Dramatic Reduction in Corneal Transplants for Keratoconus 15 Years After the Introduction of Corneal Collagen Crosslinking

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Purpose: The aim of this study was to investigate the effect of the implementation of corneal collagen crosslinking (CXL) on the frequency of corneal transplants among patients with keratoconus (KC) in the same region.

Methods: Before the introduction of CXL in 2007, 55 primary corneal transplants had been conducted in patients with KC (2005 and 2006) at the Department of Ophthalmology, Oslo University Hospital, Norway. We collected data from our corneal transplant registry for 2021 and 2022. The primary outcome was the number of corneal transplants performed in patients with KC. Age, sex, visual acuity (logarithm of the minimal angle of resolution), KC stage according to the Amsler–Krumeich classification system, and steepest keratometry reading (maximum keratometry, Pentacam, HR) were recorded. Furthermore, we registered the annual number of CXL treatments conducted from 2007 to 2022.

Results: A total of 352 corneal transplants were performed in 2021 and 2022. Among them, 11 (3.1%) were transplants for patients with KC. All included patients were male; further, 90.1% and 9.1% of the patients were graded stages 4 and 3, respectively. The mean maximum keratometry was 79.0 diopter (range 61.0–109). The mean best-corrected visual acuity (logarithm of the minimal angle of resolution) was 1.3 (range 0.2–3.0). In 2021 to 2022, 431 CXL treatments were performed.

Conclusions: There was a significant decrease in the number of corneal transplants performed in patients with KC 15 years after the introduction of CXL. This indicates that the availability of CXL treatment over many years may considerably reduce the need for keratoplasties in this group of patients.

Key Words: keratoconus, corneal collagen crosslinking, keratoplasty

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Keratoconus (KC) is characterized by gradual thinning and distortion of the cornea, which subsequently reduces visual acuity. The onset of KC usually occurs during adolescence with the risk of progression persisting until the third and fourth decade of life.[1] Spectacles or specialized contact lenses can usually sufficiently preserve visual acuity in patients with mild-to-moderate severity. In advanced cases, corneal transplantation has traditionally been the treatment of choice. However, it is limited by intraoperative challenges, postoperative complications, and the general lack of donors.[2] Therefore, there has been active research on other potential treatment modalities. Corneal intrastromal ring segments may be a treatment option for mild-to-moderate KC; however, there have been no randomized controlled trials comparing this treatment to contact lenses or spectacles.[3] Given the improvement in design and material, contact lenses remain the preferred option for many patients with KC and may also reduce the need for keratoplasty among moderately advanced cases.[4]

In 2003, corneal collagen crosslinking (CXL) was introduced as a treatment modality for halting KC progression.[5] In this treatment, there is increased biochemical stability and rigidity of the cornea through collagen crosslinking induced by riboflavin and ultraviolet-A irradiation. Since its introduction, CXL treatment has been modified to reduce the treatment time (accelerated CXL) and preserve the epithelium ("epi-on" CXL).[6–9]

Several prospective and retrospective observational studies have demonstrated the favorable effects of CXL treatment.[10–12] However, only a few randomized controlled trials have been conducted showing that CXL halts the progression of KC for a follow-up period of 1 to 5 years.[13–19] In this respect, there may be ethical concerns in randomizing patients to CXL versus no treatment with a longer follow-up. The long-term effect of CXL treatment can be indirectly determined based on the number of corneal transplants conducted in patients with KC after full implementation of CXL treatment in a population over several years. Currently, only 2 studies have reported a reduction in the number of corneal transplants among patients with KC after the

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introduction of CXL.[20,21] In one of these studies, we reported a 50% reduction in the number of corneal transplants 8 years after the introduction of CXL.[20] A subsequent nationwide registry study in the Netherlands reported a 25% reduction 7 years after the introduction of CXL.[21]

It is reason to believe that the time frame in the 2 previous studies of 7 to 8 years is too short to be able to ensure that CXL treatment is offered to all patients with progressive KC. Fifteen years have now elapsed since the introduction of CXL in our clinic; accordingly, the treatment can be considered as fully established and well-known among ophthalmologists and optometrists. The aim of this study was to examine the extent to which a longer implementation period of CXL treatment has affected the rate of corneal transplants in patients with KC.

MATERIAL AND METHODS

All corneal transplants in Norway are covered by the public health care system. Oslo University Hospital is responsible for corneal transplants in the South-Eastern Norway Regional Health Authority, which is a region of 3.1 million inhabitants, more than half the population of Norway (about 5.4 million people). Our hospital has a corneal transplant registry approved by the data protection officer/local ethics committee. Written informed consent is obtained from all patients in the registry. Until 2022, Oslo University Hospital has been the only public hospital offering CXL treatment in this region with very few procedures having been conducted in private practice.

In this study, we reviewed all corneal transplants conducted from January 1, 2021, to December 31, 2022; further, we noted the reasons for surgery. We extracted all patients with KC who underwent corneal transplants during the study period. For these patients, we noted the age at the time of surgery, sex, previous CXL treatment, visual acuity (logarithm of the minimal angle of resolution), stage of the KC (Amsler–Krumeich classification system), and steepest keratometry reading (maximum keratometry) measured on corneal tomography (Pentacam HR, Oculus, Wetzlar, Germany). In a previous study, we compared the number of patients with KC who underwent corneal transplants in 2005 to 2006 (before the introduction of CXL treatment) and 2013 to 2014 (after the introduction of CXL) in the same region.[20] These previously reported values have been referred to in the present study. Three corneal surgeons performed the transplant procedures in 2005 to 2006; among them, 2 of these 3 surgeons were involved in the corresponding procedures in 2021 to 2022.

The CXL treatment was introduced in our hospital in January 2007. During the first years of introduction, the CXL procedure was performed according to the Dresden protocol[5] as described in previous articles.[22,23] Subsequently, accelerated CXL protocols were implemented and performed as previously reported.[24] Over the years, the following intensity profiles of ultraviolet-A irradiation have been applied: irradiance of 3 mW/cm^2 (UV-X 1000, IROC Innocross AG) for 30 minutes, irradiance of 9 mW/cm^2 (UV-X 2000, IROC Innocross AG and PXL, Peschke GmbH) for 10 minutes, and pulsed irradiation (1 second on/off) of 30 mW/cm^2 (Avedro Inc., KXL System) for 8 minutes. During the years, different riboflavin solutions have been used. Riboflavin with dextran was applied in the first years and later riboflavin with methylcellulose has become the standard riboflavin solution.[24,25] Hypotonic riboflavin has been used in case of intraoperative corneal thinning.[23,25] "Epi-on" CXL was performed in a very few cases, that is, in children, persons with a developmental disability, and in cases of extremely thin corneas. We collected information both regarding the annual number of CXL treatments between 2007 and 2022 from the hospital's electronic database. We also collected data on the annual number of consultations in our department with the *International Classification of Diseases, 10th Revision* (*ICD-10*) coding H18.6.

RESULTS

A total of 352 keratoplasties were performed in 2021 and 2022. KC was the reason in 11 patients (3.1%). Table 1 presents the baseline characteristics of these 11 patients. The median age was 40 years (range, 20–70 years), with only 1 patient younger than 30 years. The most common indication was Fuchs endothelial dystrophy (n = 221; 62.8%), and endothelial keratoplasty was the most common type of transplant (n = 316; 89.8%). Figure 1 shows an increase in the total annual number of keratoplasties from 2005 to 2022 with a short decline during the years 2019 to 2021 and thereafter a substantial increase in 2022. In the same period, there was a steady decline in the annual number of keratoplasties for KC. Table 2 compares the number of keratoplasties and the characteristics of patients with KC who underwent keratoplasties in the 3 study periods.

Since the introduction of CXL treatment in our hospital, there was a steady increase in the annual rate of CXL treatments, with a flattening trend the last year (Fig. 2). In the same period, there was an increase in the annual number of consultations of patients with KC (Fig. 2). Among the 11 patients, only 1 had previously undergone CXL. This patient has been diagnosed with advanced KC at the age of 17, with a maximum keratometry of 86.1 D and a minimal corneal thickness of 323 μm. An epi-on CXL was performed, with the patient undergoing corneal transplantation after 3 years.

DISCUSSION

In this study, 15 years after the introduction of CXL, only 11 keratoplasties were performed for KC, a marked decrease from the 55 keratoplasties recorded in 2005 to 2006.[20] Furthermore, only 1 patient younger than 30 years underwent corneal transplantation for KC between 2021 and 2022.

Compared with other corneal diseases, KC involves a lower risk of graft rejection because it rarely involves ingrowth of vessels.[26] Nonetheless, the risk of graft rejection is approximately 49% after 20 years.[27] In addition, the rate of postoperative corneal astigmatism may often be unacceptably high because of the disparity between donor and recipient tissue thickness.[27] Thus, there is no doubt that CXL is a much

TABLE 1. Baseline Characteristics of the 11 Patients With KC Who Underwent Corneal Transplants Between 2021 and 2022

Patients	
Age, median (range); mean ± SD in yr	40 (20–70); 44.3 ± 13.4
20–29	1
30–39	2
40–49	5
50–59	2
60 69	0
70–79	1
Sex	11 men
Previous corneal collagen crosslinking	1
Best-corrected visual acuity (logMAR), median (range); mean ± SD	1.3 (0.2–3.0); 1.32 ± 0.85
K_{max}, median (range); mean ± SD in diopter	78.4 (61.0–109); 79.0 ± 16.8
Amsler–Krumeich classification	Stage 1: 0 Stage 2: 0 Stage 3: 1 (9.1%) Stage 4: 10 (90.9%)

K_{max}, maximum keratometry; LogMAR = logarithm of the minimal angle of resolution.

more gentle and less invasive treatment than keratoplasty. However, the CXL procedure is resource-intensive, especially the original Dresden protocol, which is time-consuming (surgery duration ≈1 hour).[14] CXL treatment seeks to halt disease progression rather than improve vision. Given the possibility of postoperative discomforts such as pain and blurred vision, as well as the rare possibility of serious complications,[28] ascertaining the safety and effectiveness of CXL treatment is important. In our study, almost no young patients with KC underwent corneal transplantation. As a consequence, a total 431 CXL procedures were performed during the study period.

KC progression typically occurs in young individuals. In most studies, the age at the time of CXL treatment is reported to be approximately 20 to 25 years.[15,25,29] However, KC may continue to progress after age 30 years.[30] In our area, 26, 8, and 1 patients younger than 30 years underwent transplantation in 2005 to 2006, 2013 to 2014, and 2021 to 2022, respectively (Table 2).[20] More than half of the patients in this study were older than 40 years, which suggests that their disease progression occurred before the full implementation of CXL treatment. Assuming that KC progression often occurs before the age of 30 years, one could hope that the number of keratoplasties for KC in the future will reach almost zero. However, some patients with KC may require corneal transplants despite full access to CXL. This could be attributed to the failure to consult an optometrist or ophthalmologist until the vision is substantially reduced. Moreover, older patients may experience satisfactory vision with contact lenses for an extended period, until the contact lenses eventually become insufficient or intolerable.

In addition to the introduction of CXL, other factors may have contributed to the reduced number of keratoplasties performed in patients with KC. For example, the indications for surgery may have changed over the past years owing to corresponding changes in surgeons or treatment modalities. In our hospital, 2 of the 3 surgeons involved in corneal transplants in 2005 to 2006 performed all surgeries in 2021 to 2022. Therefore, changes in the indications for surgery due to different surgeons contributing to the dramatic reduction in the number of transplants for KC are unlikely. Another reason for the reduced number of keratoplasties could be the wider application of contact lenses or other types of surgery. Other corneal surgeries, such as intrastromal corneal ring segments and combined CXL and photorefractive keratectomy, have been performed on a small scale in our department, with an average of fewer than 5 procedures per year from the introduction of CXL until 2022. Hence, these procedures had a minor influence on the reduction of keratoplasties in KC.

Over the past 2 decades, scleral contact lenses have gained increasing popularity in patients with KC due to better centration, increased stability, better ocular comfort, and easier adaptation for practitioners than traditional contact lenses previously used in KC.[31,32] Studies have shown that scleral contact lenses may reduce the need for keratoplasties.[4,33–35] Two of these studies emphasize that the impact of CXL on the rate of keratoplasty could not be assessed because of the recent implementation of CXL in the United States in 2016.[33,34] Although we do not have a register showing the scope of contact lens use among patients with

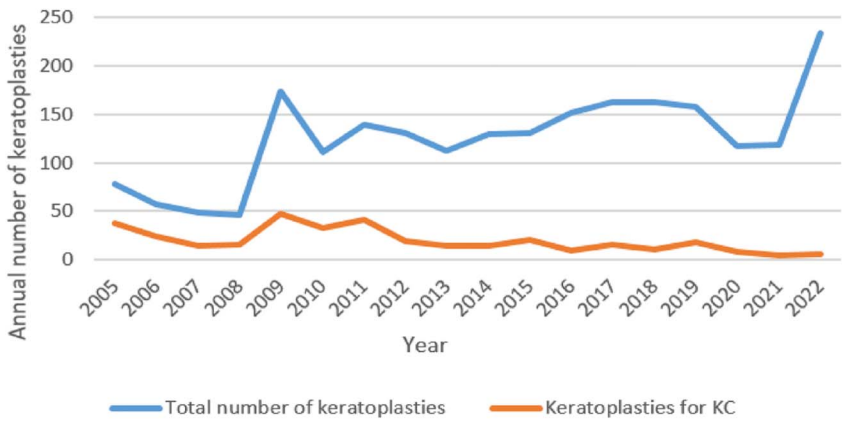

FIGURE 1. Total annual number of keratoplasties compared with the annual number of keratoplasties for keratoconus in the period 2005 to 2022.

TABLE 2. Comparison of the Total Number of Keratoplasties Collected From the Oslo University Hospital Corneal Transplant Register and the Characteristics of Patients With Keratoconus Who Underwent Keratoplasty in 2005–2006 (Before the Introduction of CXL Treatment), 2013–-2014, and 2021–-2022 (Present Study Period)

	2005–2006[20]	2013–2014[20]	2021–2022
No. keratoplasties	137	231	352
No. keratoplasties for keratoconus (% of all keratoplasties)	55 (40.1)	26 (11.3)	11 (3.1)
Age (yr)			
<25	13 (23.6%)	3 (11.5%)	1(9%)
25–30	13 (23.6%)	5 (19.2%)	0
>30	29 (52.7%)	18 (69.2%)	10 (91%)
Age, mean ± SD (range) in yr	34.6 ± 12.6 (15–63)	36.7 ± 12.4 (20–69)	44.3 ± 13.4 (20–70)
Amsler–Krumeich classification	Stage 1: 1 (1.8%)	0	0
	Stage 2: 1 (1.8%)	0	0
	Stage 3: 18 (32.7%)	1 (3.8%)	1 (9.1%)
	Stage 4: 35 (63.6%)	25 (96.2%)	10 (90.9%)

KC in our department, there has been increasing use of scleral contact lenses in our area during the last decade. Although scleral lenses have influenced the rate of transplants for KC, we believe that our 15-year follow-up time after the introduction of CXL implies that this treatment has had a major impact on the reduction of keratoplasties in patients with KC.

As shown in Table 2, KC was more advanced at the time of transplantation during the study period than before the implementation of CXL treatment. This may be attributed to the more widespread use of specially designed contact lenses during the moderate stages of KC than 16 years ago. Accordingly, the indications for corneal transplants may have been more liberal before the implementation of CXL treatment. However, a comparison of the degree of KC between 2013 to 2014 and 2021 to 2022 suggests that the indications for transplants in KC were similar and still the number of transplants decreased by 50% (Table 2).

Another reason for the marked reduction in the number of keratoplasties for KC could be attributed to reduced access to donor corneas during the study period compared with before the introduction of CXL. However, the opposite was the case because the total number of keratoplasties over the years more than doubled (Table 2), mainly because of the expansion of the indications for endothelial keratoplasties over the last decade.[36] In our study, the cause of transplants was KC in 40% and 3% of cases in 2005 to 2006 and 2021 to 2022, respectively (Table 2).

Another unlikely reason for the reduction in the number of keratoplasties for KC is a decrease in the incidence of KC over the last few decades. A previous Norwegian nationwide registry study estimated that the prevalence of KC in the general population was 192.1 per 100,000.[37] Moreover the estimated annual incidence was 19.8 per 100,000, with a slight increase over the period of 2010 to 2018. Studies from other countries have indicated an increase in the prevalence of

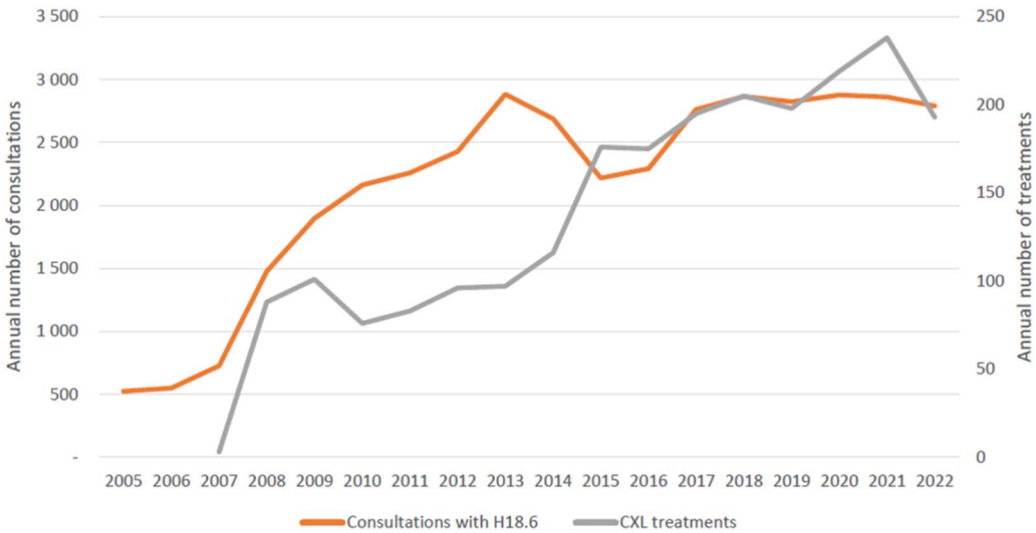

FIGURE 2. Annual number of corneal collagen crosslinking performed and of consultations with *International Classification of Diseases, 10th Revision* coding H18.6 in the period 2005 to 2022.

KC.[38,39] However, this could be attributed to improvements in diagnostic tools, which allow the early detection of KC and the identification of candidates for CXL.

It should be considered that the study period during 2021 and 2022 was soon after the corona virus disease 2019 pandemic which had a large impact on health care systems globally, including ophthalmic care, resulting in suspension of elective surgery.[40,41] Our department was also affected with a short period of decline in the total number of keratoplasties in 2020 to 2021; however, there was a considerable increase in 2022. During the same period, the number of keratoplasties for KC steadily decreased. Therefore, we believe that the corona virus disease 2019 pandemic did not affect the number of keratoplasties performed for KC during the third study period.

Besides our previous report showing that the number of transplants was halved 8 years after the introduction of CXL, only 1 study has reported a reduction in the absolute number of transplants for KC.[21] Specifically, this previous nationwide registry reported a 25% decrease in the number of corneal transplants 7 years after the introduction of CXL. Although other studies have reported a significant decrease in the proportion of corneal transplants for KC, this was because of an increase in the number of endothelial keratoplasties rather than a decrease in the absolute number of transplants.[42,43] Furthermore, although CXL was introduced in Europe 20 years ago, KC remains the most common cause of corneal transplants in many regions.[44–46] Reports have found a reduction in the number of keratoplasties for KC, suggesting that improved contact lens technology is the main reason for this reduction.[34,35] Other reasons may be the economic costs in countries where medical care is mostly based on private insurance or a high rate of immigrants from countries without access to CXL treatment. In addition, the association between genetics and ethnicity combined with factors specific to low-income countries may result in many patients with advanced KC lacking the opportunity to receive CXL treatment in the early stages.[47,48]

The main strength of the present study is the long period since the introduction of CXL in a defined area in Norway, where all corneal transplants and almost all CXL treatments were performed in 1 hospital, yielding reliable real-world data. However, a limitation of this study is the relatively small number of transplants included in our local corneal registry compared with other much larger registries.

In conclusion, we observed a dramatic decrease in transplants for KC 15 years after the introduction of CXL. Despite the widespread use of contact lenses for moderate to advanced KC in the last decade, we assume that this observed reduction can be largely attributed to CXL offered to most patients with progressive KC. Nevertheless, future long-term studies involving large corneal registries in countries with complete access to CXL over a long period are required to confirm our findings.

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