Original Article

# Corneal Cross-Linking in Pellucid Marginal Degeneration: Evaluation after Five Years

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## Abstract

**Purpose:** To evaluate the long-term outcome of corneal cross-linking (CXL) for pellucid marginal degeneration (PMD).

**Methods:** In a retrospective study, forty eyes of forty patients were enrolled. All subjects had undergone CXL for PMD at least 5 years before the assessments. Visual acuity, refraction, and topography data were compared to their respective values before CXL.

**Results:** The comparison between mean preoperative logMAR uncorrected visual acuity and 5-year postoperative evaluation revealed no significant change (1.20 ± 0.65 and 1.17 ± 0.64, $P > 0.05$). No statistically significant difference was noted comparing preoperative mean logMAR best-corrected visual acuity (BCVA) and postoperative mean logMAR BCVA (0.24 ± 0.19 and 0.22 ± 0.20, $P > 0.05$). We did not find any significant difference between pre- and postoperative spherical equivalent and spherical refractive errors ($P = 0.419$ and $P = 0.396$, respectively). Regarding the BCVA Snellen lines, 23 eyes had no significant change in pre- and postoperative examinations, 11 eyes had improvement, and 6 subjects showed worsening defined as significant when two or more lines change. The spherical equivalent refractive error improved in 4 subjects, was stable in 25, and worsened in 11 subjects, while a 0.5 diopter or more myopic change was considered significant. Furthermore, regarding steep keratometry values, 25 subjects were stable, 7 had improvements, and 8 worsened.

**Conclusion:** CXL appears to be a safe and effective procedure to halt the progression of PMD.

**Keywords:** Corneal cross-linking, Corneal ectasia, Pellucid marginal degeneration

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## Introduction

Pellucid marginal degeneration (PMD), initially described by Krachmer in 1978, is a bilateral noninflammatory progressive corneal ectatic disorder. The disease mainly affects the inferior and peripheral portions of the cornea.[1,2] PMD manifests as impaired vision due to high against the rule and irregular astigmatism with a characteristic butterfly appearance or crab-claw pattern in corneal topography.[3-5] Schlaeppi[6] noticed the absence of lipid deposition, scarring, or vascularization in PMD, the so-called pellucid. There is no known etiology for PMD yet, and no unanimous consensus whether PMD, keratoconus, and keratoglobus are distinct diseases or just different phenotypes of the same disorder.[7] According to one of the large-scale studies on PMD, published by Sridhar *et al*. in 2004, including 116 eyes from 58 patients, 77.6% of patients were male. These findings were in agreement with prior studies.[2] PMD is mostly diagnosed between the second and fifth decades of life. Studies show that PMD is observed in all races and is not confined to a specific geographical region. Currently, there is no evidence of PMD being a hereditary disease, but studies have discussed that moderate-to-severe astigmatism is observed in the immediate relatives of PMD patients.[7]

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The current treatment plans for PMD consist of nonsurgical and surgical methods. Nonsurgical methods used to treat PMD are glasses and gas permeable hard contact lenses. Biswas *et al*.[8] concluded that patients with high degrees of astigmatism using spherocylindrical glasses with high refraction indices, had acceptable visual acuity. Furthermore, Kompella *et al*.[9] and other researchers[2,10] recommended toric soft contact lenses for high irregular astigmatism. Surgical methods are often used in patients with advanced progressive disease or cases that cannot use contact lenses. Surgical methods consist of intrastromal corneal ring segment,[11] penetrating keratoplasty,[2,12] lamellar crescentic keratoplasty,[13,14] and more novel methods such as sliding keratoplasty.[15]

Corneal cross-linking (CXL) is a technique that can halt the progression of keratoconus. And is one of the most popular methods for treating patients diagnosed with keratoconus.[16] There have been studies centered on the use of CXL in PMD patients, but most of these studies are case reports.[17-21] Few studies with a more extensive scope have only evaluated patients after a short-term follow-up.[22,23] Sorkin and Varssano[24] and Jinabhai *et al*.[7] have noted the need for long-term evaluation of CXL on PMD in their reviews. CXL, whenever proved to be effective in halting or slowing down the progression of PMD, can lessen the need for more aggressive and complex surgeries with a high risk for complications.

In this study, we evaluated the long-term efficacy of the CXL to stabilize vision, refraction, and topography in PMD after 5 years of follow-up.

## Methods

This study abides by the Declaration of Helsinki of ethical standards and is also approved by the Ethics Committee of the Isfahan University of Medical Sciences. This was a quasi-experimental retrospective study. Forty eyes of forty patients were enrolled. All participants had undergone CXL at least 5 years before evaluation, during a 2-year period in a tertiary referral hospital, with a preoperative examination, including corrected and uncorrected visual acuity (UCVA) assessment, refraction, and corneal tomography. The inclusion criteria for intervention were progressive PMD with a clear cornea and minimum cornea pachymetry of more than 400 μ at the thinnest point at initial corneal imaging. Initial PMD diagnosis was established by a cornea subspecialist according to clinical manifestations described by Krachmer[1] and topographical patterns described by Karabatsas and Cook[3] and later by Koc *et al*.[5] The criteria defining progression and eligibility for CXL had been increasing by more than 1 diopter (D) of steepest keratometry value, or a worsening of 0.5 D in refraction spherical equivalent during a year. Specified criteria were established by the authors' consensus and are in line with prior research by Pircher *et al*.[23] All participants had the best spectacle-corrected vision of 20/25 or worse. Otherwise, the ophthalmology examination was normal regarding anterior and posterior segments.

The standard epithelium-off CXL procedure was done by total corneal epithelium removal with a blunt spatula. The stroma was saturated by pouring isotonic 0.1% riboflavin 5 phosphates in 20% dextran solution (VibeX, Avedro Inc., USA) every 3 min for 30 min. After the stroma was sufficiently saturated, which was confirmed by slit-lamp examination, the cornea was treated with ultraviolet (UV)-A light for 30 min at 3 mW/cm$^2$ irradiance. The technique for CXL was according to the original Dresden protocol utilizing a UV-X™-1000 device (IROC, Switzerland). We drifted the irradiation set inferiorly as the irradiation circle tangent to the inferior limbus for maximum irradiance in the lower portion of the cornea.

Patients were recalled for a follow-up examination consisting of visual acuity assessment, refraction, and corneal tomography (Pentacam HR, Oculus, Germany). Any possible adverse events attributable to the intervention were recorded. Patients who failed to return for follow-up examinations, or had not consented to participate in the study, were excluded from this study.

We statistically analyzed preoperative and postoperative values to find significant differences. Comparing pre- and postoperative data, patients were categorized into three subgroups of stable, improvement, and worsening. For keratometry, we set the cut-off at 1 D, an increase of more than a diopter in steep simulated K was regarded as worsening, while a decrease in the same value of more than 1 D was considered an improvement. Otherwise, the sample was categorized as stable. Furthermore, we set the cut-off for visual acuity at two lines or more of the Snellen lines as significant. These cut-offs were 0.5 D and 1 D for spherical equivalent and refractive astigmatism, respectively.

### Statistical analyses

Data were analyzed using the SPSS software version 21.0 Statistical package (SPSS Inc., Chicago, IL, USA). The normality of continuous data was evaluated using the Shapiro–Wilk test. Nonparametric statistical tests, such as the Wilcoxon test, were utilized when the requirements for normal distribution were not met. The statistical significance level was set at $P < 0.05$.

## Results

There were 30 (75.0%) male and 10 (25.0%) female patients in this study. The mean age was 39.75 ± 9.99 years. The follow-up period for the participants in this study was 60–85 months, with a mean of 74.5 ± 5.1 months. The mean preoperative logMAR UCVA was 1.20 ± 0.65, and the mean preoperative logMAR best-corrected visual acuity (BCVA) was 0.24 ± 0.19. At the 5-year postoperative evaluation, the mean logMAR UCVA was 1.17 ± 0.64, and the mean logMAR BCVA was 0.22 ± 0.20. We were not able to disclose any significant changes regarding the UCVA and BCVA up to the latest follow-up examination ($P = 0.637$ and $P = 0.657$, respectively).

The difference between pre- and postoperative spherical equivalent and spherical refractive errors was not statistically

significant ($P$ = 0.419 and $P$ = 0.396, respectively). Our findings demonstrated that the amount of pre- and postoperative cornea plane refractive cylindrical error was not significantly different (4.82 ± 2.89 and 4.86 ± 2.87 D, respectively, $P$ = 0.781). In addition, we did not find any differences comparing pre- and postoperative Q-Value and Belin/Ambrosia Deviation Display ($P$ = 0.576 and 0.322, respectively). None of the subjects in this study had any complications, such as hydrops or corneal scarring. Table 1 provides a summary of the pre- and postoperative values.

Table 2 demonstrates the categories of "stable," "worsened," and "improved" outcome measures according to the preset cut-off points described in the methods section. Regarding the BCVA, 23 subjects were stable, 11 had improvements, and 6 were categorized as worsening. There was only one subject with worsening of more than three Snellen lines. Based on steep simulated keratometry values, 25 subjects were stable, 7 had improvements, and 8 had deteriorated.

Figure 1 demonstrates the subjects with worsened steep simulated keratometry, BCVA, and refractive astigmatism. One patient had deterioration in all categories. This subject was a 29-year-old male. There was another 48-year-old male subject that had worsened in all categories except UCVA. Table 3 provides a comparison between these subjects' pre- and postoperative records with the mean values from the entire study's population.

## Discussion

PMD as a progressive corneal ectatic disorder causes irregular and against the rule astigmatism with consequent visual impairment and decreased quality of life.[2] CXL is proposed to halt the progression of cornea ectatic disorders by stabilizing the corneal structure.[16,24] In this study, we evaluated the long-term (5-year follow-up) outcome of CXL in patients with PMD regarding vision, refraction, and topography. We had a 3:1 male-to-female ratio of subjects, which is in line with previous studies.[2] We observed that CXL in the long-term stabilized or improved the acuity and keratometry values in the majority of cases. The procedure can be beneficial in halting the progression of PMD, decreasing the need for more invasive procedures. In this study, two cases had been worsened in all outcome measures. We were not able to identify any risk factors for the worsening of these cases. In our study, CXL seemed to be most effective in improving BCVA. The refraction astigmatism and UCVA were the most stable measurements. The spherical equivalent refraction had the greatest number of worsening while the 0.5 D cut-off had made it a sensitive variable.

The distinction between PMD and inferior keratoconus could be confusing. The importance of such differentiation lies

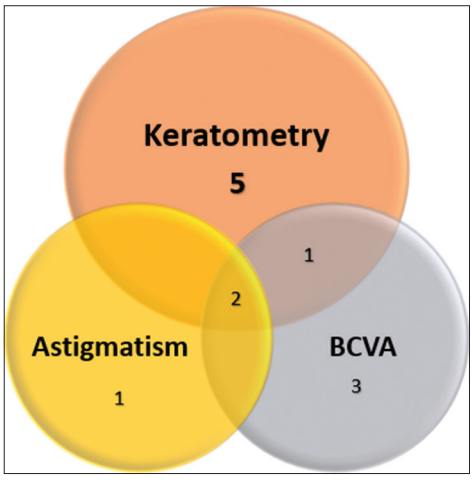


**Figure 1:** Venn diagram of subjects with worsening in refractive astigmatism, steep simulated keratometry, and BCVA. BCVA: Best-corrected visual acuity

**Table 1: Comparison of the pre- and postoperative variables**

| Variables | Preoperative | Postoperative | *P* |
|---|---|---|---|
| $K_{flat}$ (diopters)* | 42.79±2.99 | 43.02±2.94 | 0.429 |
| | 42.45 (37.3–50.9) | 42.5 (36.6–50.2) | |
| $K_{steep}$ (diopters)** | 47.10±3.87 | 47.20±3.59 | 0.732 |
| | 46.40 (40.6–55.7) | 46.25 (40.9–56.3) | |
| LogMAR UCVA | 1.20±0.65 | 1.17±0.64 | 0.637 |
| | 1.00 (0.15–2.00) | 1.00 (0.22–2.00) | |
| LogMAR BCVA | 0.24±0.19 | 0.22±0.20 | 0.657 |
| | 0.22 (0.09–1.00) | 0.15 (0.00–1.00) | |
| Sphere | −1.47±2.33 | −1.60±2.67 | 0.396 |
| | −1.0 (−8.5–3.5) | −1.0 (−10.0–4.0) | |
| Cylinder | −4.82±2.89 | −4.86±2.87 | 0.781 |
| | −3.87 (−9.50 – −0.50) | −4.25 (−10.0 – −1.0) | |
| Spherical equivalent | −3.88±2.45 | −4.03±2.67 | 0.419 |
| | −3.62 (−9.50 – −0.37) | −3.56 (−11.00–0.00) | |
| *Q* value | −0.007±0.82 | −0.15±0.33 | 0.576 |
| | −0.09 (−0.89–0.46) | −0.10 (−0.90–0.45) | |
| Belin/Ambrosia Deviation Display | 5.72±16.71 | 5.98±3.70 | 0.322 |
| | 5.22 (0.92–16.40) | 5.46 (0.71–15.67) | |

*Paired samples *t*-test was used for comparison, **Wilcoxon test was used for comparing other variables in pre- and postoperative records. Mean±SD and median (minimum–maximum). UCVA: Uncorrected visual acuity, BCVA: best-corrected visual acuity, SD: Standard deviation

**Table 2: The subgroups based on different outcome measures**

| Feature | Stable, *n* (%) | Improvement, *n* (%) | Worsening, *n* (%) |
|---|---|---|---|
| Steep keratometry | 25 (62.5) | 7 (17.5) | 8 (20.0) |
| UCVA | 36 (90.0) | 2 (5.0) | 2 (5.0) |
| BCVA | 23 (57.5) | 11 (27.5) | 6 (15.0) |
| Refractive astigmatism | 36 (90.0) | 1 (2.5) | 3 (7.5) |
| Spherical equivalent | 25 (62.5) | 4 (10) | 11 (27.5) |

Definition for change: Simulated steep keratometry: >1 diopter, Visual acuity: two lines or more of the Snellen lines, Spherical equivalent: >0.5 diopter, Refractive astigmatism: >1 diopter. UCVA: Uncorrected visual acuity, BCVA: best-corrected visual acuity

**Table 3: Preoperative values of subjects with worsening in outcome measures compared to the entire study population**

| Preoperative variable | All samples | Subject 1 | Subject 2 |
|---|---|---|---|
| $K_{flat}$ (diopters) | 42.79±2.99 | 43.6 | 42.6 |
| | 42.45 (37.3–50.9) | | |
| $K_{steep}$ (diopters) | 47.10±3.87 | 45 | 45.8 |
| | 46.40 (40.6–55.7) | | |
| LogMAR UCVA | 1.20±0.65 | 0.69 | 2 |
| | 1.0 (0.15–2.0) | | |
| LogMAR BCVA | 0.24±0.19 | 0.15 | 0.52 |
| | 0.22 (0.0–1.0) | | |
| Sphere | −1.47±2.33 | −0.5 | −0.5 |
| | −1.0 (−8.5–3.5) | | |
| Cylinder | −4.82±2.89 | −3 | −4.5 |
| | −3.87 (−9.50 – −0.50) | | |
| Spherical equivalent | −3.88±2.45 | −2 | −2.75 |
| | −3.62 (−9.5 – −0.375) | | |

Subject 1 was a 29-year-old male that had deterioration in all of the obtained measurements. Subject 2 was a 48-year-old male that had worse postoperative measurements in all categories except UCVA. Mean±SD and median (minimum–aximum). UCVA: Uncorrected visual acuity, BCVA: Best-corrected visual acuity

in the different prognosis and management strategies.[25] As Sedaghat *et al*.[26] demonstrated, corneal biomechanical values obtained by ocular response analyzer (ORA) are dissimilar between these categories. We did not have access to ORA in this research. Martínez-Abad and Piñero[25] and Mohr *et al*.[27] proposed Scheimpflug imaging-based devices and wide-field spectral domain optical coherence. tomography (SD-OCT) cornea sublayer pachymetry for differentiating these two conditions. We did not have any OCT imaging of the cornea; however, all cases in this research had Scheimpflug cornea imaging at first and follow-up visits. The Pentacam Belin/Ambrosia Deviation Display, presented in Table 1, is in the first place designed for the detection of keratoconus and may not suitably demonstrate the pathologic findings of the cornea tomography in PMD, yet the difference between pre- and postoperative values was not significant. Similarly, the cornea asphericity expressed as Q value in the Table 1 might not be a direct indicator of the progression of the PMD.

There are published articles demonstrating that CXL might be a promising treatment to stabilize PMD.[22,28,29] These studies have revealed minimal improvement in visual acuity in early follow-ups. However, we were not able to find a statistically significant change in this regard.[16] In our case-by-case assessment, we also observed the majority of cases had improvements or stabilized PMD, which is in line with previous studies. In their review article, Yong and Hatch[16] concluded that CXL seems to be effective and safe in halting the progression of PMD although they have emphasized that long-term studies are necessary.

In a case report by de Almeida Ferreira *et al*.,[30] a patient diagnosed with PMD was treated with intracorneal ring segments in the left eye, and bilateral CXL was followed for 6 years. The patient complained of a progressive decrease in vision. Cornea topographical evaluation during 6 years of follow-up demonstrated an irregular progressive corneal flattening and visual loss with haze formation in this patient. As a rare complication, excessive flattening of the cornea after CXL[31-33] has been reported. None of the patients in our study had any adverse events attributable to CXL.

There have been studies on the simultaneous use of surface excimer laser ablation combined with CXL in treating patients diagnosed with PMD.[21] Yong and Hatch[16] deemed this combination safe and effective as well, yet the conclusion was based on relatively short-term studies. We cannot approve the safety of the cornea ablation procedure in PMD despite the relatively long-term efficacy of the CXL in the current study.

While compared to similar published manuscripts, a large number of cases are included in the current study. A limitation regarding the statistical power was the relatively small sample size to prove the equality caused by the uncommonness of the eligible cases and impediments in the following up the subjects in an extended-term study. The other limitation of our study was that earlier, and intermediate follow-up records were not uniformly available and admissible for the analysis.

In conclusion, the CXL is a safe and effective treatment to halt the progression of PMD, which can, in the majority of cases, lead to improved or stable vision. However, in a small number of cases, PMD might still worsen, despite having CXL done in earlier stages.

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### *Conflicts of interest*
There are no conflicts of interest.

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