

Asthma and Keratoconus: An analysis of the risk factors association with the severity of keratoconus

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Abstract

Background: A cross-sectional study was undertaken in Australia to explore a wide range of risk factors associated with keratoconus. A questionnaire addressing age, gender, educational background, ocular and medical history, smoking and alcohol consumption, and physical examination comprising anthropometric measurements was collected; eye examination was undertaken. The associations between a range of risk factors and keratoconus was determined using univariate and multivariable linear regression analyses.

Main Text: A total of 260 keratoconus subjects were included in this study. Mean age of subject was 35.5 (SD= 14.8) years and the majority of the subjects were European 171 (68.2%). Initial univariate regression analysis identified the following risk factors at the $p < 0.1$ level with keratoconus: higher body mass index, smoking cigarettes, diabetes, rheumatoid arthritis and asthma were associated with increased severity of keratoconus, whereas eczema was associated with less severe keratoconus. Following multivariable regression analysis, only asthma remained as a significant risk factor associated with 2.2 diopters (D) steeper average mean keratometry compared to keratoconus subjects having no asthma [$p = 0.03$; $\beta = 2.18$; 95% confidence intervals: 1.22, 4.14].

Conclusion: Our study describes the comprehensive assessment of all the known risk factors in a large keratoconus cohort recruited in Australia. Our study has reported asthma as the only risk factor found to be significantly associated with keratoconus. The results of this study allow us to better understand the aetiology of keratoconus and such a knowledge could be useful in instigate systemic management of patients to slow or prevent keratoconus.

Background

Keratoconus (KC) typically presents as a bilateral, asymmetric condition characterised by progressive corneal thinning resulting in corneal protrusion, irregular astigmatism and decreased vision. The prevalence of KC ranges from 1:2000 cases (reported in 1986)[36] to 1:375 (reported in 2016 [16]. Glasses and contact lenses are the main treatment options for the mild and moderate stages of KC. In severe KC cases, the central cornea becomes extremely thin and irregular and corneal transplantation surgery may be required to restore vision. KC is the commonest indication for corneal transplantation in Australia, accounting for 31% of grafts[21]. The aetiology of KC is likely multifactorial reflecting the interplay of a range of genetic and environmental factors[12] but may also be influenced by mechanical trauma such as eye rubbing[4, 15].

There is no medical treatment to halt the progression of KC apart from stiffening of the cornea by corneal collagen crosslinking (CXL)[10]. While diagnosing the end stage of KC for corneal transplantation is relatively straightforward, diagnosing and detecting the earlier stages when most vision can be retained still presents challenges. Despite KC being a relatively common corneal disease, there is a lack of large,

prospective clinical studies of the disease. Indeed the USA-based Collaborative Longitudinal Evaluation of Keratoconus (CLEK) [5, 46, 49, 53, 54, 55] study and the UK based Dundee University Scottish Keratoconus Study (DUSKS)[50] are the only two longitudinal prospective studies evaluating KC. These two studies looked into the characteristics and clinical data that might influence KC progression, but they did not include all the assessment of known environmental risk factors. Other studies investigating risk factors in KC had methodological limitations including: retrospective study design [1, 51], small sample size[19, 23, 33, 51], postal questionnaires[34], the absence of ocular biometric measures[6, 7, 8, 28, 30, 45], found a relatively weak association [33] and lack of a comprehensive environmental risk factor questionnaire[6, 7, 8, 28, 30]. There is an growing need to better understand the aetiology of the condition not only due to the recent increase in rates of case but also due to the costs associated with the diagnosis and management of keratoconus that represent a significant economic burden to the patient as well as the society [9].

Methods

This current prospective study recruited patients of both genders over a wide age range together with corneal tomography and a detailed questionnaire (including all currently known major risk factors) in order to assess the association of these factors with KC. The results will allow us to better understand the etiology of KC and also assist in early diagnosis of KC so as to provide early disease management and ultimately arrest progression of this disease without the need for corneal transplantation.

The subjects for this study were recruited from public clinics at the Royal Victorian Eye and Ear Hospital (RVEEH), private ophthalmologists' rooms, optometry clinics or consenting general public with KC. The study protocol was approved by the RVEEH Human Research and Ethics Committee (Project # 10/954H). This protocol followed the tenets of the Declaration of Helsinki and all privacy requirements were met. A patient information sheet, consent form, privacy statement and patient rights were provided to all individuals participating in the study.

All KC patients were required to complete a study questionnaire, and clinical and physical examination, which included the anthropometric measurements of height and weight. Inclusion and exclusion criteria have been described elsewhere[39, 40, 41]. In brief, KC was diagnosed on the basis of the presence of one or more of the following: an irregular cornea (as determined by distortion of keratometric mires and/or corneal topography/tomography imaging), scissoring of the retinoscopic reflex, and demonstration of at least one biomicroscopic sign, including Vogt's striae, Fleischer's ring, or corneal thinning and/or scarring typical of KC. To assess the association of risk factors on disease, we obtained corneal curvature data from the four-map selectable display of the Pentacam tomography system (Oculus, Wetzlar, Germany).

The study questionnaire collected the following information: age, gender, educational background, birth history, childhood infections, time spent undertaking near work, intermediate work and outdoors, duration of keratoconus, ocular and medical history and smoking and alcohol consumption habits, information on the subject's general health status and current medication and eye rubbing. Questions on a number of

disorders and diseases related to common medical conditions including clinically diagnosed asthma, eczema, diabetes, hypertension, rheumatoid arthritis, migraine, allergy, connective tissue disorders and sleep disorders were recorded. The specific type, date of onset and medications and/or other treatments were recorded.

Biometric Measurements

All individuals had their height (H) measured using a wall-mounted measuring scale (Livingstone International, Rosebery, Australia) and their weight measured using calibrated electronic scales (Livingstone International, Rosebery, Australia). The two variables (height and weight) were then placed in the universally recognised formula ($W[\text{kg}] / H[\text{m}]^2$), that allowed determination of the participant's body mass index (BMI).

Statistical Analysis

All statistical analyses were conducted using Stata version 14.0 (Stata Corp, College Station, TX). Normality of the variables was examined using boxplots, Kolmogorov-Smirnov and Shapiro-Wilks tests. Continuous variables (age and BMI) are presented as median (interquartile range [IQR]) for skewed distribution and mean (standard deviation [SD]) for normal distribution, whereas categorical variables are presented as absolute (n) and relative frequencies (%). Mean corneal curvature of each eye was calculated automatically by Pentacam imaging as the mean value of central radial curvatures (Avg Km). Univariate regression analysis was performed to explore the association of a number of risk factors with KC. As all the subjects had asymmetric, bilateral KC, the steepest Avg Km of either the right or left eye was used to identify risk factor association. In the second step, multivariable linear regression analysis was performed on all parameters which showed a $p < 0.1$ significance with KC in the univariate analysis. All continuous variables were examined for correlations and multi-collinearity using Pearson Product-Moment Correlation. A two-tailed p -value < 0.05 was considered statistically significant.

Results

General Characteristics

The study included a total of 260 KC subjects, of whom 159 subjects (61.2%) were male. Of the 260 subjects, 251 (96.5%) completed the general and medical questionnaire. The mean age of the recruited subjects who completed all aspects of the study was 35.5 (SD = 14.8) years. The majority of the subjects, 171 (68.2%) were European, while 37 (14.6%) were Asians (primarily South, South-East Asians) and the remaining 43 (17.2%) were of other ethnicity (including Middle Eastern, Africans and Mixed) (Table 1).

Table 1
Demographic features of the Keratoconus
study subjects

Variables	N (%)
Gender (male)	152 (61.2)
Ethnicity	
European	171 (68.2)
Asians	37 (14.6)
Others	43 (17.2)
Repeated infections as a child	67 (26.7)
Cigarette smoking	34 (13.5)
Alcohol consumption	130 (51.8)
Eye rubbing	175 (69.7)
Diabetes	10 (4.0)
Hypertension	24 (9.6)
Sleep disorder	8 (3.2)
Connective tissue disorder	2 (0.79)
Rheumatoid Arthritis	12 (4.8)
Migraine	7 (2.8)
Allergy (excluding hay fever)	62 (24.7)
Hay fever	38 (15.1)
Asthma	12 (4.8)
Eczema	6 (2.4)

In the general medical conditions, 24.7% (64) of the subjects reported having an allergic disorder (15.1% hay fever, 4.8% asthma and 2.4% eczema), 9.6% high blood pressure, 8% connective tissue disorder, 4.8% arthritis, 4% diabetes, 3.2% sleep disorders and 2.8% migraine. 26.7% (67) subjects reported that they suffered from repeated systemic infections during childhood. 175 subjects (69.7%) reported that they rubbed their eyes frequently. The average time since diagnosis of keratoconus for the subjects was 13.31 ± 12.80 years.

A significant number of subjects 196 (78.1%) had completed at least secondary education of whom 153 (61%) had also either attended or completed further study at a tertiary higher education institute, technical and further education or a university degree.

Risk factor assessment

As a first step, univariate regression analysis was undertaken to identify associations at $p < 0.1$. Associations with increased risk of KC were identified with higher BMI ($p = 0.075$), subjects belonging to other ethnic group ($p = 0.09$), smoking cigarettes ($p = 0.078$), having arthritis and asthma ($p = 0.05$, $p = 0.03$ respectively). Diabetes was associated with a protective effect for KC ($p = 0.08$) as was eczema ($p = 0.05$). There was no association between KC and age, gender, education level, eye rubbing, alcohol consumption, having repeated infections as a child or having other systemic condition like hypertension, migraine, connective tissue disorder, sleep apnoea, allergies and hay fever, or time spent on outdoor/intermediate/near activities. All risk factors with a $p < 0.1$ were included in the multivariate regression analysis and significant association was considered as being $p < 0.05$. Only asthma presented with a significant association of increased risk of severe KC ($p = 0.03$) whereas BMI, smoking and having any other systemic condition were not associated with increased risk of KC ($p > 0.05$).

KC subjects having asthma presented with a significant increase ($p = 0.03$) of 2.2 Diopters (D) steeper Avg Km ($\beta = 2.18$, 95% CI: 1.22, 4.14) compared to those subjects with no asthma (Table 2). Interestingly, eczema was negatively associated [β : -5.28 (95% CI: -11.02, 0.47)] with the KC, whereas rheumatoid arthritis, was positively associated [β : 1.92 (95% CI: -6.97, 0.64)]. Eczema and rheumatoid arthritis had a possible effect on KC ($p = 0.07$ and $p = 0.09$ respectively).

Table 2

Association between assessed risk factors and keratoconus in uni- and multi-variate regression analysis

Variables	Univariate regression model		Multivariable regression model	
	β (95 CI)	p	β (95 CI)	p
Continuous variables				
Age (years)	-0.03(-0.07, 0.03)	0.35	-0.04 (-0.10, 0.03)	0.25
BMI	0.06 (-0.01,0.12)	0.08	0.05 (-0.01, 0.12)	0.10
Categorical variables				
Gender (male)	0.79 (-0.79, 2.37)	0.33	1.29 (-0.43, 3.02)	0.14
Education				
Secondary school	1.14 (-3.31, 0.4)	0.22		
TAFE and university	-0.62 (-2.89, 1.65)	0.59		
Eye Rubbing	1.26 (-0.64, 3.16)	0.19		
Ethnicity				
Asian	1.14 (-1.41, 3.69)	0.38	1.25 (-1.49, 4.00)	0.37
Other	2.0 (-0.30, 4.40)	0.09	1.45 (-0.71, 3.60)	0.19
Repeated infections as a child	-0.39 (-3.76, 2.86)	0.67		
Cigarette Smoking	1.43 (-0.16, 3.02)	0.08	1.27 (-0.39, 2.94)	0.13
Alcohol consumption	0.96 (-0.69,2.62)	0.25		
Diabetes	-3.16 (-6.75, 0.42)	0.08	-3.16 (-6.97, 0.64)	0.10
Hypertension	-0.16(-3.22, 2.90)	0.92		
Sleep disorder	0.90 (-2.50,4.30)	0.60		
Connective tissue disorder	-0.96 (-8.9,6.9)	0.81		
Rheumatoid Arthritis	1.68(-0.02, 3.38)	0.05	1.92 (-6.97, 0.64)	0.09

 β - Regression Coefficient

CI-Confidence Interval

* Adjusted for confounders from univariate analysis

TAFE- Technical and Further Education

Bolding of text indicates p at either 0.1 (univariate analysis) or 0.05 (multivariate analysis)

Variables	Univariate regression model	Multivariable regression model	
Migraine	0.18(-2.5, 2.87)	0.89	
Allergy (excluding hay fever)	-0.51(-2.24, 1.22)	0.56	
Hay fever	-0.08(-2.16, 1.99)	0.94	
Asthma	2.20 (1.16, 4.24)	0.03	2.18(1.22,4.14) 0.03
Eczema	-5.31 (-10.55, -0.07)	0.05	-5.28 (-11.02, 0.47) 0.07
Duration of KC	-0.02(-0.12,0.09)	0.74	
Time spent on outdoor activities	0.04 (-3.69, 3.03)	0.31	
Time spent on intermediate activities	0.02 (-3.80, 2.59)	0.32	
Time spent on near activities	0.02 (-3.83, 2.43)	0.37	
β - Regression Coefficient			
CI-Confidence Interval			
* Adjusted for confounders from univariate analysis			
TAFE- Technical and Further Education			
Bolding of text indicates p at either 0.1 (univariate analysis) or 0.05 (multivariate analysis)			

Discussion

We identified a statistically significant positive association between asthma and increased severity of KC for the first time. Subjects presenting with asthma had a 2.2D steeper corneal curvature compared to subjects having no asthma.

Sabiston in 1966, first described a positive association between asthma and an increased risk of KC[37] and multiple other studies have strengthened the argument for a role of asthma in KC. In a New Zealand study, it was noted that 38% out of 673 KC individuals presented with asthma compared to 18% in the general population[34] and in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study, asthma was reported at 14.9% [53]. In the Dundee University Scottish Keratoconus (DUSK) study in Dundee, KC patients with asthma were diagnosed up to 3.1 years earlier than those without asthma[50]. In addition, in an Israeli study of 662,644 adolescents, an increased risk of asthma in 807 KC patients (OR1.5, 95%CI 1.3–1.6) was reported[31]. Similarly, an association was reported in a Danish nationwide registry study (OR2.21, 95%CI 1.91–2.55)[3] as well as in a United States Nationwide Health Care Claims Database analysis (OR 1.31, 95% CI, 1.17–1.47)[51]. However, no studies have assessed asthma with effect on severity of KC.

Our finding adds to the growing evidence that asthma not only appears to be associated with KC but also appears to increase severity of the condition. This is an important finding as currently it is estimated that approximately 300 million people in the world have asthma and prevalence in Australia is reported as the highest in the world at 21% for clinical asthma[47].

Asthma & KC in children

Asthma is an inflammatory disease of the small airways of the lung and has been reported to be caused by a combination of genetic predisposition with environmental factors[11]. These environmental factors likely include indoor and outdoor allergens, tobacco smoke, chemical irritants as well as air pollution and likely prompt an allergic reaction or airway irritation. Asthma is a common chronic disease that affects people of all ages in all parts of the world. The International Study of Asthma and Allergies in Childhood reported that globally the age distribution of the burden of asthma peaks at age 10–14 years and that asthma is a cause of substantial burden of disease, including both premature death and reduced quality of life in people of all ages[13].

The onset of the KC is usually in the teens to early adulthood, but there are reports of increasing prevalence in children as young as at the age of 4 years[38]. Paediatric KC has also been shown to be more aggressive than adult KC[22]. Our current finding showing asthma has an association with increased severity of KC, is thus important in the examination and systemic management of paediatric KC subjects. While KC in adults has been studied extensively, the disease in the paediatric population has not. Visual impairment in paediatric patients may affect social and educational development, thus negatively impact on their quality of life. Our recent findings show that the quality of life in KC patients is lower than that in patients with later-onset eye diseases such as age-related macular degeneration or diabetic retinopathy,[39] highlighting the significant long-term morbidity associated with KC. It is therefore necessary to consider asthma as a major contributing risk factor in paediatric KC cases, which may lead to a paediatric-specific therapeutic algorithm.

Shared genetic path for Asthma and KC

A large number of genetic loci have been implicated in asthma through the use of linkage, genome wide association studies (GWAS) and animal studies. There is some evidence to support a possible shared genetic contribution between asthma and KC. A previous Genome Wide Association Study (GWAS) conducted on asthma in an Australian population identified significant association with the single nucleotide polymorphism (SNP) rs4129267 (odds ratio 1.09, $p = 2.4 \times 10^{-8}$) in the interleukin-6 receptor (IL6R) gene [14]. The ligand for this receptor is the interleukin 6 (IL6) gene. IL6 is known to be a potent pleiotropic cytokine that regulates cell growth and differentiation and plays an important role in immune response[20]. Shetty et al recently reported up-regulation of IL6 mRNA in tears of KC patients[44]. Thus, it could be postulated that increased IL6 levels lead to enhanced up-regulation of the immune response through binding with its receptor (IL6R), followed by subsequent activation of the JAK-STAT pathway. While increased IL6 mRNA expression has been detected in tears of KC patients, this does not necessarily

confirm IL6 as a causative agent in KC. Interestingly, the cornea is one of the tissues of the eye exhibiting the highest expression of IL6R whereas IL6 has a low expression in this tissue (Ocular Tissue Database, University of Iowa). Ultimately, a direct comparison of gene expression or protein levels will be required in KC compared to non-KC corneal tissue to substantiate these findings. Interestingly, the convergence of immune genes and pathways from different diseases has recently been demonstrated in a meta-analysis of GWAS in ten paediatric autoimmune diseases where such signalling pathways are a common denominator[29].

Other risk factors

In addition to asthma we also assessed several other commonly reported risk factors which haven't been assessed in KC including age, gender, educational background, birth history, childhood infections, time spent undertaking near work, intermediate work and outdoors, duration of keratoconus, ocular and medical history, smoking and alcohol consumption habits; systemic conditions and eye rubbing. Several of these were significant at the univariate level (BMI, ethnicity, cigarette smoking, arthritis, diabetes and eczema) and suggestive at the multivariate level (eczema, arthritis and diabetes with p values of 0.07, 0.09 0.1 respectively). Interestingly, arthritis showed a positive association with KC whereas diabetes and eczema were associated with a protective effect for KC. The significant "protective effect" of diabetes against KC[2, 24, 25, 26, 27, 32, 35, 42] has been previously described in the literature and researchers have investigated the biochemical properties of cornea to explain this effect[17, 43, 48]. We report findings on time spent on near work, intermediate work and outdoor activities for the first time. As KC typically affects teens to early adults, we were expecting a positive association with near work-related activities as seen in myopia[18]. However, no such trend was evident suggesting that KC is more patho-physiologically driven than by these environmental conditions.

Strengths & Limitations

The main strength of the current study is that it included a wide range of risk factors that could be assessed with their association with KC. To the best of our knowledge, there are no previous studies which looked at the association of hypertension or migraine with KC and there are very few studies that assess potential risk factors such as cigarette smoking and alcohol consumption. The design of this study has addressed several methodological issues found in previous studies on KC, such as small sample size[23], postal questionnaires[34], data from medical record[52] the absence of ocular biometric measures[6, 7, 8, 28, 30, 45] and the lack of a comprehensive environmental risk factor questionnaire[6, 7, 8, 28, 30]. Findings from this study are therefore envisaged to lead to substantial progress in our understanding of the aetiology of KC and classifying it as quasi-inflammatory condition.

The limitation of the study is the lack of a clinically quantified severity risk factor questionnaire for some of the collected measures. Data collected on eczema and asthma did not record severity, number of episodes and length of time presenting with these indicators. It would have been interesting to find out more details about these two conditions including severity of asthma and current treatments as our results and the literature suggest an association of these with KC and with severity of KC.

Conclusions

In conclusion, this study describes the assessment of a range of risk factors in a large KC cohort recruited in Australia. Our study has reported asthma as the only risk factor found to be significantly associated with KC following multivariate analysis. In addition, as multifactorial disorders, keratoconus and asthma may share some overlapping risk factors such as shared genes or common environmental factors. Future studies are needed to be undertaken to confirm our findings as well as undertake GWAS to uncover some of the genetic associations with KC in an unbiased manner and will help in elucidating potential gene pathways involved in KC.

Significance

Our results show that asthmatic patients tend to have more severe KC and thus close monitoring for disease progression would be advised, as treatments such as corneal cross linking can be performed stabilise the disease, which may reduce the need for future corneal transplantation.

List Of Abbreviations

Keratoconus- KC

Crosslinking -CXL

Collaborative Longitudinal Evaluation of Keratoconus -CLEK

Dundee University Scottish Keratoconus Study – DUSKS

Royal Victorian Eye and Ear Hospital - RVEEH

Body mass index -BMI

Interquartile range- IQR

Standard deviation -SD

Mean value of central radial curvatures -Avg Km

Diopters -D

Regression Coefficient- β

Confidence Interval- CI

Technical and Further Education- TAFE

Odd's Ratio - OR

Genome wide association studies - GWAS

Single nucleotide polymorphism - SNP

Interlukin-6 receptor - IL6R

Messenger Ribonucleic acid - mRNA

JAK-STAT- Janus Kinase/Signal Transducer and Activator of Transcription

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Royal Victorian Eye and Ear Hospital Human Research and Ethics Committee (Project # 10/954H). This protocol followed the tenets of the Declaration of Helsinki and all privacy requirements were met. A patient information sheet, consent form, privacy statement and patient rights were provided to all individuals participating in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PNB and SS were involved in the conception of the project. SS recruited all the subjects and was a major contributor in writing the manuscript. EC, MD, GS assisted in recruiting the subjects. JX analyzed and

interpreted the patient data. All authors read and approved the final manuscript.

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