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Article

Ethnicity, Progressive Keratoconus, and Outcomes after Corneal Cross-Linking in South Israel

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Simple Summary: In this study, we assessed the clinical outcomes of Corneal Cross-Linking (CXL) intervention in populations diagnosed with progressive keratoconus. We conducted a comparative analysis between the Bedouin and Jewish populations in the South of Israel. Our results suggest that the Bedouin group displayed a more progressive stage of the disease compared to the Jewish group. After a 12-month follow-up, we observed similar efficacy of CXL treatment across both groups. Although there are different studies discussing the relationship between minorities with low socio-economic status and the risk for health complications, our study is the first to compare CXL treatment and outcomes between these two specific groups. This study is valuable by both enhancing awareness of Keratoconus disease and the importance of its early treatment, and by underlining the necessity of facilitating access to medical information and screening tests for socio-economically disadvantaged groups.

Abstract: *Purpose:* To assess clinical outcomes of corneal cross-linking (CXL) intervention in a population diagnosed with progressive keratoconus. *Methods:* This single-center retrospective cohort study included consecutive patients who underwent standard CXL or accelerated CXL for progressive keratoconus at a major teaching hospital in south Israel between January 2015 and December 2019. Patient medical files were reviewed to extract demographic, clinical, and tomographic data from outpatient clinic reports before treatment and one year post-operatively. *Results:* This study included 166 patients (representing 198 eyes), out of which 98 patients (123 eyes) were ethnically Bedouin, and 68 patients (75 eyes) were ethnically Jewish. Overall, 126 patients (144 eyes) had a follow-up of at least 12 months (16.84±5.76). The mean patient age was 20.62 ± 7.1 years old. There were significant baseline differences between the two ethnic groups in best-corrected visual acuity (BCVA; $p < 0.001$), uncorrected visual acuity (UCVA; $p < 0.001$), mean keratometry ($p = 0.028$), and corneal thickness ($p < 0.001$). Significant changes in BCVA, UCVA, and pachymetry parameters within each group were found after 12 months. Negative binomial regression analysis showed a maximal keratometry below 55D (RR=1.247, $p < 0.001$) and a standard CXL procedure (RR=1.147, $p = 0.041$) are significantly related to the stability of KC after 12 months. However, the effect size of the origin of patients is negligible (RR=1.047, $p = 0.47$). *Conclusions:* In this study, the Bedouin population suffered from more progressive keratoconus when compared to the Jewish population. CXL was significantly effective in improving BCVA and UCVA in both groups after 12 months of follow-up.

Keywords: epidemiology; ectasia; Bedouin; Jewish; Kmax

1. Introduction

Keratoconus (KC) is a common bilateral non-inflammatory ectatic corneal disorder characterized by stromal thinning, irregular astigmatism of the cornea, and reduced visual acuity (VA) [1]. The disease is multifactorial with many risk factors, including familial, environmental, and regional factors as well as atopy and eye rubbing. Incipient stages of the disease can be asymptomatic and are often diagnosed only by revealing the changes of the corneal parameters by corneal tomography [2]. This method is considered the gold standard for diagnosis and monitoring the disease. Tomographic parameters reveal steeping of the anterior and posterior surface and the corneal thickness (pachymetry) [3,4]. As the disease progresses, cone-shaped cornea may be visible at the slit lamp [3], VA deteriorates, and patients may require penetrating keratoplasty. Hence, stabilization of the disease in its early stages is crucial.

Corneal cross-linking (CXL) has improved the treatment of ectatic corneal disorders, particularly KC [5]. CXL forms chemical bonds among collagen fibrils based on an interaction between ultra-violet A irradiation at a wavelength of 370 nm and riboflavin [6,7]. Case-control studies showed a significant decrease in the disease progression after CXL treatment, particularly presented by improvements in keratometry values and in VA in progressive disease cases [8].

Soroka University Medical Center (SUMC) is a major teaching hospital in the Negev area in south Israel and serves both Jewish (approximately 60%) and Bedouin (approximately 36%) populations [9]. The prevalence of KC in the Middle East has been found to be about 2%-5% [10–12]. In Israel, KC has been associated with eye rubbing, a family history of KC, and lower socio-economic status [13]. Additionally, Chorney and colleagues have found the socioeconomically challenged Bedouin minority [14] to be at risk for health complications such as diabetic retinopathy [15]. In this study, we focused on the corneal differences between SUMC's ethnically diverse KC patients.

A previous meta-analysis population study on the natural progression of KC has found that ethnicity significantly affects corneal characteristics such as topography, VA, and pachymetry [16]. Maximum keratometry (Kmax) for example, has been found to naturally increase significantly greater among Middle Eastern populations when compared to European and East-Asian populations [16]. This study seeks to compare these corneal characteristics between the populations we encounter in SUMC after an intervention such as a CXL procedure. We expect that assessment of the differences between two ethnic groups with different approaches towards health and diseases [17] in terms of the consequences of KC treatment will elucidate the gravity of the disease and will help us understand treatment efficiency for each population.

2. Materials and Methods

2.1. Participants

This single-center retrospective cohort study included consecutive patients who underwent CXL or accelerated CXL (A-CXL) for progressive KC at the Department of Ophthalmology at a major teaching hospital in south Israel (SUMC) between January 2015 and December 2019. We included 166 patients (representing 198 eyes), of which 98 patients (123 eyes) belonged ethnically to the Bedouin group and 68 patients (75 eyes) belonged ethnically to the Jewish group. In total, 126 patients (144 eyes) had a follow up of at least 12 months (16.84 ± 5.76). The mean age $\pm$ std. deviation of patients was 20.62 ± 7.1 years old, and 62.6% had been identified as male in their patient files. Table 1 shows patient demographic and clinical characteristics stratified by ethnic groups.

Table 1. Demographic and clinical characteristics.

Patient Characteristics	Jewish group (68 patients, 75 eyes)	Bedouin group (98 patients, 123 eyes)	p-Value
Demographical characteristics			
Time until follow-up, months			
Mean ± SD (n)	17.55 ± 6.58 (57/75)	16.38 ± 5.14 (87/123)	0.256
Median	15.00	14.00	
Min; Max	12.00;40.00	12.00;34.00	
Age, years			
Mean ± SD (n)	23.64 ± 6.90 (75)	18.68 ± 6.60 (123)	<0.001
Median	22.00	18.00	
Min; Max	9.10;45.00	7.60;41.00	
Gender, % (n/N)			
Male	77.9% (53/68)	54.0% (53/98)	0.002
Treated eye, % (n/N)			0.770
Right eye	46.7% (35/75)	49.6% (61/123)	
Family History of KC, % (n/N)			<0.001
Yes	12.1% (8/66)	39.1% (36/92)	
Vernal Keratoconjunctivitis per history, % (n/N)			0.138
Yes	18.4% (12/65)	29.4% (28/95)	
Wearing of Glasses, % (n/N)			1.000
Yes	37.1% (23/62)	37.0% (30/81)	
Clinical characteristics			
Type of CXL, % (n/N)			0.013
Standard	32.0% (24/75)	16.3% (20/123)	
Accelerated	68.0% (51/75)	83.7% (103/123)	
UCVA, logMAR			<0.001
Mean ± SD (n)	0.59±0.45 (73)	0.89±0.59 (106)	
Median	0.47	0.70	
Min; Max	0.00; 2.00	0.00; 3.00	
BCVA, logMAR			<0.001
Mean ± SD (n)	0.30±0.21 (73)	0.45±0.24 (107)	
Median	0.22	0.47	
Min; Max	0.00; 1.00	0.00; 1.00	
K Max, D			0.229
Mean ± SD (n)	56.28±6.62 (75)	58.15±8.94 (119)	
Median	54.10	56.50	
Min; Max	45.00; 81.40	44.60; 88.90	
K Mean, D			0.028
Mean ± SD (n)	48.34±4.28 (75)	50.24±5.87 (122)	
Median	47.40	49.40	
Min; Max	42.20; 62.70	38.70; 69.20	
MCT, μm			<0.001
Mean ± SD (n)	465.18±46.42 (75)	434.85±49.52 (122)	
Median	464.00	436.00	
Min; Max	338.00; 560.00	244.00; 531.00	
MCT, % (n/N)			<0.001
<400μm	8.0% (6/75)	8.0% (22/122)	
400μm <Thickness<450μm	30.7% (23/75)	41.8% (51/122)	
450μm <Thickness<500μm	30.7% (23/75)	32.0% (39/122)	

>500µm	30.7% (23/75)	8.2% (10/122)
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Note. N = number of patients; SD = standard deviation; D = diopter; UDVA = uncorrected distance visual acuity; BCVA = best corrected visual acuity; K = keratometry; MCT = minimum corneal thickness.

Progression was defined as an increase of 1.50 diopters (D) in mean keratometric value, a 1.00 D increase in Kmax, or a decrease of 5.0% in central corneal thickness at two consecutive evaluations by Scheimpflug-based corneal tomography (Pentacam HR; Oculus Optikgeräete, Wetzlar, Germany) [18–22]. In cases of suspected progression, a repeat exam including imaging was performed to confirm diagnosis. Exclusion criteria were a follow-up of less than 12 months, a history of previous ocular surgery, autoimmune diseases, diabetes mellitus, pregnancy or lactation, and sensitivity to riboflavin or any other substance used in CXL procedure. Patients were instructed to avoid eye rubbing prior to and during every follow-up. Patients with signs or symptoms of vernal keratoconjunctivitis were treated appropriately to reduce the chances of eye rubbing.

2.2. Data Collection

Medical files of all patients were reviewed, and the following data were extracted: age, gender, ethnicity, date of CXL procedure, minimal corneal thickness (MCT), anterior/posterior mean keratometric power, anterior/posterior flat keratometric power, anterior/posterior steep keratometric power, maximum keratometric power, and uncorrected/corrected distance visual acuity. Keratometry and total corneal thickness were measured with Pentacam. Data regarding corneal thickness, keratometric power, and VA were measured before and after CXL was performed.

2.3. Main Outcomes Measures

The primary outcome in this study was the Δ of the Kmax in the two study populations prior to CXL procedure and the most recent visit (12 to 34 months after CXL). Secondary outcomes in this study were VA measures (uncorrected/corrected distance visual acuity) and corneal topography data of both anterior and posterior segments of the cornea: average keratometry value (Kmean), steep keratometry (Ksteep) and flat keratometry (Kflat), corneal astigmatism, and corneal pachymetry prior to CXL and the most recent visit (12 to 34 months after CXL), as well as the occurrence of any adverse events throughout the study period. Progression after CXL treatment, as defined by a maximal corneal curvature reading at the corneal apex (Kmax), increase of 1.5D within a year.

2.4. Surgical Technique

Following topical anesthesia with 0.4% benoxinate hydrochloride drops, MCT was confirmed by ultrasound pachymeter (PachPen; Accutome, Malvern, PA). Following removal of the central 8 mm of epithelium, the MCT was re-measured to ensure MCT above 400 µm. Randomly, either standard CXL (S-CXL) or A-CXL was then performed. S-CXL was performed similarly to the Dresden Protocol.

Briefly, iso-osmolar 0.1% riboflavin solution (Medio-Cross 0.1%; Peschke Meditrade, Huenenberg, Switzerland) was instilled every 2 min for 20 min. Adequate riboflavin penetration was confirmed by appropriate flare in the anterior chamber. The cornea was then continuously irradiated at 365 nm with either an intensity of 3 mW/cm² for 30 min (S-CXL, total fluence 5.4 J/cm²) or an intensity of 9 mW/cm² for 10 min (A-CXL, total fluence 5.4 J/cm²) using a commercially available device (LightLink-CXL; LightMed, San Clemente, CA). The patient was instructed to fixate on the light source and adequate centration was constantly monitored by one of the two surgeons (BK or RMK). In cases where MCT was less than 400 µm, contact lens assisted CXL modification was performed using a method similar to Matlov Kormas and colleagues [23].

2.4. Statistical Analysis

Clinical parameters were tabulated and analyzed using SPSS (version 23; IBM, Armonk, NY). For the analysis of demographical and clinical characteristics, t-test was used for normally distributed

variables and Mann-Whitney test - continuous variables departing from normal distribution. To compare continuous parameters before and after treatment, we used paired t-test and Wilcoxon test normally distributed variables and other factors, respectively. A negative binomial regression model was performed to estimate an independent effect of various factors while adjusting to other factors. We used generalized estimating equations to adjust for clusters created by patients who were treated for both eyes.

3. Results

There were significant baseline differences between the two ethnical groups in best-corrected visual acuity (BCVA), uncorrected visual acuity (UCVA), mean keratometry and corneal thickness. Deeper analysis of the corneal thickness thinnest point showed a significant difference between the groups in different levels, while the thickness tends to be significantly higher in the Jewish group (see Table 1).

Intra-group comparison showed no significant difference in Kmax and Kmean after 12 months when compared to the baseline. However, there was a significant difference in BCVA, UCVA, and corneal thickness (central, apical, and minimal point) after 12 months.

We found a significant difference between the Jewish and Bedouin population in the Negev area of south Israel in corneal thickness prior to CXL interventional procedure (see Table 1). The differences in corneal thickness were also significant between each group before and after CXL was performed (see Table 2).

Table 2. Preoperative and 12 months postoperative clinical parameters by ethnic group.

Clinical Parameters	Jewish group (52 Patients, 57 Eyes)			Bedouin group (71 Patients, 87 Eyes)		
	Baseline (N=57)	>12 months (N=57)	P value	Baseline (N=87)	>12 months (N=87)	P value
UCVA (logMAR)						
Mean±sd (n)	0.57±0.44 (55)	0.44±0.39 (52)	0.003	0.90±0.59 (76)	0.62±0.46 (69)	<0.001
Median	0.4	0.26		0.74	0.5	
Min; Max	0.00; 2.00	0.00; 2.00		0.00; 3.00	0.00; 2.00	
BCVA (logMAR)						
Mean±sd (n)	0.32±0.22 (55)	0.23±0.21 (52)	0.008	0.45±0.25 (79)	0.39±0.36 (79)	0.003
Median	0.22	0.2		0.48	0.3	
Min; Max	0.00; 1.00	0.00; 1.00		0.00; 1.00	0.00; 2.00	
Kmax (D)						
Mean±sd (n)	55.80±6.02 (57)	55.66±6.22 (57)	0.981	57.15±7.24 (85)	57.74±7.93 (87)	0.624
Median	54.1	52.7		56.1	56.6	
Min; Max	47.40; 72.00	45.60; 70.30		44.60; 79.60	46.20; 85.90	
K1 Flat front (D)						
Mean±sd (n)	45.87±3.42 (57)	46.06±3.73 (57)	0.257	48.05±5.17 (87)	48.30±5.24 (87)	0.566
Median	45.3	46		47.1	47.3	
Min; Max	38.20; 55.70	37.70; 56.60		36.90; 66.50	38.80; 65.00	
K2 steep front (D)						
Mean±sd (n)	50.07±4.31 (57)	49.61±4.26 (57)	0.238	52.37±5.77 (87)	52.65±6.11 (87)	0.979
Median	50.4	49.1		52.5	51.9	
Min; Max	42.80; 63.30	42.20; 65.20		40.50; 72.10	43.50; 70.80	
K mean front (D)						
Mean±sd (n)	47.76±3.62 (57)	47.74±3.82 (57)	0.711	50.00±5.31 (87)	50.40±5.43 (86)	0.391
Median	47.1	47.3		49.6	49.5	
Min; Max	42.20; 59.20	40.10; 60.60		38.70; 69.20	41.40; 67.20	
K mean back (D)						
Mean±sd (n)	-7.41±0.82 (57)	-7.00±0.73 (57)	0.479	-7.46±0.92 (85)	-7.42±1.39 (85)	0.194

Median	-7.2	-6.9		-7.4	-7.5	
Min; Max	-9.90; -6.00	-9.60; -5.90		-11.00; -5.60	-10.70; 0.60	
Astigmatism front (D)						
Mean±sd (n)	4.18±2.57 (57)	3.56±2.17 (57)	0.125	4.31±2.00 (87)	4.28±2.05 (87)	0.859
Median	3.5	2.9		4	4.2	
Min; Max	1.00; 13.70	0.40; 9.80		0.10; 11.30	0.00; 10.20	
Astigmatism back (D)						
Mean±sd (n)	0.83±0.45 (57)	0.74±0.43 (57)	0.166	0.89±0.38 (86)	0.91±0.82 (87)	0.104
Median	0.8	0.7		0.8	0.8	
Min; Max	0.00; 2.10	0.10; 2.00		0.20; 1.80	0.00; 6.40	
CCT (μm)						
Mean±sd (n)	488.49±44.36 (57)	480.64±41.09 (57)	0.003	454.77±41.30 (85)	440.75±56.84 (85)	<0.001
Median	484	483		454	442	
Min; Max	384.00; 574.00	385.00; 560.00		356.00; 547.00	119.00; 609.00	
ACT (μm)						
Mean±sd (n)	482.19±44.36 (57)	470.45±46.42 (57)	<0.001	448.01±41.80 (87)	430.47±59.21 (85)	<0.001
Median	480	470		444	435	
Min; Max	346.00; 542.00	355.00; 563.00		346.00; 542.00	108; 599.00	
MCT (μm)						
Mean±sd (n)	466.86±45.96 (57)	453.19±50.12 (57)	<0.001	434.70±44.04 (87)	418.54±45.69 (86)	<0.001
Median	463	460		432	423.5	
Min; Max	338.00; 560.00	277.00; 541.00		339.00; 531.00	297.00; 517.00	
Corneal volume (mm ³)						
Mean±sd (n)	57.32±4.84 (57)	56.68±4.74 (57)	0.003	55.98±3.96(85)	55.11±4.68 (87)	0.004
Median	57.4	56.6		55.3	55.2	
Min; Max	35.60; 68.70	34.60; 66.70		48.30; 68.20	30.50; 66.00	

Note. N = number of patients; SD = standard deviation; D = diopter; UDVA = uncorrected distance visual acuity; BCVA = best corrected visual acuity; K = keratometry; CCT = central corneal thickness; ACT = apical corneal thickness; MCT = minimum corneal thickness.

Moreover, we found that corneal thickness was significantly higher among the Jewish group than the Bedouin group (see Table 1).

CXL procedure has been found significantly effective in improving UCVA and BCVA in both groups after 12 months of follow-up (see Table 2). However, no significant findings were found in comparison between the groups in the mean change of corneal characteristics (see Table 3).

Table 3. Mean change in outcomes 12 months post CXL by ethnicity.

Change (calculated as 12+ months post procedure minus at baseline)	Jewish group (52 Patients, 57 Eyes)	Bedouin group (71 Patients, 87 Eyes)	P-Value
UCVA (logMAR)			
Mean±sd (n)	-0.12±0.35 (52)	-0.23±0.53 (66)	0.56
Median	-0.17	-0.11	
Min; Max	-1.00; 1.40	-2.00; 0.90	
BCVA (logMAR)			
Mean±sd (n)	-0.07±0.21 (50)	-0.08±0.29 (73)	0.864
Median	-0.02	-0.02	
Min; Max	-0.80; 0.60	-0.78; 1.00	
Kmax (D)			
Mean±sd (n)	-0.16±2.45 (56)	0.09±2.14 (84)	0.973
Median	0	0.1	
Min; Max	-4.40; 8.60	- 8.60; 7.00	

K1 Flat front (D)			0.588
Mean±sd (n)	0.18±2.02 (57)	0.25±1.9 (87)	
Median	0	0	
Min; Max	-10.40; 4.70	-3.20; 11.70	
K2 steep front (D)			0.35
Mean±sd (n)	0.45±(57) 3.01	0.28±3.10 (87)	
Median	0.2-	0	
Min; Max	-19.00; 7.60	-5.10; 22.90	
K mean front (D)			0.776
Mean±sd (n)	-0.02±2.40 (57)	0.33±2.24 (86)	
Median	0	0.1	
Min; Max	-14.00; 6.60	-3.60; 12.80	
K mean back (D)			0.747
Mean±sd (n)	-0.02±0.31 (57)	0.08±8.65 (83)	
Median	0	0	
Min; Max	-1.30; 1.10	-1.70; 6.95	
Astigmatism front (D)			0.327
Mean±sd (n)	-0.61±2.18 (57)	-0.02±1.65 (87)	
Median	-0.3	0	
Min; Max	-8.60; 4.50	-7.10; 4.90	
Astigmatism back (D)			0.932
Mean±sd (n)	-0.08±0.37 (57)	0.03±0.8 (86)	
Median	-0.1	-0.05	
Min; Max	-1.50; 0.60	-0.90; 5.00	
CCT (μm)			0.639
Mean±sd (n)	-7.84±19.24 (57)	-14.92±45.77 (83)	
Median	-11	-10	
Min; Max	-57.00; 40.00	-344.00; 93.00	
ACT (μm)			0.733
Mean±sd (n)	-11.73±18.52 (57)	-18.04±44.02 (85)	
Median	-12	-11	
Min; Max	-60.00; 35.00	-333.00; 92.00	
MCT (μm)			0.686
Mean±sd (n)	-13.67±19.78 (57)	-16.6±24.94 (86)	
Median	-13	-15	
Min; Max	-83.00; 39.00	-98.00; 27.00	
Corneal volume (mm³)			0.896
Mean±sd (n)	-0.63±1.63 (57)	-1.02±3.63 (85)	
Median	-1	-0.6	
Min; Max	-4.60; 3.40	-27.50; 3.90	

Note. N = number of patients; SD = standard deviation; D = diopter; UDVA = uncorrected distance visual acuity; BCVA = best corrected visual acuity; K = keratometry; CCT = central corneal thickness; ACT = apical corneal thickness; MCT = minimum corneal thickness.

Stability was defined as an increase in less than 1.5D or a decrease in Kmax after 12 months after CXL procedure was performed. This study has found that the stability was 77.2% in the Jewish group and 88.2% in the Bedouin group (see Figure 1).

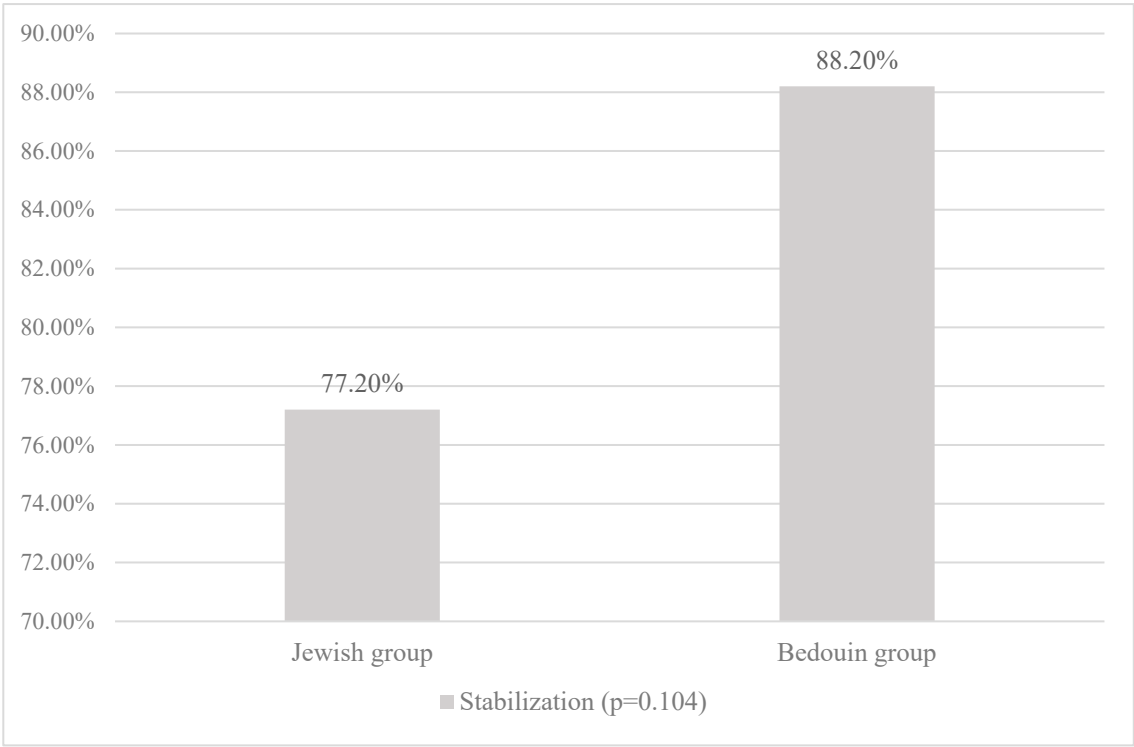


Figure 1. Percentage of patients with a Kmax decreased or increased in less than 1.5D in 12 months after CXL procedure by ethnicity. *Note.* Kmax = maximum keratometry; CXL = corneal cross-linking.

A negative binomial regression analysis (see Table 4) showed Kmax below 55D (RR=1.247, P<0.001) and a S-CXL procedure (RR=1.147, P=0.041) are significantly related to the stability of KC after 12 months of follow up. However, the effect size of the origin of patients is negligible (RR=1.047, P=0.472 for Jewish origin).

Table 4. Factors related to KC stability within 12 months after CXL (multivariate analysis results).

Patient Characteristics	RR	p-Value	95% Confidence Interval (RR)	
			Lower	Upper
Kmax < 55 at baseline	1.24	<0.001	1.11	1.39
MCT > 450 at baseline	1.08	0.171	0.96	1.23
Standard CXL procedure	1.14	0.041	1.01	1.31
Jewish origin	1.05	0.472	0.92	1.19
Vernal Keratoconjunctivitis per history	1.06	0.486	0.91	1.23

Note. RR = relative risk; K = keratometry; MCT = minimum corneal thickness; CXL = corneal cross-linking.

4. Discussion

KC is a relatively common multifactorial disease. Even though previous studies suggested both genetic and environmental risk factors [24,25], the etiology of KC disease remains unknown. KC has been associated with eye rubbing, atopy, floppy eyelid syndrome, pregnancy, and thyroid hormone disturbances [25]. Studies regarding eye rubbing, for example, showed a reduction of 18.4% in epithelial thickness immediately after rubbing [26]; and some even found eye-rubbing as the most significant risk factor for KC [27]. Atopy has also been associated with KC [28], though some authors suggested that the association is indirect only via itch which leads to eye-rubbing [27]. Kaya and colleagues showed that KC patients with atopy had a steeper and thinner ectatic cornea [29]. Studies evaluating the effect of pregnancy showed that KC progressed during the pregnancy period and continued to progress during the post-partum period [30].

The tendency of corneal thickness to be higher among the Jewish group than the Bedouin group (see Table 1) can be viewed through the risk factors associated to KC.

Data regarding eye rubbing can be complicated to compare between groups; however, its association to KC development and progression can be compared indirectly through atopy [27]. Regarding atopy, asthma, for example, has been found to be more prevalent among low socioeconomic populations in 63.0% of studies reviewing the issue [31]. Being a socioeconomically challenged population in south Israel means also significant exposure to dust and sand. Thus, some corneal characteristics of the Bedouin group can be explained by these risk factors. Since KC has been found to progress during pregnancy, extremely high birth rate among the Bedouin population might also contribute to the progression of KC among this population [30,32,33]. This finding could possibly explain the higher number of Bedouin women (46.0%) in comparison to Jewish women (22.1%) in our study group (see Table 1).

In addition to corneal thickness, other baseline corneal and clinical parameters were significantly inferior in the Bedouin group than in the Jewish group (e.g., UCVA, BCVA, and Kmean). These parameters can emphasize the fact that Bedouin patients have more progressed levels of KC. Studies regarding genetic factors and consanguinity, a prevalent phenomenon among the Bedouin population in the Negev [34] have found that children of consanguineous parents have a four-fold risk of KC when compared to children of unrelated parents [35]. In our study, positive family history of KC has been found significantly higher among the Bedouin group (see Table 1), a factor considered to increase risk for KC [11] can help explain the inferior corneal condition of this group.

Studies regarding compliance among the Bedouin population in a variety of diseases and disorders (e.g., cardiovascular disorders [36], diabetes mellitus [37], and genetic screening tests [38]) have concluded that compliance in this population is lower than in the Jewish population. Lower mean levels of corneal characteristics among the Bedouin group (see Table 2) can be explained via this fact also.

CXL procedure has been found significantly effective in improving UCVA and BCVA in both groups after 12 months of follow-up with no significant difference between the groups. Our multivariate analysis showed the effect size of the origin of the patients is negligible. These findings implicate that CXL procedure is effective in halting the progression of KC regardless of ethnic group or level of KC. Moreover, stabilization rates which were found to be similar in both groups, confirming this conclusion.

The corneal differences we report in this study arise questions regarding steps which possibly can be taken towards the Bedouin minority for prevention, diagnosis and treatment of KC (e.g., screening tests). First, rising the awareness for such pathology and its ramification may lead to better collaboration and early diagnosis. A clear and plain explanation of the disease causes, prevention, treatment, and routine follow-up, both clinically and tomographically, may increase both awareness and response to routine check-up. Secondly, improving the availability of ophthalmology services for Bedouin population and performing routine examinations may identify patients with KC in early stages. For example, retinoscopy is a simple screening test that can implicate the existence of KC. Al-Mahrouqi and colleagues have found that retinoscopy can serve as sensitive and reliable test for detection of KC even in early stages [39]. Another example of a screening tool is imaging. Corneal and epithelial thickness map and patterns, in addition to corneal topography or tomography, can be used to improve the screening of KC disease with a sensitivity of 97.8% [40].

Regarding stability, our multivariate analysis has found connection between preoperative maximal keratometry less than 55D to stabilization of CXL after 12 months of follow up (see Table 4). Koller and colleagues also found higher Kmax a significant risk factor for failure of CXL ($K_{max} > 58D$) [41]. Another study showed that patients with $K_{max} > 60D$ were at higher risk for failure. S-CXL procedure has also been found positively related to stability [42] (see Table 4). This finding is supported by other studies which have found S-CXL associated with higher stabilization rates than A-CXL [43,44]. Regarding differences between the Jewish and Bedouin populations, our multivariate study has found the differences to be negligible (see Table 4), suggesting that the procedure results do not depend on the ethnical origin of the patients but on the preoperative severity of the disease.

A delay in diagnosis among the Bedouin population and the rapid deterioration emphasizes that early intervention should be considered. Performance of CXL procedure under the age of 17 years old, was not found significantly different than among patients over 17 years old [45], implicating that early intervention is effective for early stabilization and better progress of corneal parameters [46]. Therefore, we suggest in order to achieve better rates of stability and halt the disease in earlier stages among the Bedouin population, intervention should follow diagnosis as soon as possible.

We have found CXL to be effective in halting the progression of KC for at least one year regardless of ethnicity and stage at diagnosis. We have also found significant tomographic and clinical differences between the Jewish and Bedouin populations in south Israel. These differences can be explained by a delayed diagnosis, cultural differences (e.g., consanguinity), negative influences of some environmental factors (allergy, atopy) and poor compliance to treatment and follow up. We suggest that health promotion regarding the consequences of untreated KC, screening tests (e.g., refraction, retinoscopy and corneal topography) and early intervention should take place in the community clinics of the minority population in the Negev.

Considering the Bedouin population in the Negev is a socioeconomically challenged minority with limited access and compliance to healthcare, our conclusions might be relevant to similar minority groups around the world.

5. Study Limitations and Future Research

This study does have limitations. As a retrospective study, the conclusions are limited to available data. A future prospective study would allow more control, which could lead to more specific conclusions for each population. In addition, only 72.0% of patients who had undergone CXL procedure had a follow up of at least 12 months. Thus, our conclusions could bias the comparison between the groups towards only compliant patients. Future work could ensure a more stringent follow-up protocol.

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