

Estimation of the Incidence and Factors Predictive of Corneal Scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study

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Purpose: The multicenter Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study is a prospective, observational study of 1209 keratoconus patients. We report methods to define incident corneal scarring and baseline factors predictive of incident corneal scarring in nonsurgical eyes of CLEK Study keratoconus patients through their fifth year of follow-up.

Methods: Of the 1209 patients, 878 patients with at least one unscarred cornea at baseline were included in this study. The cumulative 5-year incidence of scarring is defined as the proportion of patients who developed central corneal opacification as detected by a clinician examining the patient with a slit-lamp biomicroscope and by masked readings of corneal photographs at the CLEK Photography Reading Center. Logistic regression analysis was used to test for relationships between baseline factors and incident corneal scarring. Baseline factors analyzed included age, sex, race, atopic disease, contact lens wear, family history of keratoconus, corneal curvature, and central corneal fluorescein staining, among others.

Results: The 5-year incidence of corneal scarring was 13.7% (120 of 878) overall, 16.7% (102 of 609) for contact lens-wearing eyes, and 38.0% (46 of 121) for contact lens-wearing eyes with corneal curvature greater than 52 D. Baseline factors predictive of incident scarring included corneal curvature greater than 52 D (odds ratio [OR] = 4.79; 95% confidence interval [CI], 3.08, 7.45; $P < 0.001$), contact lens wear (OR = 2.50; 95% CI, 1.40, 4.76; $P = 0.003$), marked corneal staining (OR = 2.38; 95% CI, 1.49, 3.76; $P = 0.0002$), and age less than 20 years (OR = 6.34; 95% CI, 2.57, 15.00; $P < 0.0001$).

Conclusions: Multivariate analyses of 5-year prospective data from the CLEK Study cohort showed that baseline corneal curvature, contact lens wear, corneal staining, and younger age were predictive of the development of corneal scarring. The 5-year incidence of scarring is 13.7% for the overall sample and 38.0% for those eyes with corneal curvature greater than 52 D that wore contact lenses. Contact lens wear increased the risk of incident scarring more than 2-fold. These findings suggest a causal contribution of contact lens wear to corneal scarring in keratoconus and imply that corneal scarring might be reduced by modifying the contact lens fit.

Key Words: cornea, keratoconus, opacification, scarring

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Keratoconus is a progressive, bilateral disease characterized by irregular astigmatism and steepening of the apical cornea. It is described as noninflammatory and can be differentiated from keratoglobus, pellucid marginal degeneration, and mechanically induced irregular astigmatism such as from contact lens wear or surgery.^{1–3} Other clinical signs include corneal scarring, Vogt striae, Fleischer ring, and corneal thinning. Corneal scarring causes reduced vision, especially the reduction of low-contrast visual acuity, in keratoconus.^{4,5}

Korb et al⁶ suggested that incident corneal scarring in keratoconus may be associated with the contact lens fitting method used, reporting on a small clinical trial where 4 of 7 eyes fitted flat developed corneal scars compared with 0 of 7 eyes fitted steep. Mascai et al⁷ reported that contact lens wear might be a risk factor for keratoconus. These clinical findings may be supported by basic laboratory studies in keratoconus and other corneal diseases in the past decade. Keratocyte and stromal alteration associated with proteolytic enzyme and protease inhibitor imbalances in the cornea lead to corneal thinning and scarring of the cornea.^{8–11} Wilson and Kim¹² suggested that epithelial trauma may be responsible for premature keratocyte apoptosis and further stromal changes in keratoconus and other corneal diseases. Fini et al¹³ and Daxer and Fratzl¹⁴ described the haphazard arrangement of collagen fibrils and abnormal proteoglycan and collagen types and remodeling and regeneration of the cornea after mechanical injury. It is possible that the mechanical trauma of contact

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lens wear may induce further adverse changes mediated by these mechanisms.

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study is a multicenter, observational study designed to prospectively characterize the changes in clinical findings in keratoconus. We have previously reported that, at baseline, corneal opacification (hereafter referred to as scarring) was associated with contact lens wear, steeper corneal curvature, Fleischer's ring, older age, and marked corneal staining.¹⁵ With follow-up data collected prospectively, we can now study these and other baseline factors for their potential causal role in the onset of corneal scarring in keratoconus.

MATERIALS AND METHODS

The CLEK Study is a 16-center, longitudinal observational study of patients with keratoconus. A total of 1209 eligible patients were enrolled between May 31, 1995 and June 29, 1996. The protocol used for the study is described in detail elsewhere.³ The procedures outlined below are those relevant to this report. The CLEK Study protocol was approved by each clinic's institutional review board, and the clinics obtained informed consent from each patient. Before examination, patients completed a survey that included questions about hours of contact lens wear per day, the number of times the contact lenses were removed per day, glare tolerance rated from "1 = not at all hindered" to "5 = can't do because of glare," and their vision from "1 = excellent" to "5 = poor." Trained and certified clinicians followed a specified slit-lamp biomicroscopic examination and scarring documentation protocol in the CLEK clinics. Trained and certified photograph readers evaluated standardized photographs of the corneas and graded corneal scarring in a masked fashion at the CLEK Photography Reading Center.¹⁶ Corneal scarring was graded as "definitely not scarred," "probably not scarred," "probably

scarred," or "definitely scarred" by the clinicians and the photograph readers. Figures 1 and 2 show examples of the variety of incident scars observed. Corneal photography consisted of 4 parallelepiped photographs of the central cornea, followed by 2 oblique photographs of the entire cornea after pupil dilation as described in the standardized CLEK protocol. Scar density (0–4 scale), size, and shape were graded relative to standard photographs.

Reliability and concurrent validity of the scarring protocol were evaluated in a 10% random sample of patients ($n = 138$) who completed a second baseline examination. These results have been reported elsewhere.¹⁵ Briefly, agreement at the baseline examination and the repeat examination on the presence or absence of scarring (as calculated using a weighted κ statistic) was 0.77 for photography readers (95% confidence interval [CI], 0.72–0.82), 0.83 for clinicians (95% CI, 0.78–0.88), and 0.69 (95% CI, 0.66–0.71) between photography readers and clinicians. Agreement between repeat gradings of the same photographs selected randomly for quality assurance monitoring ranged from 0.79 to 0.95 throughout the study.

The sample for this report consists of patients who had 1 or both eyes at risk for scarring at baseline and at least 1 follow-up examination. Eyes with a corneal transplant at baseline and eyes classified as scarred at baseline were excluded from this sample. At baseline, the presence of scarring was defined as a grading of "probably" or "definitely" scarred in the central 6 mm of the cornea by either the CLEK clinic examiner or the masked reader at the CLEK Photography Reading Center. This definition of baseline scarring identified 331 patients who were excluded from this report and 878 patients with 1 or both eyes at risk for scarring who are included in this report. Eyes undergoing corneal transplantation during follow-up are included up to and including the last visit before their corneal transplant.

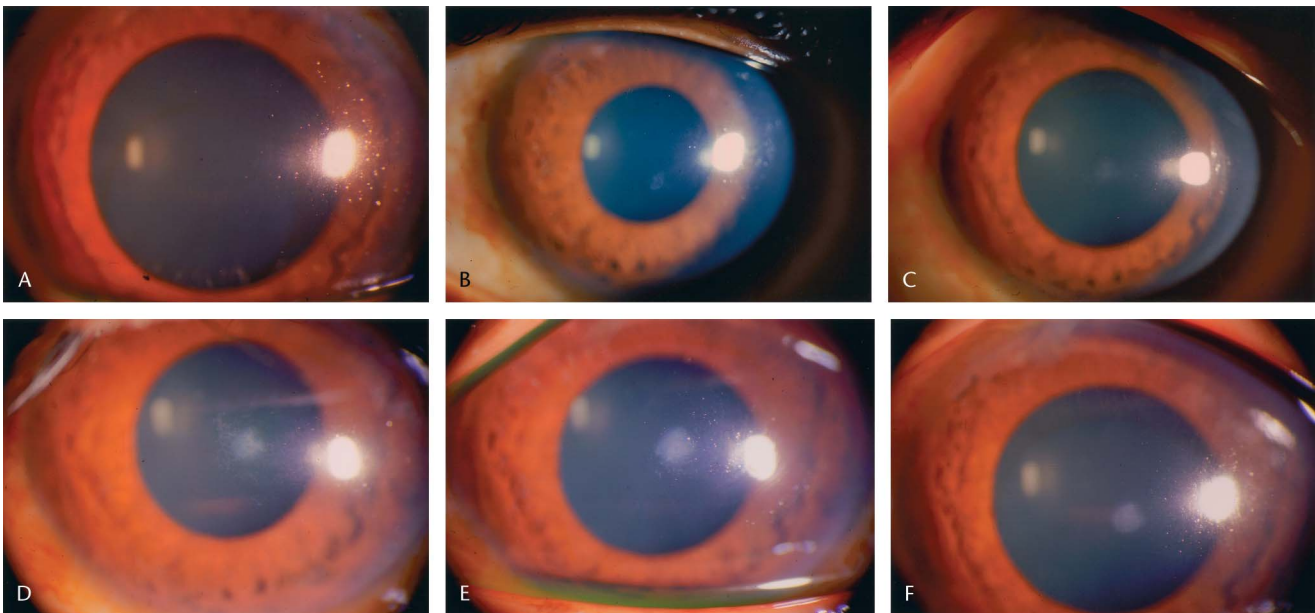


FIGURE 1. A representative patient's unscarred cornea at baseline (A) and scarred cornea at years 1 to 5 (B–F).

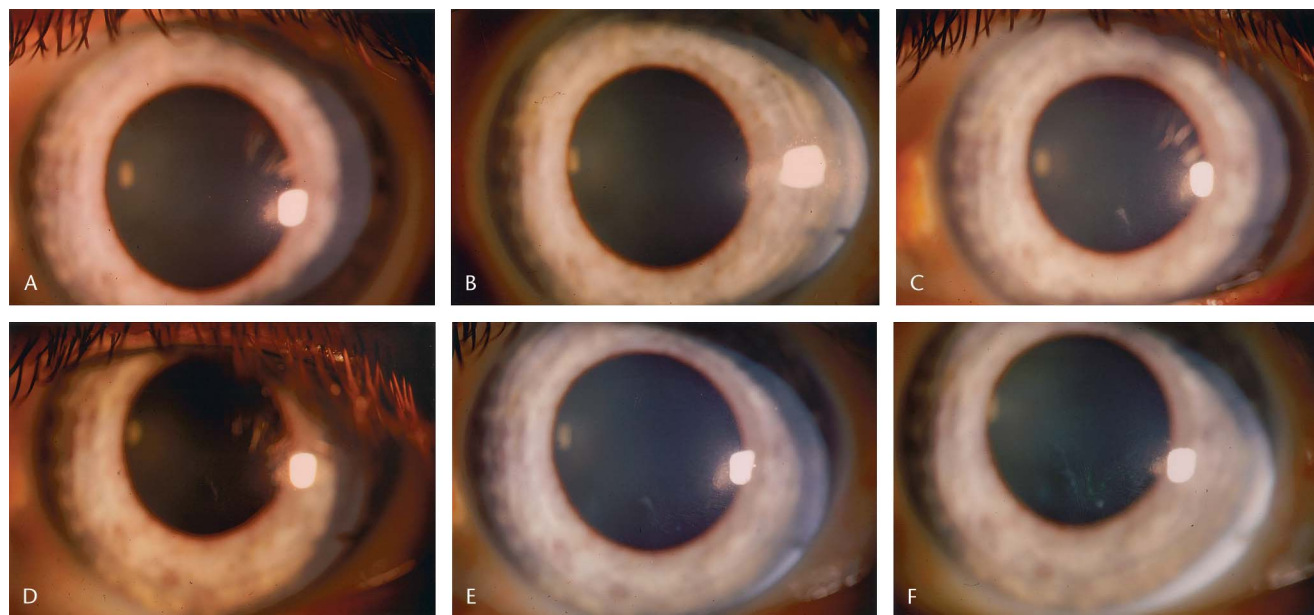


FIGURE 2. A representative patient's unscarred cornea at baseline and year 1 (A and B) and scarred cornea at years 2–5 (C–F).

The 5-year incidence of scarring is defined as the detection of scarring up through the fifth annual examination in patients whose cornea(s) were not scarred at baseline. The primary definition of incident scarring as present was when both the CLEK clinic examiner and the masked photograph reader independently graded the eye as “probably” or “definitely” scarred, and the scar was in the central 6 mm of the cornea as determined by the photograph reader.

We also evaluated a more restrictive definition of scarring—one with higher specificity—that required both the clinician and the masked photograph reader to independently grade the eye as “definitely scarred” at 2 consecutive annual visits. This definition also required that the scar be located in the central 6 mm of the cornea as determined by the photograph reader on both visits. Data from year 6 were used to confirm scarring detected at the year 5 examination.

The restrictive definition was not used in the primary analyses for this report. The purpose of the restrictive definition was to provide a lower bound to the estimate of scarring and to evaluate the robustness of multivariate models.

Corneal staining after the instillation of fluorescein was graded by the clinicians as “definitely not present,” “probably not present,” “probably present,” or “definitely present.” Location and shape (arc, punctate, foreign body, swirl, dimple veiling, coalesced, and full-thickness epithelial defect) were recorded. Because most eyes had corneal staining, we grouped eyes into 2 levels of corneal staining severity. For the purpose of this report, corneal staining was classified as marked when the clinician graded the eye as “definitely” stained on the 4-point staining certainty scale and described its shape as punctate, coalesced, or a full-thickness corneal defect within the central 6-mm corneal zone. Foreign body staining, peripheral staining, such as typical 3:00 and 9:00 o'clock staining, and arc-shaped corneal staining were not included. These latter

forms of staining were deemed unlikely to be associated with corneal scarring.

A protocol for determining the first definite apical clearance lens (FDACL) to provide a measure of corneal curvature¹⁷ was developed specifically for the CLEK Study. A rigid gas permeable contact lens from the CLEK Study trial lens set with a base curve radius equal to the steep keratometric reading was applied. If the initial lens was judged to be flat relative to the corneal apex, a steeper lens was applied to the eye for fluorescein evaluation. If the initial lens was judged to be steep relative to the corneal apex, a flatter lens was applied to the eye for fluorescein evaluation. These procedures were repeated until a first definite apical clearance fluorescein pattern was achieved. The FDACL base curve (in D) is the flattest lens that clears the corneal apex. Steep and flat keratometry measurements were also performed at baseline. Eyes were grouped by whether the corneal curvature was greater than or less than or equal to 52 D.¹⁷

Before analysis, the following baseline variables were selected for this report: age; sex; race; family history of keratoconus; ocular trauma; atopic disease; contact lens wear; Vogt striae; Fleischer ring; scarring status in the fellow eye; marked corneal fluorescein staining; corneal curvature; high- and low-contrast entrance visual acuity; high- and low-contrast best-corrected acuity; and patient-reported glare tolerance and vision. In the subset of eyes corrected by rigid gas permeable contact lenses at baseline, we examined hours of contact lens wear per day, the number of times the contact lens was removed per day, contact lens comfort (“1 = very comfortable” to “5 = irritating”), and the flatness of the entrance rigid contact lens fit. Contact lens fit (flatness) was defined as FDACL (in D) minus the habitually worn rigid contact lens's base curve (radius of curvature in D).

One eye of each patient was selected for analysis. In patients with a unilateral corneal transplant at baseline, the

fellow eye was selected for analysis. In eyes that underwent corneal transplantation during follow-up, the period before the corneal transplant was included. If scarring developed in 1 eye, that eye was selected for analysis. If both eyes had the same scarring status at year 5, 1 eye was selected randomly.

Univariate (unadjusted) odds ratio (ORs) and their 95% CIs were computed using logistic regression analysis. All variables with $P < 0.10$ in the univariate logistic regression analyses were selected for inclusion in a stepwise, multivariate logistic regression analysis. Three measures of corneal curvature were taken: FDAFL, the steep keratometric reading, and the flat keratometric reading. Corneal curvature was analyzed as a 2-level variable (≤ 52 and >52 D) as in previous CLEK publications.^{3,5,15,18} When the association of more than 1 of these measures of corneal curvature with scarring was statistically significant in the univariate logistic regression, a separate stepwise logistic regression was run to select the best candidate. The same approach was used to select the best candidate among the 4 measures of visual acuity: high- and low-contrast entrance acuity and high- and low-contrast best-corrected acuity. In the multivariate logistic regression models, a variable needed $P < 0.05$ to be retained, and the overall model needed to exhibit adequate goodness-of-fit using the Hosmer-Lemeshow test criterion of $P > 0.10$.¹⁹ (The Hosmer-Lemeshow criterion computes a statistical threshold for determining goodness-of-fit for logistic regression models.) Adjusted ORs and their 95% CIs are reported for baseline factors in the multivariate models. Because of the uncertainty as to whether corneal staining is a risk factor for corneal scarring or is an early marker of scarring, the multivariate model for the primary analysis, which included corneal staining, was also run without the corneal staining variable. Data were analyzed using SAS version 8 (SAS Institute, Cary, NC).

Multivariate logistic regression analyses were repeated with the more restrictive definition of incident scarring to determine if the same baseline factors for incident scarring were identified. Because this restrictive definition of incident scarring would yield fewer incident cases, P values for inclusion in the multivariate model were relaxed from 0.05 to 0.10 in the multivariate logistic regression analysis.

The ORs for all analyses of dichotomous variables reflect the odds of developing an incident scar when going from “no” to “yes” or from “absent” to “present.” For visual acuity, the OR reflects the change in odds for every 5 letters; for contact lens fit flatness, it is the change for each diopter. For mean glare, vision rating, and contact lens comfort, the odds ratios reflect a change in the odds of scarring for each additional point on a 5-point scale where higher values indicate worsening.

RESULTS

Of the 1209 patients enrolled in the CLEK Study, 878 patients who had at least 1 eye at risk for corneal scarring at baseline and who had completed at least 1 follow-up examination are included in this report. Forty percent of these patients (350 of 878) had 1 eye at risk for scarring at baseline, and 60.1% (528 of 878) had both eyes at risk. Among those patients with both eyes at risk for scarring, 3% (16 of 528) developed scarring in both eyes. In these 16 patients, 1 eye was

selected randomly for analysis. Eighty percent (702 of 878) of these patients completed at least 5 years of follow-up. The mean size of the central-most incident scar was 1.4 ± 0.7 (SD) mm, and its mean density was 1.8 ± 0.65 mm.

Table 1 reports baseline factors and their associations (unadjusted) with incident corneal scarring for all patients. Table 2 reports baseline visual function and contact lens wear in patients related to whether or not they developed incident corneal scarring. Tables 3 and 4 report baseline factors and their associations (unadjusted) with incident corneal scarring for patients wearing rigid gas permeable contact lenses at baseline. In the overall sample of 878 patients, a higher percentage of those under 20 years of age at baseline developed incident scarring (35.71%, 10 of 28) compared with those 20 years of age and older (12.94%, 110 of 850; OR = 3.74; 95% CI, 1.62, 8.16). The incidence of scarring among patients 20 years of age and older did not differ substantially from decade to decade and did not increase with older age. For this reason, age was treated as a dichotomous variable—under 20 years of age and 20 years of age and older. Patients who developed scarring had poorer low-contrast entrance visual acuity (30.4 ± 12.1 letters correct) compared with those who did not develop scarring (33.5 ± 13.0 letters correct). For each additional line of low-contrast entrance visual acuity, the odds of developing scarring was reduced by almost 10% (OR = 0.92; 95% CI, 0.86, 0.98). The odds of scarring was higher among patients wearing any type of contact lens at baseline (OR = 2.98; 95% CI, 1.72, 5.54) and those who had marked corneal staining (OR = 2.93; 95% CI, 1.90, 4.47), Vogt striae (OR = 2.12; 95% CI, 1.44, 3.15), or corneal curvature greater than 52 D, whether curvature was measured by FDAFL (OR = 4.51; 95% CI, 2.96, 6.85) or by keratometry. Many putative, predictive factors for scarring (eg, atopic disease, previous ocular trauma, or a history of eye rubbing) had little or no relationship with incident scarring in univariate analyses (Table 1).

Results of the stepwise multivariate logistic regression are presented in Table 5. Age less than 20 years was associated with an increased risk of scarring (OR = 6.34; 95% CI, 2.57, 15.00) in the multivariate analysis. Other baseline factors significantly associated with increased risk of scarring in the multivariate analysis were contact lens wear (OR = 2.50; 95% CI, 1.40, 4.76), corneal staining (OR = 2.38; 95% CI, 1.49, 3.76), and corneal curvature (FDAFL) greater than 52 D (OR = 4.79; 95% CI, 3.08, 7.45). Because marked corneal staining occurs more frequently in eyes corrected with contact lenses and may be a precursor to corneal scarring, the multivariate analysis was also run without corneal staining in it. When marked corneal staining was excluded from the multivariate model, the ORs for contact lens wear, age, and corneal curvature varied slightly from the same ORs in the model with staining included. The cumulative proportion of patients developing scarring from baseline through year 5 was examined using Kaplan-Meier life table plots and was found to be proportional over the entire follow-up period (Fig. 3).

Among patients corrected with rigid gas permeable lenses at the baseline visit (Table 5), factors associated with incident scarring in the multivariate analysis were marked corneal staining (OR = 2.22; 95% CI, 1.33, 3.66), corneal

TABLE 1. Baseline Factors and 5 Year Incident Corneal Scarring in the CLEK Study (n = 878)

Variable	Subgroup	N	Percent Incident Scarred	Unadjusted Odds Ratio	95% Confidence Interval	P
Age (years)*	<20	28	35.71%	3.74	1.62, 8.16	0.001
	>/= 20	850	12.94%			
Race	Non-white	258	16.28%	1.35	0.89, 2.02	0.15
	White	620	12.58%			
Sex	Male	481	14.76%	1.23	0.83, 1.83	0.30
	Female	397	12.34%			
Family history of keratoconus?	Yes	116	17.24%	1.38	0.80, 2.29	0.23
	No	762	13.12%			
History of ocular trauma?	Yes	28	17.86%	1.39	0.46, 3.46	0.51
	No	836	13.52%			
Atopic disease?†	Yes	493	13.59%	0.99	0.67, 1.46	0.94
	No	385	13.77%			
Contact lens wear?	Yes	650	16.31%	2.98	1.72, 5.54	0.0002
	No	228	6.14%			
Eye rubbing?	Yes	426	15.02%	1.22	0.83, 1.81	0.32
	No	419	12.65%			
Fleischer ring?	Yes	623	14.13%	1.14	0.75, 1.78	0.55
	No	254	12.60%			
Vogt's striae?	Yes	371	18.87%	2.12	1.44, 3.15	0.0002
	No	506	9.88%			
Fellow eye scarred?	Scarred	303	13.20%	0.94	0.62, 1.41	0.77
	Not Scarred	575	13.91%			
Marked corneal staining‡	Staining	155	26.45%	2.93	1.90, 4.47	<0.0001
	No staining	723	10.93%			
FDACL (D)	>52	152	32.89%	4.51	2.96, 6.85	<0.0001
	</= 52	714	9.80%			
Steep keratometry	>52	166	30.12%	3.95	2.61, 5.97	<0.0001
	</= 52	712	9.83%			
Flat keratometry	>52	46	43.48%	5.63	3.00, 10.43	<0.0001
	</= 52	832	12.02%			

*Odds ratio for age reflects the increased odds of being under 20 years old versus 20 years old or older.

†Atopic disease; patient indicated that he or she had hay fever, asthma, or atopic dermatitis at baseline.

‡Marked corneal staining: the clinician examining the patient says there is definitely corneal staining, that the staining is located within the central 6 mm (diameter) of the cornea and that the shape of the staining is either punctate, coalesced, or a full-thickness epithelial defect.

TABLE 2. Visual Function, Contact Lens Wear, and 5 Year Incident Corneal Scarring in the CLEK Study

Variable	Patients Who Did Not Develop Scarring (n = 758)	Patients Who Developed Scarring (n = 120)	Unadjusted Odds Ratio	95% Confidence Interval	P
Hours of contact lens wear	12.54 ± 4.34	13.30 ± 3.97	1.05	0.99, 1.11	0.10
Contact lens comfort (1–5 scale)	2.45 ± 1.17	2.38 ± 1.05	0.95	0.79, 1.14	0.58
Flatness (FDACL-base curve radius) (D)	1.89 ± 2.65	3.74 ± 3.37	1.22	1.13, 1.31	<0.0001
High-contrast, best-corrected VA/5 letters*	50.74 ± 7.03	49.30 ± 0.61	0.88	0.76, 1.01	0.07
Low-contrast, best-corrected VA/5 letters*	37.50 ± 8.81	35.16 ± 8.82	0.86	0.77, 0.97	0.02
High-contrast, entrance VA/5 letters*	47.98 ± 9.53	46.23 ± 9.49	0.92	0.83, 1.02	0.09
Low-contrast, entrance VA/5 letters*	35.13 ± 11.02	32.16 ± 10.37	0.89	0.82, 0.98	0.014
Glare score (1–5 scale)	2.45 ± 0.81	2.37 ± 0.89	0.89	0.68, 1.15	0.37
Vision score (1–5 scale)	2.73 ± 1.08	2.77 ± 1.11	1.04	0.86, 1.27	0.67

Incident scarring is described as “probably scarred” or “definitely scarred” by both the clinician and the masked photograph reader at the same visit. Continuous variables are described in terms of mean ± SD. Unadjusted odds ratios and their 95% confidence intervals are reported.

*Odds ratios for visual acuity are expressed in units of 5 letters (1 line).

TABLE 3. Baseline Factors and 5 Year Incident Corneal Scarring in Rigid Gas Permeable Contact Lens Wearers in the CLEK Study

Variable	Subgroup	N	Percent Incident		Unadjusted Odds Ratio	95% Confidence Interval	P
				Scarred			
Age (years)*	<20	18		38.89%	3.32	1.20, 8.66	0.016
	≥20	591		16.07%			
Race	Non-white	179		18.44%	1.18	0.74, 1.86	0.47
	White	430		16.05%			
Sex	Male	330		17.88	1.19	0.78, 1.84	0.42
	Female	279		15.41			
Family history of keratoconus?	Yes	80		22.50	1.54	0.85, 2.68	0.14
	No	529		15.88			
History of ocular trauma?	Yes	19		21.05	1.34	0.38, 3.79	0.61
	No	579		16.58			
Atopic disease?†	Yes	339		17.11	1.06	0.69, 1.63	0.79
	No	270		16.30			
Eye rubbing?	Yes	304		17.76	1.10	0.72, 1.70	0.65
	No	287		16.38			
Fleischer's ring?	Yes	446		16.82	1.01	0.63, 1.66	0.97
	No	162		16.67			
Vogt's striae?	Yes	276		22.10	2.02	1.31, 3.13	0.0015
	No	333		12.31			
Fellow eye scarred?	Scarred	239		15.06	0.82	0.52, 1.27	0.37
	Not scarred	370		17.84			
Marked corneal staining‡	Staining	137		28.47	2.58	1.63, 4.07	<0.0001
	No staining	472		13.35			
FDACL	>52 D	119		37.82	4.54	2.86, 7.22	<0.0001
	≤52 D	483		11.80			
Steep keratometric reading	>52 D	130		34.62	3.92	2.48, 6.18	<0.0001
	≤52 D	479		11.20			
Flat keratometric reading	>52 D	41		46.34	5.05	2.60, 9.74	<0.0001
	≤52 D						

*Odds ratio for age reflects the increased odds of being under 20 years old versus 20 year old or older.

†Atopic disease; patient indicated that he or she had hay fever, asthma, or atopic dermatitis at baseline.

‡Marked corneal staining: the clinician examining the patient says there is definitely corneal staining, that the staining is located within the central 6 mm (diameter) of the cornea and that the shape of the staining is either punctate, coalesced, or a full-thickness epithelial defect.

curvature greater than 52 D (OR = 3.55; 95% CI, 2.07, 6.08), age less than 20 years (OR = 4.13; 95% CI, 1.24, 12.74), and each diopter of flatness in contact lens fit (OR = 1.13; 95% CI, 1.04, 1.21). When corneal staining was excluded from this multivariate model, corneal curvature continued to have a statistically significant, strong association with incident corneal scarring (OR = 3.62; 95% CI, 2.12, 6.16), along with each diopter of flatness of the contact lens fit (OR = 1.13; 95% CI, 1.04, 1.22) and age less than 20 years (OR = 4.36; 95% CI, 1.36, 12.97). Eye rubbing, hours of contact lens wear, contact lens comfort, removal of contact lenses more than once per day, glare tolerance, and self-reported vision were not related to the risk of corneal scarring (Tables 3 and 4).

Univariate and multivariate analyses were repeated using the more restrictive definition of scarring with 48 incident cases. These analyses confirm the selection of corneal staining and curvature as predictive factors, but age and contact lens wear dropped out, largely because of low statistical power and violation of the Hosmer-Lemeshow goodness-of-fit test.

Exploratory subgroup analyses were conducted to see if incident scarring increased in a linear fashion over the range of

corneal curvatures as a function of contact lens wear at baseline. For this exploratory data analysis, corneal curvature was grouped into 3 levels of severity: mild, <45 D; moderate, 45 to 52 D; severe, >52 D. For each corneal curvature group, the 5-year incidence of scarring was compared with eyes wearing contact lenses at baseline (n = 643) and eyes not wearing contact lenses at baseline (n = 223). The 5-year incidence of scarring was higher in eyes wearing contact lenses compared with eyes not wearing contact lenses in each corneal curvature group (Fig. 4). The incidence of scarring in each contact lens wearing group increased as curvature increased. This exploratory analysis confirms the multivariate model in which contact lens wear and corneal curvature were independent factors, each contributing in a linear fashion to an increased risk of corneal scarring (Fig. 5).

DISCUSSION

This is the first report from prospectively collected, 5-year follow-up data that would allow identification of potential causal relationships between baseline factors and the development of corneal scarring in keratoconus. Using the

TABLE 4. Visual Function and 5 Years Incident Corneal Scarring in Rigid Gas Permeable Contact Lens Wearers in the CLEK Study

Variable	Patients Who Did Not Develop Scarring (n = 758)	Patients Who Developed Scarring (n = 120)	Unadjusted Odds Ratio	95% Confidence Interval	P
High-contrast, best-corrected VA/5 letters*	50.16 ± 7.63	49.52 ± 7.56	0.95	0.84, 1.07	0.39
Low-contrast, best-corrected VA/5 letters*	36.58 ± 10.29	35.35 ± 9.05	0.94	0.86, 1.04	0.22
High-contrast, entrance VA/5 letters*	46.71 ± 11.61	44.88 ± 11.12	0.94	0.87, 1.02	0.11
Low-contrast, entrance VA/5 letters*	33.49 ± 13.01	30.35 ± 12.12	0.92	0.86, 0.98	0.01
Glare score (1–5 scale)	2.47 ± 0.81	2.37 ± 0.88	0.87	0.68, 1.10	0.23
Vision score (1–5 scale)	2.88 ± 1.12	2.94 ± 1.18	1.05	0.89, 1.25	0.55

*Odds ratios for visual acuity are expressed in units of 5 letters (1 line).

Incident scarring is described as “probably scarred” or “definitely scarred” descriptions of a central scar by both the clinician and the masked photograph reader at the same visit. Continuous variables are described in terms of mean ± SD. Unadjusted odds ratios and their 95% confidence intervals are reported.

definition of incident corneal scarring developed in the CLEK Study, the 5-year crude incidence of corneal scarring was 13.7% overall and 16.7% for patients who wore contact lenses of any type at baseline. Baseline factors predictive of corneal scarring in multivariate analyses included age under 20 years, corneal staining, contact lens wear, and steeper corneal curvature. When baseline corneal staining was excluded from the multivariate model, the same core factors remained statistically significant in the model, and the odds of scarring associated with contact lens wear increased slightly. The multivariate model for incident scarring seems to be robust to varying definitions of incident scarring and the selection of candidate risk factors for incident scarring.

In cross-sectional analyses of baseline data, older age was associated with increased prevalence of corneal scarring.¹⁵ In analyses of these prospective data, age less than 20 years was associated with an increased risk of incident corneal

scarring. Patients less than 20 years of age had a 6-fold adjusted risk of incident scarring compared with patients 20 years of age and older. The increase in the prevalence of corneal scarring with older age observed at baseline could result from the accrual of incident cases among keratoconus patients over time. Results from longitudinal data indicate that the highest risk of incident corneal scarring may be early rather than later in the course of the disease.

Steeper corneal curvature had the strongest association with incident scarring in all multivariate analyses. Steeper corneas at baseline (FDA CL > 52 D) were nearly 4.5 times more likely to scar than flatter corneas. Wearing any type of contact lens increased the risk of incident scarring by almost 3 times over no contact lens wear. Additionally, among rigid contact lens wearers, flatness of fit was significantly associated with incident scarring.

Corneal staining can occur as a natural finding in keratoconus and may be attributable to the disease and/or to contact lens wear. In CLEK Study patients, corneal staining was associated with contact lens wear. The presence at baseline of marked corneal staining increased the risk of incident corneal scarring by 2.4. Although corneal staining may occur without subsequent corneal scarring, it seems rational that clinicians would try to prevent or minimize corneal staining with contact lens wear in keratoconus.

TABLE 5. Multivariate Analyses of Baseline Factors Predictive of Incident Scarring for All Eyes and for the Subset of Rigid Gas Permeable Contact Lens-wearing Eyes

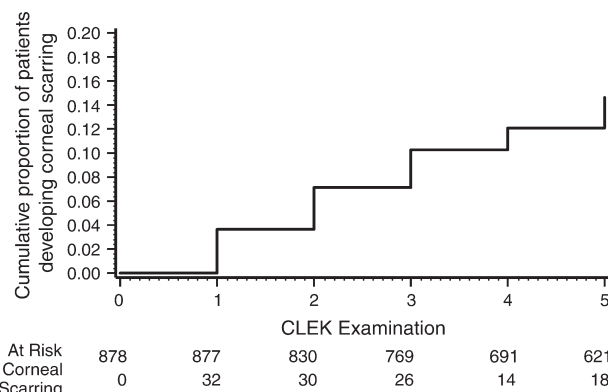
Variable	Odds Ratio	95% Confidence Interval	P
All eyes			
Age <20 years*	6.34	2.57, 15.00	<0.0001
Corneal staining†	2.38	1.49, 3.76	0.0002
FDA CL >52 D‡	4.79	3.08, 7.45	<0.0001
Contact lens use	2.50	1.40, 4.76	0.003
RGP-wearing eyes			
Corneal staining†	2.22	1.33, 3.66	0.002
FDA CL >52 D‡	3.55	2.07, 6.08	<0.0001
Age <20 years*	4.13	1.24, 12.74	0.02
Flatness of contact lens fit (D)‡	1.12	1.04, 1.21	0.002

Incident scarring is described across 5 years of follow-up and is defined as “Probably scarred” or “definitely scarred” descriptions of a central scar by both the clinician and the masked photograph reader at the same visit.

*Odds ratio for age reflects the increased odds of being under 20 years old versus 20 year old or older.

†Marked corneal staining: the clinician examining the patient says there is definitely corneal staining, that the staining is located within the central 6 mm (diameter) of the cornea and that the shape of the staining is either punctate, coalesced, or a full-thickness epithelial defect.

‡Per 1.00D.

**FIGURE 3.** Kaplan-Meier plot of the cumulative proportion of patients developing corneal scarring in 1 or both eyes during 5 years of follow-up.

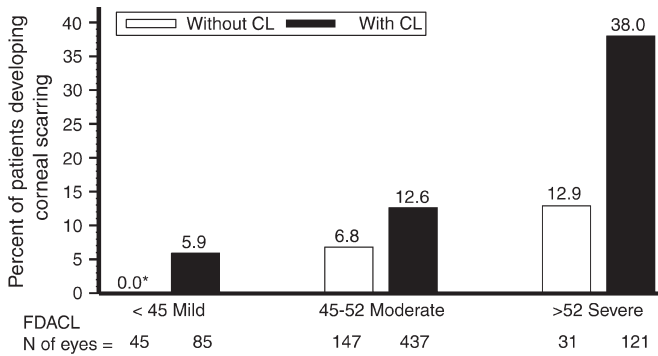


FIGURE 4. Percent of patients developing corneal scarring at 5 years as a function of FDACL and contact lens wear status. The incidence rates differ slightly from those reported in Table 1 because of a reduction in sample size because of the requirement of a baseline FDACL measurement. *No patients in this group developed corneal scarring.

Ihalainen²⁰ observed that corneal opacities were found in “practically all” of the keratoconus patients who had corneas with a flatter meridian steeper than 42 D, whether they wore contact lenses or not. Maguen et al²¹ monitored 21 eyes of 12 patients who were fitted with Polycon rigid gas permeable contact lenses for 3 years (range of follow-up, 27–41 months). Forty-five percent of this cohort had mean keratometric readings greater than 51 D. By the third year, 95% of eyes were fitted with central apical touch, and all eyes had corneal staining. Results of these studies are generally in agreement with our findings.

Many keratoconus patients with corneas steeper than 50 D wear contact lenses. Smiddy et al²² studied 115 consecutive keratoconus patients who had been referred for keratoplasty, almost all of whom had corneas steeper than 50 D. Eighty-seven percent (165 eyes) could be refitted for contact lenses, and only 13% of eyes could not be fitted and were referred for keratoplasty. Of those refitted with contact lenses, 69% did not need keratoplasty after an average period of 63 months wearing contact lenses.

Given that many patients with corneas steeper than 50 D continue to wear contact lenses and may not have keratoplasty, it is important to understand the relationship between contact lens wear, contact lens fit, corneal staining, and corneal scarring in keratoconus. In their report of incident scarring in a small treatment trial, Korb et al⁶ reported that 4 of 7 eyes fitted flat developed corneal scarring in 1 year, whereas no eyes fitted with apical corneal clearance developed incident corneal scarring. Steep keratometric readings in the study of Korb et al ranged from 43.12 to 56.25 D. Two of the 4 corneas that scarred had staining associated with the scarring. The 4 scarred eyes in their sample were fitted 3.25, 7.50, 8.25, and 12.12 D flatter than the steep keratometric reading, whereas the unscarred eyes were fitted 0.25, 8.37, and 10.00 D flatter than the steep keratometric reading with rigid gas permeable contact lenses with 8.4-mm optic zone diameters. At baseline, CLEK Study rigid contact lens wearers were fitted 2.86 ± 3.31 D flatter than FDACL on average, with a trend toward flatter contact lens fittings being associated with steeper corneas.²³ These data suggest that flatter fitting contact lenses may be associated with corneal scarring. However, steeper corneas are more likely to scar even without contact lens wear (Fig. 5). Nevertheless, one cannot conclude that flat-fitting contact lenses cause corneal scarring until prospective, controlled studies of rigid contact lens fitting are performed.

In our multivariate analyses, flatter fit at baseline was associated with an increased risk of incident scarring. Wearing a contact lens of any type was associated with incident scarring in multivariate analyses that adjusted for corneal curvature (Fig. 5). The CLEK Study is the first to report an estimate of incident corneal scarring in keratoconus as well as the first study to identify risk factors for incident scarring. Multivariate analyses strongly implicate contact lens wear in the causal pathway of corneal scarring, even after statistical adjustment for corneal curvature, corneal staining, and other baseline factors. Patients wearing contact lenses at baseline, predominantly apical touch contact lens fit, had more than a 2-fold increase in the risk of corneal scarring at 5 years. CLEK Study findings suggest that patients corrected by contact lenses may need to be informed about the potential of corneal

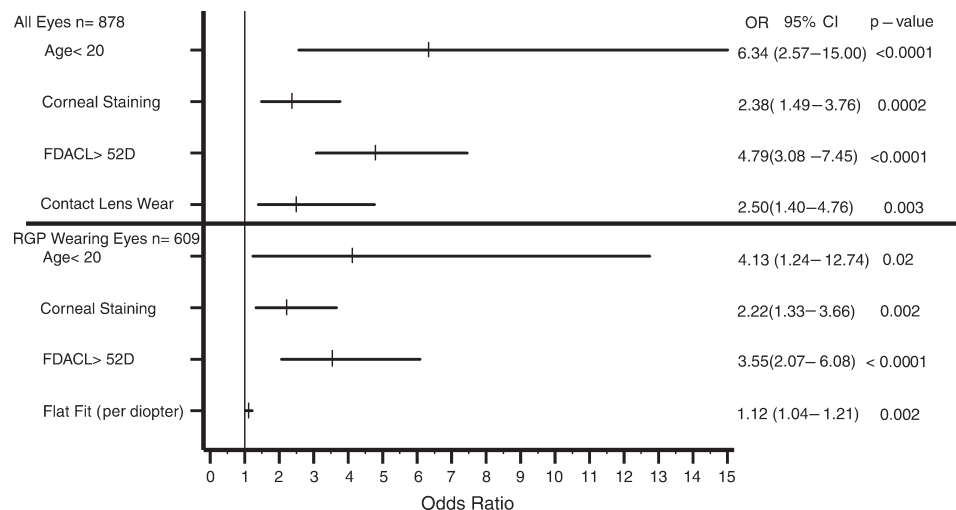


FIGURE 5. ORs (95% CIs) for baseline factors predicting 5-year incident corneal scarring for all patients (n = 878) and a subset of patients wearing rigid gas permeable contact lenses (n = 609).

scarring as an adverse effect of contact lens wear even though the effects of scarring are not clear. Whether apical clearance would reduce the incidence of corneal scarring cannot be answered by the CLEK Study because the study is observational in nature. Patients in the CLEK Study were not randomized to different contact lens fitting strategies, nor was a standard contact lens fitting protocol followed. Rigorous comparison of the safety and efficacy of apical clearance versus apical touch lens fitting strategies would require a randomized clinical trial.

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