 (0%)	1 (0.3%)	0.0
Hours outdoors in childhood and early adolescence			
Less than an hour	4 (2.6%)	2 (0.6%)	Reference
1–4 hours	56 (35.9%)	135 (43.3%)	0.21 (0.0–1.2)
4 or more hours	96 (61.4%)	175 (56.1%)	0.27 (0.5–1.5)
Dominant hand			
Right	136 (87.2%)	292 (93.6%)	Reference
Left	18 (11.5%)	17 (5.4%)	2.24 (1.1–4.4)
Ambidextrous	2 (1.3%)	3 (1.0%)	1.77 (0.3–11.0)
Socioeconomic stratum			
1	16 (10.3%)	69 (22.1%)	Reference
2	55 (35.3%)	114 (36.5%)	2.09 (1.1–4.0)
3	38 (24.4%)	64 (20.5%)	2.56 (1.3–5.1)
4	38 (24.4%)	53 (17.0%)	3.08 (1.5–6.2)
5	9 (5.6%)	12 (3.9%)	3.18 (1.1–9.0)

OR – Odds ratio, CI – Confidence interval
Reference: In a table from a case-control study where the Odds Ratio (OR) is calculated, the term "reference" refers to the group used as the point of comparison to interpret the results. This reference group has an OR equal to 1 because it represents the baseline category against which the other categories are compared.

Patients with keratoconus more frequently had a family history of keratoconus (OR 13.0, 95% CI 5.5–30.8), were more likely to have been diagnosed with atopy (OR 2.2, 95 % CI 1.5–3.2), slept in such a way that they could cause ocular compression (OR 1.7, 95% CI 1.0–2.7), and coming from the highest socioeconomic stratum (Table 3). However, no relationship was found between having keratoconus and the other variables.

Finally, the conditional multivariate analysis showed that eye rubbing and family history of keratoconus were the two most relevant risk factors associated with keratoconus, after adjusting for socioeconomic stratum, sleeping position, nocturnal ocular compression, and history of atopy, which were statistically significant only in the univariate analysis. Thus, it can be stated that in the population studied, patients with keratoconus were 10.3 (95% CI 2.3–44.9) times more likely to have a family history of keratoconus and 6.9 (OR 3.8–12.5) times more likely to have a history of eye rubbing more than once a day, with a significant interaction between both factors, since when the two coincided the OR increased up to 74.1 times (95% CI 19.7–278.1).

DISCUSSION

The objective of this study was to determine the risk factors associated with keratoconus in the population of Bucaramanga, Colombia, using a case-control study matched by age and sex. To the best of our knowledge, this is the first study of its kind conducted in Latin America.

The eye-rubbing habit during childhood and early adolescence, as well as a family history of keratoconus, were significant factors in the univariate and multivariate analyses. Socioeconomic stratum, sleeping position, nocturnal ocular compression, and atopy were statistically significant only in the univariate analysis. The lack of significant association in the multivariate analysis indicates that these dependent variables do not appear to be independently associated with the outcome variable (the presence of keratoconus). The association detected in the univariate analysis could be due to the effect of other variables that are correlated with both, and which could serve as confounding variables.

In most case-control studies of keratoconus, the most analyzed risk factors include the factors related to heredity

as family history, and risk factors related to environment, as eye rubbing, atopy, and sun exposure; all considered in this research. Despite the available literature in this area, the contribution of each risk factor is still imprecise, and there are some contradictory results in the literature [1].

Repetitive mechanical trauma caused by eye rubbing has been one of the most studied risk factors and is accepted as influential in the pathophysiology of keratoconus. It has even been stated that it is a *sine qua non* condition for the appearance of the disease and that it is possibly its only cause [24].

In the multivariate analysis, we found that individuals who reported frequent or very frequent eye rubbing had 6.9 (95% CI 3.8–12.5) times higher odds of presenting keratoconus than the controls. Other authors, such as Gordon-Shaag et al. [20], Hashemi et al. [25], and Bawazeer et al. [23], also found a high relationship between eye rubbing and the presence of keratoconus, with OR values relatively similar: 10.2 (95% CI 4.4–23.5), 6.3 (95% CI 1.6–24.3) and 5.4 (95% CI 2.1–14.1), respectively. Mazharian et al. described a strong association of eye rubbing during the day with the presence of highly asymmetric keratoconus (OR of 135.0, 95% CI 6.44–2868.2) [16]. On the other hand, a systematic review and meta-analysis that evaluated the relationship between eye rubbing with keratoconus reported a consolidated OR of 3.1 (95% CI 2.2–4.0) [12]. In our study, we also observed a gradient in the frequency of eye rubbing and the diagnosis of keratoconus. The OR was not significant for eye rubbing frequencies of once a day or less. However, patients who reported rubbing their eyes frequently (2 to 9 times a day) or very frequently (10 or more times a day) showed a significant OR, which was higher for the latter group (Table 3). The finding of the increase of the OR in direct relation to the higher frequency of eye rubbing reinforces the existence of an association between this factor and the disease. Nevertheless, the identification of eye rubbing as a predictive factor for keratoconus has not been universal: in the publications by Millodot et al. [12,26] and Shneor et al. [3], no statistically significant relationship was found between eye rubbing and keratoconus, with OR of 1.8 (95% CI 0.7–4.7) and 2.2 (0.6–7.8), respectively. Additionally, it is noteworthy that, as observed in other studies, some individuals with keratoconus (3.2% of cases in the present study) reported never having had the habit of rubbing their eyes. Conversely, 34.4% of the controls reported having had the habit of eye rubbing, either frequently or very frequently, without developing the disease [27].

Genetically determined susceptibility to keratoconus has been strongly debated in recent decades [1,28]. The family history of keratoconus has been analyzed in multiple investigations and by various authors. However, not all show results similar to those found in our study [OR in the multivariate analysis of 10.3 (95% CI 2.3–44.9)]. The meta-analysis published in 2020 by Hashemi et al. analyzed this predictive factor and the consolidated calculation was that patients with keratoconus were 6.4 (95% CI 2.6–10.2) times more likely to have relatives with a diagnosis of keratoconus [12]. Some studies included in this meta-analysis that support this association were: Millodot et al. with an OR of 17.1 (95% CI 5.0–57.8) [26], Gordon-Shaag et al. with an OR of 9.7 (95% CI of 2.8–33.1) [17] and Naderan et al. with an OR of 7.1 (95% CI 3.7–13.6) [2]. The above findings align with the registry of familial keratoconus cases and the identification of both autosomal dominant and recessive inheritance patterns in genetic linkage studies [1]. Nevertheless, other authors such as Moran et al., Mazharian et al., and Bawazeer et al. have reported that a family history of keratoconus did not show a statistically significant relationship with its appearance [15,16,23].

When analyzing the combined effect of these two factors, the most significant ones identified in this study, the habit of eye rubbing and the family history of keratoconus, an interaction between them was found, as the combined effect of both is slightly higher than the product of the two independent OR (OR 74.1, 95% CI 19.7–278.1). These notable values of increased risk seem to support

Table 4. Studies with OR calculation for eye rubbing and family history of keratoconus

Publication	Country	Eye rub – OR (95% CI)	Family history of keratoconus – OR (95% CI)
Bawazeer et al., 2000[23]	Canada	5.4 (2.1–14.1)	6.31 (0.6–66.0)
Gordon–Shaag et al., 2013[20]	Israel	10.2 (4.4–23.5)	1.93 (0.6–6.5)**
Gordon–Shaag et al., 2015[17]	Israel	3.4 (1.7–6.8)	9.68 (2.8–33.1)
Hashemi et al., 2014[25]	Iran	6.3 (1.6–24.3)	11.40 (2.5–51.3)
Millodot et al., 2011[12,26]	Israel	1.8 (0.65–4.7)*	17.1 (5.0–57.8)
Naderan et al., 2015[2]	Iran	3.4 (2.4–4.8)	7.09 (3.7–13.6)
Shneor et al., 2014[3]	Israel	2.2 (0.6–7.8)	Not calculated
Moran et al.,[15]	France	8.3 (3.9–18.3)	1.88 (0.3–15.7)
Mazharian et al., 2020[16]	France	135.0 (6.4–2868.2)	1.97 (0.1–32.5)**
Almusawi et al., 2021[21]	Iraq	4.9 (1.8 –13.3)	25.52 (2.6–254.4)

OR – Odds ratio, CI – Confidence interval
**Reported in the meta-analysis published by Hashemi et al.*
***Univariate analysis*

the theory that, in a person with a specific genetic substrate, the environmental trigger (eye rubbing) can precipitate the onset of the disease. Table 4 shows studies with OR calculation for eye rubbing and family history of keratoconus.

Consanguinity is another factor that could be related to keratoconus and that supports the genetic component of this pathology. It has been found that patients who are the product of a consanguinity relationship have approximately three to four times greater probability of being diagnosed with keratoconus [20,21]. This phenomenon has been studied in Middle Eastern countries, where this type of marital relationship is more frequent [3,20]. In the present study, no relationship was found between keratoconus and parental consanguinity, a finding that coincides with other publications of case-control studies [17].

Various studies proved a statistically significant relationship between atopy, allergy, and asthma with keratoconus. Hashemi et al. in their meta-analysis concluded that eczema, asthma, and allergy increase the risk of keratoconus by 3.0 (95% CI 1.3–4.6), 1.9 (95% CI 1.3–2.6), 1.4 (95% CI 1.1–1.8) times, respectively [12]. Another investigation (Lin et al.) reported that individuals with asthma were 1.2 times more likely to develop keratoconus (95% CI 1.1–1.3) [29]. Likewise, other authors (Woodward et al.) found that asthma increased the risk of suffering from keratoconus (OR 1.3, 95% CI 1.2–1.5) [30]. On the other hand, studies such as those by Lee et al. did not find a statistically significant association between asthma, atopy, and eczema and the development of keratoconus [31]. In our study, atopy was significant in the univariate analysis, but not in the multivariate analysis. This could be due to the effect of another concurrent factor, eye rubbing, which may be a consequence of atopy and is part of its pathophysiology. It is possible that, considering the influence of eye rubbing, there is no direct relationship between atopy and keratoconus. In this research, the definition of atopy from the Nomenclature Review Committee of the World Allergy Organization in 2003 was applied, which defines atopy as "personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema" [32]. However, this concept has not been standardized in all keratoconus studies, which could also partly explain the disparity in results.

More recently it has been suggested that the contribution of mechanical ocular compression due to sleeping position could also play a role in the development of keratoconus [1]. In the study by Moran et al., it was documented that lateral and prone decubitus sleeping positions increased the risk of developing keratoconus significantly by 10.2 (95% CI 3.8–33.7) and 11.6 (95% CI 3.9–38.2) times respectively [15]. Another investigation found that sleeping in the lateral and prone sleeping position was significantly associated with the development of unilateral or highly asymmetric keratoconus (OR 65.0, 95% CI 5.1–573.9) [16]. In our study, nocturnal ocular compression did not show statistical significance in the multivariate analysis, unlike the univariate analysis. It is important to note that when asked "Do you get up in the same position in which you initially fell asleep?", only 27.6% of the cases and 34.6% of the controls answered "yes", that is, most of the subjects either did not get up in the same position or were unsure. This suggests that self-reported information is unreliable on this issue, and therefore real information is absent regarding sleeping position for most of the night. Without a doubt, the lack of instruments designed to objectively quantify sleeping positions represents a weakness in the investigation.

Exposure to ultraviolet rays leads to increased production of free radicals and thus increased oxidative stress on the corneal surface. Consequently, it has been suggested that the high prevalence of keratoconus in sunny countries versus North America and other European countries could be explained by this risk factor [33]. It has also been described that ultraviolet radiation could induce corneal collagen cross-linking, which would prevent the progression of the disease [21,33]. However, it is a factor difficult to evaluate. In one of their studies, Gordon-Shaag et al. found that wearing a hat in outdoor environments increased the risk of keratoconus (OR 5.5 95% CI 1.4–21.9) [17] and, in another study, the same authors reported that wearing sunglasses was a protective factor for keratoconus (OR 0.4, 95% CI 0.2–0.8) [20]. In our study, there was no relationship between sun exposure in childhood and keratoconus, similarly to that reported by other authors [2,21].

There are different results in the literature on the relationship between socioeconomic status and keratoconus. In our study, a gradient was found between stratum and keratoconus (the higher the socioeconomic level, the greater the probability of keratoconus), but only in the univariate analysis. Similarly, in the publication by Almusawi et al., no association was found between these two variables [21]. Conversely, in another study, patients with Medicare insurance (low-income people) had a higher risk of presenting severe keratoconus with an OR of 1.9 (95% CI 1.1–3.3), and of requiring a corneal transplant, OR of 1.7 (95% CI 1.1–2.8) [34]. However, in this study, the eye rubbing and the family history of keratoconus were not analyzed, which greatly limits its analysis [35].

This study has several limitations. A significant portion of the data is based on subjects' verbal responses to a questionnaire, which involves the risk of recall bias. Additionally, some variables are difficult to measure objectively (sun exposure and sleeping position). Despite the potential memory bias limitation of surveys, the present study not only found a significant association between a history of frequent or very frequent eye rubbing and the presence of keratoconus, but also identified a gradient effect related to the frequency of this habit. This suggests that the survey instrument was performed appropriately, as it is highly unlikely that random variation alone could produce such results.

Currently, there is an intense debate within the ophthalmological scientific community regarding the influence of hereditary factors in keratoconus. A group of French researchers, led by Gatinel, argues that hereditary factors are not associated with the disease, proposing the "no rub, no cone" theory. They cite cases of identical twins where only one twin was affected by keratoconus [36]. Additionally, two case-control studies conducted in Paris [15,16] found no significant association between a family history of keratoconus and the disease in multivariate analysis.

However, our current research, conducted in a geographical area previously unstudied in this context, aligns with findings from regions such as Israel: OR 17.1 [26], OR 9.7 [17] and Iran: OR 7.1 [2], OR 11.4 [25] which suggest a familial association with keratoconus (Table 4). This independent study supports the plausibility that hereditary factors play a role in the etiopathogenesis of keratoconus. It suggests that genetic predisposition may create a conducive environment for the disease to develop, especially if an environmental trigger, such as eye rubbing, is present, as proposed by Rabinowitz's hypothesis. This hypothesis is further supported by findings in the present study, indicating that the concurrence of genetic predisposition and environmental triggers can significantly increase the risk of developing keratoconus, with an OR of 74.1, surpassing the combined OR of these factors when considered independently. Ultimately, these findings reinforce the notion that, at least in our region and in some other areas of the world, a family history should not be dismissed as an associated factor in keratoconus.

In conclusion, keratoconus is a complex disease, in which environmental and heritable factors seem to intervene. This research identified that both eye rubbing and a family history of keratoconus are the most important risk factors for this pathology in our population, confirming the findings of various studies in other countries. It was also found that the coexistence of these two factors increases the risk of suffering from keratoconus by up to approximately 74 times. Therefore, controlling the habit of rubbing the eyes could be an effective preventive measure for this condition, particularly in those with a family history. Other factors such as sun exposure, sleeping position, and atopy could play a role in the pathophysiology of the disease. However, additional studies with more objective measurements are required.

Funding

This study did not receive funding from public or private institutions.

Disclosure

The study authors declare that no conflict of interest exists in the compilation, theme, and subsequent publication of this professional communication and that it is not supported by any pharmaceutical company.

ACKNOWLEDGMENTS

We would like to express our gratitude to engineer Sandra Carmona for her indispensable and priceless support in facilitating the logistics of this study. We also thank Diego Vega and Nicolás Rivero for their invaluable assistance in data collection.

REFERENCES

1. Rabinowitz YS, Galvis V, Tello A, Rueda D, García JD. Genetics vs chronic corneal mechanical trauma in the etiology of keratoconus. Exp Eye Res. 2021;202:1-8.
2. Naderan M, Shoar S, Rezagholizadeh F, Zolfaghari M, Naderan M. Characteristics and associations of keratoconus patients. Contact Lens Anterior Eye [Internet]. 2015;38(3):199-205. Available from: http://dx.doi.org/10.1016/j.clae.2015.01.008
3. Shneor E, Millodot M, Gordon-Shaag A et al. Prevalence of Keratoconus among Young Arab students in Israel. Int J Keratoconus Ectatic Corneal Dis. 2014;3(1):9-14.
4. Gordon MO, Steger-May K, Szczotka-Flynn L, et al. Baseline Factors Predictive of Incident Penetrating Keratoplasty in Keratoconus. Am J Ophthalmol. 2006;142(6):923-930.
5. Gorskova E, Sevostianov E. Epidemiology of keratoconus in the Ural. Vestn Oftalmol. 1998;114:38-40.
6. Torres Netto EA, Al-Otaibi WM, Hafezi NL et al. Prevalence of keratoconus in paediatric patients in Riyadh, Saudi Arabia. Br J Ophthalmol. 2018;102(10):1436-1441.
7. Santodomingo-Rubido J, Carracedo G, Suzaki A et al. Keratoconus: An updated review. Cont Lens Anterior Eye. 2022;45(3):101559. doi: 10.1016/j.clae.2021.101559
8. Galvis V, Tello A, Jaramillo JA et al. Prevalencia de queratocono en pacientes que consultaron con deseos de cirugía refractiva en un centro oftalmológico de referencia de Bucaramanga, Colombia. [Prevalence of keratoconus patients who consulted with a desire refractive surgery in ophthalmology center reference Bucaramanga, Colombia]. Rev Soc Colomb Oftalmol. 2011;44(2):129-134. Spanish.
9. Barraquer Coll C, Barrera Rodríguez RE, Molano González N. Prevalencia de pacientes con queratocono en la Clínica Barraquer en Bogotá, Colombia. [Prevalence of keratoconus patients at the Barraquer Clinic in Bogotá, Colombia]. Rev Soc Colomb Oftalmol. 2020;53(1):17-23.
10. Mejia-Salgado G, Cifuentes-González C, Rojas-Carabali W, et al. Colombian Ocular Diseases Epidemiology Study (CODES): Incidence and sociodemographic characterisation of keratoconus between 2015 and 2020. BMJ Open Ophthalmol. 2023;8(1):1-9.
11. Galvis V, Sherwin T, Tello A et al. Keratoconus: An inflammatory disorder? Eye. 2015;29(7):843-859.
12. Hashemi H, Heydarian S, Hooshmand E, Saatchi M, Yekta A, Aghamirsalim M, et al. The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2020;39(2):263-270.
13. Crawford AZ, Zhang J, Gokul A, McGhee CNJ, Ormonde SE. The enigma of environmental factors in keratoconus. Asia-Pacific J Ophthalmol. 2020;9(6):549-556.
14. Gatinel D, Galvis V, Tello A et al. Obstructive Sleep Apnea-Hypopnea Syndrome and Keratoconus: An Epiphenomenon Related to Sleep Position? Cornea. 2020;39(4):e11-e12.
15. Moran S, Gomez L, Zuber K, Gatinel D. A Case-Control Study of Keratoconus Risk Factors. Cornea. 2020;39(6):697-701.
16. Mazharian A, Panthier C, Courtin R et al. Incorrect sleeping position and eye rubbing in patients with unilateral or highly asymmetric keratoconus: a case-control study. Graefe's Arch Clin Exp Ophthalmol. 2020;258(11):2431-2439.
17. Gordon-Shaag A, Millodot M, Kaiserman I et al. Risk factors for keratoconus in Israel: A case-control study. Ophthalmic Physiol Opt. 2015;35(6):673-681.
18. Mazharian A, Flamant R, Elahi S et al. Medium to long term follow up study of the efficacy of cessation of eye-rubbing to halt progression of keratoconus. Front Med. 2023;10:1152266. doi: 10.3389/fmed.2023.1152266

19. Shetty R, Rao H, Khamar P et al. Keratoconus Screening Indices and Their Diagnostic Ability to Distinguish Normal From Ectatic Corneas. Am J Ophthalmol [Internet]. 2017;181:140-148. Available from: http://dx.doi.org/10.1016/j.ajo.2017.06.031
20. Gordon-Shaag A, Millodot M, Essa M et al. Is consanguinity a risk factor for keratoconus? Optom Vis Sci. 2013;90(5):448-454.
21. Almusawi LA, Hamied FM. Risk factors for development of keratoconus: A matched pair case-control study. Clin Ophthalmol. 2021;15:3473-3479.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform [Internet]. 2009;42(2):377-381. Available from: http://dx.doi.org/10.1016/j.jbi.2008.08.010
23. Bawazeer AM, Hodge WG, Lorimer B, Rapuano CJ. Atopy and keratonus: A multivariate analysis. Evidence-Based Eye Care. 2001;2(2):84-85.
24. Gatinel D. Eye Rubbing, a Sine Qua Non for Keratoconus? Int J Keratoconus Ectatic Corneal Dis. 2016;5(1):6-12.
25. Hashemi H, Khabazkhoob M, Yazdani N et al. The prevalence of keratoconus in a young population in Mashhad, Iran. Ophthalmic Physiol Opt. 2014;34(5):519-527.
26. Millodot M, Shneor E, Albou S, Atlani E, Gordon-Shaag A. Prevalence and associated factors of keratoconus in jerusalem: A cross-sectional study. Ophthalmic Epidemiol. 2011;18(2):91-97.
27. Gatinel D. Challenging the "No Rub, No Cone" Keratoconus Conjecture. Int J Keratoconus Ectatic Corneal Dis. 2018;7(1):66-81.
28. Bykhovskaya Y, Rabinowitz YS. Update on the genetics of keratoconus. Exp Eye Res [Internet]. 2021;202:108398. Available from: https://doi.org/10.1016/j.exer.2020.108398
29. Lin KK, Lee JS, Hou CH et al. The Sociodemographic and Risk Factors for Keratoconus: Nationwide Matched Case-Control Study in Taiwan, 1998-2015. Am J Ophthalmol [Internet]. 2021;223:140-148. Available from: https://doi.org/10.1016/j.ajo.2020.09.040
30. Woodward MA, Blachley TS, Stein JD. The association between sociodemographic factors, common systemic diseases, and keratoconus an analysis of a nationwide heath care claims database. Ophthalmology. 2016;123(3):457-465.
31. Lee HK, Jung EH, Cho BJ. Epidemiological Association Between Systemic Diseases and Keratoconus in a Korean Population: A 10-Year Nationwide Cohort Study. Cornea. 2020;39(3):348-353.
32. Johansson SGO, Bieber T, Dahl R et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October2003. J Allergy Clin Immunol. 2004;113(5):832-836.
33. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The genetic and environmental factors for keratoconus. Biomed Res Int. 2015;2015:795738.
34. Ahmad TR, Kong AW, Turner ML et al. Socioeconomic Correlates of Keratoconus Severity and Progression. Cornea. 2023;42(1):60-65.
35. Tello A, Gatinel D, Galvis V et al. Letter Regarding: Socioeconomic Correlates of Keratoconus Severity and Progression. Cornea. 2023;42(6):E9.
36. Bitton K, Dubois M, Moran S, Gatinel D. Discordant Keratoconus in Monozygotic Twins. Case Rep Ophthalmol. 2022;13(1):313-317.