

Keratoconus and Allergic Diseases Among Israeli Adolescents Between 2005 and 2013

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Purpose: The aim of this study was to evaluate the association between keratoconus (KC) and common allergic conditions, such as asthma, atopic dermatitis, and allergic rhinitis in a large-scale database-based epidemiological study.

Methods: We conducted a cross-sectional study to estimate the epidemiologic relationship between KC and allergic diseases. The study population included all Israeli adolescents who underwent medical evaluation by the Israeli Defense Force, between the years 2005 and 2013. The presence of KC was determined by corneal topography read by an ophthalmologist.

Results: A statistically significantly increased odds ratio (OR) for the presence of KC was found for asthma [OR: 2.0; 95% confidence interval (CI): 1.6–2.5; $P < 0.001$], allergic rhinitis (OR: 1.6; 95% CI: 1.3–2.0; $P < 0.001$), and the combination of allergic conjunctivitis, chronic blepharitis, and vernal keratoconjunctivitis (AC/CB/VKC), for which a particularly strong association was found (OR: 6.0; 95% CI: 4.0–9.2; $P < 0.001$). No significant association was found between angioedema, urticaria, history of anaphylaxis, allergy to hymenoptera sting or atopic dermatitis, and KC. After stratifying the patients according to the severity of the allergic disease, the association between severe (AC/CB/VKC) and KC was very high (OR: 36.5; 95% CI: 20.4–65.4; $P < 0.001$).

Conclusions: In this study, we demonstrated a substantial association between (AC/CB/VKC), asthma, allergic rhinitis, and KC, with no significant association between other allergic diseases and KC. The severity of the allergic status is without doubt associated with a greater risk of having KC. The mechanism causing this association is still unclear.

Key Words: keratoconus, allergic diseases, allergic conjunctivitis, chronic blepharitis, vernal keratoconjunctivitis, asthma

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Keratoconus (KC) usually appears around the second and third decades of life and causes deterioration of vision.^{1–5} It is a common corneal disorder, affecting 2.3% of the population in Israel⁶ and India.⁷ Prevalence rate differs geographically with lower rates in other countries such as Russia (0.003%)⁷ and the United States (0.5%).⁸

The etiology of KC still remains unclear.⁹ Despite the investigation of various candidate factors such as genetic and chromosomal disorders and environmental exposure, the exact cause is still unknown.¹⁰ The pathophysiology of the disease is related to progressive degeneration of all or most of the layers, with stromal changes being the most prominent finding. Previous studies have suggested increased protease activity as the cause of these changes,¹¹ whereas other studies have suggested that free radicals,¹² formed in the absence of the enzyme aldehyde dehydrogenase, cause the disease.¹³ Despite the fact that KC is not considered an inflammatory illness, several studies¹⁴ have shown overexpression of inflammatory cytokines in the tear film of patients with KC.

KC usually progresses over 10 to 20 years until it stabilizes.¹⁵ Progression may vary, but early diagnosis may lead to a better prognosis. Treatment of KC depends on the severity of the disease. Therapies are aimed at either improving the refractive status or at changing corneal biomechanics, thus halting disease progression.¹⁰ Refractive treatments range from spectacles and soft contact lenses in mild cases to rigid contact lenses and intracorneal ring segments. Therapies proven to halt disease progression include corneal collagen cross-linking and keratoplasty. In severe cases, where scarring and fibrosis exist, keratoplasty serves both as an optical/refractive treatment and as a means to halt disease progression.¹³

Allergic diseases,¹⁶ such as asthma, atopic dermatitis, and allergic rhinitis, are characterized by a hypersensitivity reaction to an allergen. These diseases are very common, with prevalence estimated as 13% of the American population for asthma,¹⁷ 17% for atopic dermatitis, and up to 16% for allergic rhinitis.¹⁸ KC has been shown to be associated with allergic diseases such as asthma and atopic dermatitis.¹⁹ However, the studies that examined this association used a relatively small sample size^{20,21} or found a relatively weak association.¹⁶

Allergic conjunctivitis (AC),²⁰ with signs and symptoms ranging from simple intermittent tearing, itching, or hyperemia to severe sight-threatening corneal complications, affects approximately 25% of the world population. Vernal keratoconjunctivitis (VKC) is a seasonally exacerbated

allergic inflammation of the ocular surface, involving tarsal and/or bulbar conjunctiva particularly seen among children and young adults living in regions with hot and dry climate, such as the Middle East. Several studies²⁰ have demonstrated substantially higher severity of KC in patients who also have VKC or AC. It has been presumed that excessive eye rubbing might exacerbate KC.²¹ Matrix metalloproteinase (MMP), specifically MMP-2 and MMP-9, also known as gelatinases, are enzymes involved in normal epithelial turnover and are normally present in the tear film.²² Overexpression of these enzymes results in excessive extracellular matrix degradation and tissue destruction. MMP-2 originates mainly from activated fibroblasts during the course of wound healing, and MMP-9 is expressed mainly by regenerating epithelial cells and is involved in recruiting inflammatory cells to the wound area.²³ The involvement of T cells, which infiltrate the conjunctiva in AC,²⁴ in the expression and regulation of MMPs^{25,26} may lead to an increase in the rate of epithelial turnover and expression of MMP-9, possibly contributing to the pathogenesis of KC.

A 7-year, retrospective, observational case-control study by Nemet et al,¹⁶ published in 2010, examined the association of KC with allergic and autoimmune diseases among 426 patients diagnosed with KC and 1704 age- and gender-matched controls. A mildly (yet statistically significant) increased odds ratio (OR) among KC cases was found for asthma and environmental allergy, as well as various autoimmune disorders, when compared with controls.

It is unclear what exactly links allergic diseases and KC. Corneal injury caused by excessive eye rubbing secondary to allergy has been suggested as a possible mechanism. However, the findings of Nemet et al,¹⁶ which linked autoimmune diseases with KC, are not explained by this hypothesis. Our study was conducted to evaluate the link between KC and various allergic diseases, to quantify the risk of KC in patients with these diseases, and to compare the risk of KC between different types of allergic diseases.

METHODS

We conducted a cross-sectional study to estimate the epidemiologic relationship between KC and allergic diseases.

Source of Data

As a part of the military preconscription assessment, most Israeli civilians undergo a routine medical evaluation and fitness-for-service (FFS) classification at a prespecified age. The medical evaluation includes questionnaires filled by the candidate and his family physician and a physical examination including anthropometrics, vital signs, and visual acuity measurements, a physical examination by a physician, as well as further tests and consultations deemed required by the physician. A candidate is referred to an ophthalmology specialist in cases of known ocular history, reduced visual acuity, any complaint of qualitative visual change, a recent change in refraction, or any other relevant finding in anamnesis or physical examination.

A referral for corneal topography is made at the discretion of the examining ophthalmologist. At the conclusion

of this process, one or more FFS classification numerical codes indicative of both a medical diagnosis (or similar diagnoses grouped by pathogenesis) and a functional status, as fit for combat duty or not, are stored in the candidate's personal and medical record. From the conscripts' medical records, we retrieved demographic details (gender, FFS determination date, and age at that time) and FFS codes. AC, VKC, and chronic blepharitis (CB) are all represented by the same FFS numerical codes in the examinees' records and therefore were grouped in our analysis as well.

An FFS code consistent with KC diagnosis and severity is given based on the above-described ophthalmologic examination and corneal topography. The study was approved by the Israeli Defense Force (IDF) institutional review board, and the subjects' anonymity was strictly kept.

Study Population

The study population included all Israeli teenagers who underwent medical evaluation by the IDF as part of the preconscription assessment between January 2005 and December 2013. We excluded subjects who were younger than 16 years and those who were older than 20 years at the time of their medical evaluation because these subjects underwent the conscription process outside the standard conscription age range and therefore were prone to differ from the regular conscripts in terms of socioeconomic status and health care access. Moreover, their number was very small (<0.1% of the entire cohort).

Statistical Analysis

All data were summarized and displayed as mean ($\pm$ SD) for continuous variables and as number (percentage) of patients in each group for categorical variables. Continuous variables were compared using the independent sample *t* test or ANOVA (the Scheffe test was used for post hoc multiple comparison), whereas categorical variables were compared using a χ^2 test and binary logistic regression models.

Based on the presence of the corresponding FFS code, we grouped the KC FFS functional status (fit and unfit for combat duty) into 1 KC group. We then divided the entire study cohort into 2 groups: cases (of the respective allergic condition tested) and controls (without the respective allergic condition tested). Then, we divided both cases and controls into 2 groups of KC cases and controls in a similar manner, yielding a 2 $\times$ 2 table. We calculated the OR, confidence interval (CI), and statistical significance for the presence of the tested allergic condition between KC cases and controls. A multivariate analysis was performed to assess the specific relationship between asthma and KC while neutralizing confounding variables as age, gender, conscription year, and the presence of other allergic conditions.

We calculated the OR between KC and the different levels of functioning status of the allergic conditions to achieve a semi dose-response analysis.

A 2-tailed *P* < 0.05 was considered statistically significant; the assumed prevalence of the allergic condition in the KC group was 20% and the assumed prevalence of the

allergic condition in the general population was 15%, which yields a study power of 95.5%. All analyses were performed with SPSS 21.0 software (SPSS Inc, Chicago, IL).

RESULTS

Of the final sample of 662,644 examinees (age 17.5 years; 60% male), 807 (0.1%) were diagnosed with KC based on assignment of the corresponding numerical code. The exact diagnostic criteria of each disease and its prevalence are described in Tables 1 and 2.

A demographic analysis of the 807 patients with KC showed that the mean body mass index was 23.2, 61.5% were male, and the mean age was 17.5 years. The association between the various allergic conditions mentioned above and KC is described in Table 3A; a statistically significant increased OR for the presence of KC was found for asthma (OR: 2.0; 95% CI: 1.6–2.5; $P < 0.001$), allergic rhinitis (OR: 1.6; 95% CI: 1.3–2.0; $P < 0.001$), and the combination of AC/CB/VKC (OR: 6.0; 95% CI: 4.0–9.2;

$P < 0.001$). No significant association was found between angioedema, urticaria, history of anaphylaxis, allergy to hymenoptera sting or atopic dermatitis, and KC. After correction for age, gender, conscription year, and other allergic diseases, a statistically significant increased OR for the presence of KC was found for both asthma (OR: 1.5; 95% CI: 1.3–1.6 $P < 0.001$) and AC/CB/VKC (OR: 5.4; 95% CI: 3.2–7.6 $P < 0.001$).

After stratifying the different allergic conditions for the functional status, we found that the OR for KC in the “non-limiting for combat duties” functional status allergic conditions was generally lower than the OR between KC and the same allergic conditions in a limiting for combat duty functional status (Table 3). This difference was statistically significant only in asthma: nonlimiting asthma (OR: 1.6; 95% CI: 1.2–2.5; $P = 0.005$), limiting asthma (OR: 2.3; 95% CI: 1.8–3.0; $P < 0.001$), and AC/CB/VKC: nonlimiting AC/CB/VKC (OR: 3.2; 95% CI: 1.7–5.7; $P = 0.001$), limiting AC/CB/VKC (OR: 36.5; 95% CI: 20.4–65.4; $P < 0.001$).

TABLE 1. Diagnosis Criteria of the FFS Codes in the Study Database

Code	Diagnostic Criteria for Nonlimiting for Combat Duty	Diagnostic Criteria for Limiting for Combat Duty
KC	Corneal topography and an ophthalmologic consultation. When normal vision (6/6–6/9) can be achieved with glasses*	Corneal topography and an ophthalmologic consultation. When normal vision (6/6–6/9) cannot be achieved with glasses, or if a corneal transplant is needed or has been performed in the last year*
Asthma	Pulmonary function test and a pulmonology consultation. Attacks can be controlled with short-acting beta agonists, they are less than twice a week, and the forced expiratory volume in the first second (FEV1) in pulmonary function tests is decreased by less than 20% in a 4 mg/mL metacholine pulmonary stress test	Pulmonary function test and a pulmonology consultation. Attacks are frequent, and a chronic use of medication was advised, FEV1 in pulmonary function tests is decreased by more than 20% in a 4 mg/mL metacholine pulmonary stress test
Angioedema/urticaria	Self-reporting in a questionnaire and review of the patient medical records, with history of angioedema in the last 2 years that was localized and did not require chronic treatment	Self-reporting in a questionnaire and review of the patient medical records, with a history of angioedema that is localized but requires chronic treatment or at least 1 episode of systemic angioedema during lifetime
History of anaphylaxis	Self-reporting in a questionnaire, a review of the patient medical records and an allergist consultation. The insult for the anaphylactic reaction is known and can be easily avoided in the future (like contrast material or specific medication)	Self-reporting in a questionnaire, a review of the patient medical records and an allergist consultation. The insult for the anaphylactic reaction is unknown or cannot be avoided in the future (basic food as eggs or gluten)
Hymenoptera sting allergy	Self-reporting in a questionnaire and a review of the patient medical records of at least 1 episode of non-life-threatening (localized or systemic) reaction due to sting allergy, that was treated with immunization	Self-reporting in a questionnaire and a review of the patient medical records of at least 1 episode of non-life-threatening reaction due to sting allergy, which was not treated with immunization, or a systemic reaction that was life threatening such as bronchospasm
Allergic rhinitis	Self-reporting in a questionnaire and a review of the patient medical records	Review of the patient medical records with at least 5 episodes of chronic sinusitis on the last 3 years and appropriate imaging studies that show chronic sinusitis from the last year
Atopic dermatitis	Self-reporting in a questionnaire, a review of the patient medical records and a dermatology consultation, with sporadic usage of topical agents for controlling the disease	Self-reporting in a questionnaire, a review of the patient medical records and a dermatology consultation, with chronic usage of topical agents or sporadic usage of oral agents for controlling the disease
AC, CB, and VKC	Self-reporting in a questionnaire and a review of the patient medical records, showing recurrence in the last 2 years	Review of patient medical records with mention of severe chronic irritation of the eye, with mention of major loss of workdays

*These 2 FFS codes were united in this study into 1 code for statistical analysis.

TABLE 2. Prevalence of Diseases in the Study Cohort

Condition	Prevalence, %	Examinees Total (Mild*/Severe†)
KC	0.1	807 (427/380)
Asthma	6.4	42,268 (20,424/21,844)
Angioedema/urticaria	0.8	5314 (4258/1056)
History of anaphylaxis	0.2	1707 (1397/310)
Hymenoptera sting allergy	0.6	3654 (3307/347)
Allergic rhinitis	6.5	42,746 (42,155/591)
Atopic dermatitis	1.0	6395 (5378/1017)
AC, CB, and VKC	0.5	3218 (288/2930)

*Mild condition is defined as nonlimiting for combat duty.

†Severe condition is defined as limiting for combat duty.

DISCUSSION

KC is a progressive corneal ectasia with an incidence of approximately 0.1% in the general American population. Its prevalence in the Israeli adolescent population, according to our study, is estimated as 0.1% with a slight male predominance (61.5%).

Although the cross-sectional design of this study and lack of data in the FFS codes about the age of diagnosis do not allow any reasoning regarding causality, the earlier incidence age of AC, CB, VKC, and asthma^{20,27} compared with KC, provides a basis to the hypothesis that those diseases, which usually appear earlier than KC, may contribute to the development of KC rather than vice versa.

In this study, we demonstrated a substantial association between AC/CB/VKC, asthma, allergic rhinitis, and KC with no significant association with other allergic diseases. In light of the high OR of 6.0 for the presence of KC among patients with AC/CB/VKC, it may be beneficial to screen such patients for the presence of KC. Considering the young age typical of VKC and the progressive course of pediatric KC,¹³ such screening may be especially beneficial for pediatric patients, allowing early detection and disease-modifying

treatments such as corneal cross-linking, which has been shown to be effective in halting disease progression.¹²

Our statistical analysis shows that the severity of the allergic status is without doubt linked to a greater risk of having KC. We were unable to find substantial data in the literature regarding this association. This association between allergic pathology severity and KC is consistent with our hypothesis—a stronger allergic reaction would increase the risk of KC. This is especially true regarding AC/CB/VKC. However, the mechanism causing this association remains unclear.

It seems that patients with AC/CB/VKC would benefit from being evaluated for the development of KC. When generalizing the findings of this study, it should be noted that KC in allergic patients may represent a separate disease entity, as suggested by the steeper and thinner cones and inferior displacement of corneal apices, compared with patients with KC with no allergic disease.²⁷

We recognize several limitations in our study design. First, the fact that this is a retrospective cross-sectional study prevents us from deducing about temporal related issues. We strongly believe that having an allergic disease such as AC, VKC, or CB is a risk factor for developing KC later on in life, but further studies are required to investigate this. Second, the data from this study were retrieved from the FFS codes of the IDF. These codes are used to determine medical fitness, and as such, they sometime group similar diseases into 1 FFS code, such as the code for AC/CB/VKC.

In conclusion, our findings suggest that AC, VKC, and CB should all be considered risk factors for KC. Close follow-up and even screening for the development of KC should be considered in those patients. Further studies should be done to better understand the exact mechanism and to further refine the difference in disease characteristics among patients with KC in relation to atopy.

REFERENCES

1. Sorkin N, Varssano D. Corneal collagen crosslinking: a systematic review. *Ophthalmologica*. 2014;232:10–27.
2. Nishida T. Cornea. In: Krachmer JH, Mannis MJ, Holland EJ, eds. *Cornea: Fundamentals, Diagnosis and Management*. 2nd ed. Philadelphia, PA: Elsevier Mosby; 2005:3–26.
3. Edrington TB, Zadnik K, Barr JT. Keratoconus. *Optom Clin*. 1995;4: 65–73.
4. Maguire LJ, Bourne WM. Corneal topography of early keratoconus. *Am J Ophthalmol*. 1989;108:107–112.
5. Gokhale NS. Epidemiology of keratoconus. *Indian J Ophthalmol*. 2013; 61:382–383.
6. Millodot M, Shneor E, Albou S, et al. Prevalence and associated factors of keratoconus in Jerusalem: a cross-sectional study. *Ophthalmic Epidemiol*. 2011;18:91–97.
7. Gorskova EN, Sevost'ianov EN. Epidemiology of keratoconus in the Urals [in Russian]. *Vestn Oftalmol*. 1998;114:38–40.
8. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. *Am J Ophthalmol*. 1986;101:267–273.
9. Natarajan S. Keratoconus. *Indian J Ophthalmol*. 2013;61:379.
10. Vazirani J, Basu S. Keratoconus: current perspectives. *Clin Ophthalmol*. 2013;7:2019–2030.
11. Arffa R. *Grayson's Diseases of the Cornea. Chapter. 17*. Mosby; 1997: 452–454.
12. Spoerl E, Wollensak G, Seiler T. Increased resistance of crosslinked cornea against enzymatic digestion. *Curr Eye Res*. 2004;29:35–40.

TABLE 3. Association Between Various Allergic Conditions and KC

Condition	OR	95% CI	P
Asthma	2.0	1.6–2.5	<0.001
Asthma mild*	1.6	1.2–2.3	0.005
Asthma severe†	2.3	1.8–3.0	<0.001
Angioedema/urticaria	1.4	0.6–3.1	
History of anaphylaxis	0.5	0.0–3.4	
Hymenoptera sting allergy	0.7	0.2–2.1	
Allergic rhinitis	1.6	1.3–2.0	<0.001
Atopic dermatitis	1.0	0.5–2.0	
AC, CB, VKC	6.0	4.0–9.2	<0.001
Mild* AC, CB, VKC	3.2	1.8–5.8	0.001
Severe† AC, CB, VKC	36.5	20.4–65.4	<0.001

*Mild condition is defined as nonlimiting for combat duty.

†Severe condition is defined as limiting for combat duty.

13. Gondhowiardjo TD, van Haeringen NJ, Völker-Dieben HJ, et al. Analysis of corneal aldehyde dehydrogenase patterns in pathologic corneas. *Cornea*. 1993;12:146–154.
14. Lema I, Durán JA, Ruiz C, et al. Inflammatory response to contact lenses in patients with keratoconus compared with myopic subjects. *Cornea*. 2008;27:758–763.
15. Krachmer JH, Feder RS, Belin MW. Keratoconus and related non-inflammatory corneal thinning disorders. *Surv Ophthalmol*. 1984;28:293–322.
16. Nemet AY, Vinker S, Bahar I, et al. The association of keratoconus with immune disorders. *Cornea*. 2010;29:1261–1264.
17. National health interview survey 2012. Table 2–1: Lifetime asthma prevalence percents by age, United States. Centers for Disease Control and Prevention Web site. 2014. Available at: <http://www.cdc.gov/asthma/nhis/2012/table2-2.htm>. Accessed August 7, 2014.
18. Halawi AM, Smith SS, Chandra RK. Chronic rhinosinusitis: epidemiology and cost. *Allergy Asthma Proc*. 2013;34:328–334.
19. Robbins SL, Cotran RM, Kumar V, et al. Acute and chronic inflammation. In: *Robbin's Pathological Basis of Diseases*. 6th ed. Philadelphia, PA: WB Saunders; 1999:50–88.
20. Cingu AK, Cinar Y, Turku FM, et al. Effects of vernal and allergic conjunctivitis on severity of keratoconus. *Int J Ophthalmol*. 2013;6:370–374.
21. Yenid B, Alparslan N, Akarçay K. Eye rubbing as an apparent cause of recurrent keratoconus. *Cornea*. 2009;28:477–479.
22. De Souza GA, Godoy LM, Mann M. Identification of 491 proteins in the tear fluid proteome reveals a large number of proteases and protease inhibitors. *Genome Biol*. 2006;7:R72.
23. Gabison EE, Mourah S, Steinfelds E, et al. Differential expression of extracellular matrix metalloproteinase inducer (CD147) in normal and ulcerated corneas: role in epithelial-stromal interactions and matrix metalloproteinase induction. *Am J Pathol*. 2005;166:209–219.
24. Abu El-Asrar AM, Struyf S, Al-Mosallam AA, et al. Expression of chemokine receptors in vernal keratoconjunctivitis. *Br J Ophthalmol*. 2001;85:1357–1361.
25. Johnatty RN, Taub DD, Reeder SP, et al. Cytokine and chemokine regulation of proMMP-9 and TIMP-1 production by human peripheral blood lymphocytes. *J Immunol*. 1997;158:2327–2333.
26. Weeks BS, Schnaper HW, Handy M, et al. Human T lymphocytes synthesize the 92 kDa type IV collagenase (gelatinase B). *J Cell Physiol*. 1993;157:644–649.
27. Leonardi A, Lazzarini D, Bortolotti M, et al. Corneal confocal microscopy in patients with vernal keratoconjunctivitis. *Ophthalmology*. 2012;119:509–515.