

Advances in Corneal Cross-linking: A Narrative Review of Iontophoresis-assisted Approaches for the Management of Keratoconus

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ABSTRACT

Keratoconus (KCN) is a gradual ectatic corneal condition that, if not treated, can result in severe vision impairment. Corneal Collagen Cross-Linking (CCXL) is still the gold standard for stopping disease development, with the traditional epithelium-off ("Dresden protocol") technique showing long-term success. However, constraints such as postoperative discomfort, delayed epithelial healing, and infection have prompted the development of alternate approaches. Iontophoresis-Assisted Corneal Cross-Linking (I-CXL) has emerged as a potential method for increasing riboflavin penetration through the intact epithelium with a modest electrical current, hence improving patient comfort and lowering complications. This review critically examines the available data comparing I-CXL to traditional CXL in terms of effectiveness, safety, visual and topographic results, and long-term stability. While I-CXL has advantages such as faster recovery, greater patient acceptability, and lower complication rates, most studies show that its biomechanical stiffening impact and long-term effectiveness are inferior to traditional CXL. Recent improvements, such as expedited and customised iontophoresis techniques, show promise for closing this gap. Understanding the comparative merits and limitations of each strategy is critical for developing effective KCN treatment regimens.

Keywords: Collagen, Corneal linking, Riboflavin, Topographic management, Treatment regimen, Visual acuity

INTRODUCTION

The KCN is a non-inflammatory, degenerative, bilateral and progressive corneal disorder. It is characterised by stromal thinning, which results in a conical change of the cornea, uneven astigmatism, and decreased vision [1]. Although the specific aetiology is unknown, the condition is frequently related with a number of systemic and allergy conditions, including neurodermatitis, allergic asthma, allergy rhinitis, Marfan syndrome, Ehlers-Danlos syndrome, Turner syndrome, and Down syndrome. A hereditary propensity is found in about 10% of cases. In its early stages, the condition normally manifests unilaterally, but it eventually spreads to both eyes. Clinical signs include a slow loss of visual acuity, increasing myopia, irregular astigmatism, and photophobia [2]. Slit-lamp examination detects corneal thinning and protrusion, pachymetry measures corneal thickness, and computerised corneal topography identifies typical modifications to corneal curvature [2,3].

The epidemiology of KC differs widely between parts of the world. Furthermore, data is selective because study has only been conducted in a few nations [4]. The prevalence varies from 0.2 to 4790 on every 100,000 individuals, with a yearly incidence of 1.5-25 cases per 100,000 Asians. The above-mentioned signs are most common among those aged 20 to 30 years [5,6].

For several years, the therapy of KC was restricted to spectacles and rigid gas-permeable contact lenses. CXL is now the most often used surgical treatment for progressive KC. Keratoplasty (corneal scarring) may be required in advanced cases, particularly if corneal scarring exists. It should be explicitly emphasised that since the development of the CXL approach in treating progressive KC at an early stage, the percentage of patients requiring corneal transplantation for this reason has dramatically dropped [2].

The CXL was initially introduced approximately 25 years ago as a means to prevent the growth of KC. CXL, a minimally invasive procedure, has recently emerged as a promising method for slowing disease progression [5]. The approach is designed to strengthen the corneal tissue. The core principles of CXL involve the employing of riboflavin (vitamin B2) as a photosensitiser and Ultraviolet-A radiation (UV-A) to slow or stop the progression of

KC [7]. The purpose of CXL was to create strong covalent bonds inside the corneal stroma, increasing its rigidity and resistance to KC formation. Dresden protocol was named after the University of Dresden, wherein the technique originated and was developed in the late 1990s. Wollensak G et al., introduced a novel, minimally invasive technique in 2003 [8]. It was an upgraded version of the Dresden regimen, having favourable clinical outcomes. The outcomes demonstrated that the condition's progression was slowed following treatment, minimising the need for keratoplasty. Following that, a number of improved treatment regimens and procedures were developed to increase the clinical effectiveness, efficiency, and safety of CXL. These modifications include approaches such as Transepithelial or epithelium-on CXL (TE-CXL or epi-on CXL), Accelerated CXL (ACXL), Pulsed-Light CXL (PL-CXL), and numerous additional techniques, such as transepithelial I-CXL, Diluted Alcohol and I-CXL (DAI-CXL), slit-lamp CXL, or CXL plus (combined) methods [9].

Standard epithelium-off CXL (S-CXL) has been identified as the gold standard of therapy for progressive KCN [10]. However, it is unfavourable since it cannot be utilised in thin corneas, causes discomfort, momentarily impairs visual acuity, causes infections, and a haze that may last for 1 to 12 months, and is difficult to execute in children [11,12]. All of these disorders have been linked to corneal epithelial loss. As a result, the concept of epithelial-on crosslinking seems more interesting [12].

Iontophoresis has been utilised for ophthalmological drug administration since 1908, and it is employed in a variety of medical sectors, including transdermal delivery of anti-inflammatory drugs, local anaesthetics or analgesics, and transmucosal antiviral therapy [13]. More recently, it has been shown to be effective for transcorneal medication delivery. Studies have proven its safety and effectiveness in medication penetration through the cornea as well as other ocular tissues [14].

The goal of this review is to compare the efficacy, safety, and clinical outcomes of I-CXL to conventional CXL (S CXL) procedures for treating KCN. This review looks at current research to see if I-CXL

can be a feasible, less invasive solution to S CXL while achieving comparable biomechanical and optical benefits.

Enhancing the Outcomes of Corneal Cross-Linking: What Makes the Difference

Seiler T and Hafezi F found that the depth of successful CXL therapy is proportional to UVA intensity and corneal intrastromal riboflavin concentrations [15]. In epithelium-on CXL, Lombardo M et al., discovered that an intact corneal epithelium filters off an average of 20% of the UVA radiation that passes through the cornea [16]. Bottos KM et al., found that the lower effects of standard epithelium-on CXL (compared to S-CXL) were primarily due to restricted riboflavin penetration through the corneal epithelium, and that it was not a barrier to UVA transmission [17]. The overall UVA dosage remained similar across multiple CXL procedures. Therefore, the level of riboflavin penetration within the corneal stroma appears to be the main limiting factor in epithelium-on techniques.

Richoz O et al., recently revealed that photopolymerisation in CXL also requires oxygen [18]. Kamaev P et al., postulated that oxygen has a role in CXL by converting in reactive oxygen species. The undamaged corneal epithelium might operate as a barrier, preventing rapid oxygen flow into the stroma [19]. However, whether this decline reduces photopolymerisation in I-CXL had yet to be experimentally confirmed.

Dresden Protocol CXL

The Dresden technique uses UV light and a photosensitising chemical, generally riboflavin 0.1% mixed with 20% dextran, lasting 30 minutes. At the start of the procedure, the centre portion of the 7 mm corneal epithelium is massaged lightly until it is removed to allow the solution to permeate. Then, drops of riboflavin are applied to the cornea's surface and activated by UV-A light for 30 minutes, yielding an overall surface-level exposure of 5.4 J/cm² (3 mW/cm²). UV radiation induces a chemical reaction between riboflavin and collagen in the cornea, which leads to the formation of cross-linked fibres of collagen. These links strengthen and strengthen the corneal structure, reducing the possibility of future deformation and visual deteriorations. Wollensak G et al., carried out the first prospective, nonrandomised clinical pilot trial of CXL [8]. The research included 23 eyes from 22 individuals with moderate or advanced progressive KC. As a consequence, 70% of eyes had disease regression, with a reduction in maximal keratometry (Kmax) readings of 2.01 diopters (D) and refractive error of 1.14 D. The Dresden procedure remains the gold standard for treating progressive KC, which is why it is also known as the standard protocol/CCXL [10]. Corneas 400 µm or thicker can be treated to protect endothelium cells from UV-A exposure, ensuring safety. Results of long-term monitoring of the Dresden protocol's safety and efficacy are now available. Raiskup F et al., released 10-year findings for an approach based on the Dresden protocol. The authors validated the method's safety, the long-term reduction of keratometric values (from 61.5 D to 55.3 D), and the improvement of Corrected Distance Visual Acuity (CDVA) (0.14 logMAR units; approximately 1.4 lines on a standard Snellen chart) [20]. Poli M et al., showed suppression of KC progression in 89% of patients following the treatment in a 6-year research, but O'Brart DPS et al., saw no disease advancement in any of the patients included in the study over a 7-year follow-up [21,22]. Spherical refraction, Kmax and Kmean, as well as the Root Mean Square (RMS) values of corneal High-Order Aberrations (HOAs), total, high, coma, as well as spherical aberrations, all improved with time. More severe sickness at baseline was related with improvement in ocular aberrations with time. In a study done by Iqbal M et al., 40 of 49 eyes (81.6%) had a postoperative Spherical Equivalent (SE) refraction which was greater than the desired refraction. Kmax and SE refraction improved considerably and consistently from preoperative 51.95±1.90 D and -7.90±3.14 D to postoperatively 50.19±1.96 D and -6.35±2.49 D, respectively. At the end of the fifth

year of follow-up, two eyes (4%) showed signs of KC [23]. Eslami M et al., published a study that included 150 eyes from 112 KC patients that had received CXL for at least five years. The most recent follow-up session showed improvements in CDVA, spherical and cylindrical refraction, average and steepest keratometry, and corneal aberrations. The most recent follow-up session showed improvements in CDVA, spherical and cylindrical refraction, average and steepest keratometry, and corneal aberrations. During the most recent visit, 49 and 31 eyes increased their spherical and cylindrical powers by over one D, respectively, whereas 43 eyes levelled their steepest keratometry [24].

Conventional CCXL was the earliest protocol introduced for managing KCN and other corneal ectatic disorders, including pellucid marginal degeneration, post-refractive surgery ectasia, keratoglobus, Terrien's marginal degeneration, iatrogenic ectasia, and lattice corneal dystrophy. The development of this technique established CXL as a safe, effective, and minimally invasive treatment modality. The Dresden protocol serves as the foundational standard against which newer CXL techniques and modifications are evaluated, providing a benchmark for comparing their efficacy, safety, and biomechanical effects [9].

General Considerations-modifications of CXL

The ACXL is an altered version of the traditional approach. The purpose of ACXL is to achieve the same therapeutic results as traditional techniques while requiring less treatment time. ACXL utilises more energy for a shorter duration of time, often between three and ten minutes. This shorter treatment time is achieved by raising the quantity of UV-A radiation while preserving the effectiveness of the cross-linking process. This invention allows for a considerable reduction in treatment duration, from a conventional 30-minute session to as little as 3 to 10 minutes, while maintaining entire radiant exposure [25]. Reduced treatment duration can increase patient comfort, compliance, and perhaps reduce the risk of infection [24]. This function is especially beneficial for people who find traditional half-hour therapy uncomfortable or difficult to bear. Furthermore, shorter treatment times may improve the practicality of executing CXL treatments in clinical settings. However, the appropriateness of ACXL varies depending on the severity of the problem, the thickness of the cornea, and the particular patient's features. To guarantee the best possible treatment outcomes, patient selection criteria must be clearly stated. As with any new medical procedure, continuing research and clinical trials are being done to determine the safety and efficacy of ACXL. Recent research suggests that ACXL therapy is a feasible option for controlling mild to moderate KC [7]. Studies have indicated that I-CXL using an irradiation protocol of 9 mW/cm² for 10 minutes is a viable therapeutic option for managing mild to severe KCN, representing a meaningful advancement in CXL techniques and potentially extending its clinical applications to conditions such as bullous keratopathy and infectious keratitis [25,26].

The requirement for epithelial surgical excision is a major contributor to postoperative CCXL complications such as infective keratitis and abnormal wound healing. This has increased the demand for developing epi-on CXL and TE-CXL techniques. TE-CXL was developed as a modified technique in 2004. Epi-on CXL is a modified method that aims to perform CXL without extracting the epithelium, potentially leading to faster recovery and less pain. The trouble with this strategy is that the epithelium acts as a barrier, rendering it hard for riboflavin to penetrate far into the cornea. It employs a variety of riboflavin formulations and dosing methods to prevent epithelial loss. Riboflavin diffusion could be accomplished through a number of methods, such as altering corneal epithelial permeability, modifying the physicochemical properties of the riboflavin molecule, and directly delivering the riboflavin molecule into the corneal stroma through an epithelial flap/pocket. As a result, other ways

have been tested to increase the efficacy of epi-on CXL, include iontophoresis (the application of an electric current that encourages riboflavin penetration). Innovative procedures, including epi-flap CXL, have been shown to result in lower postoperative pain and anterior stromal haze compared typical epithelium-off CXL [27,28]. According to studies, TE-CXL is less effective than CCXL in halting the progression of KC, but it causes far less issues than normal epithelium-off CXL (2% vs. 4%) [28,29].

Another modified surgical method is PL-CXL, which uses UV-A irradiation in pulses to restart the photodynamic type II reaction. This promotes stromal oxygen replenishment, singlet oxygen release, and collagen crosslinking. Although theoretically safer and more efficient, brief pulse durations are of questionable utility, and PL-ACXL takes roughly twice as long as continuous ACXL without apparent clinical superiority, raising concerns in resource-limited settings [29].

The I-CXL employs a modest electric current to help riboflavin penetrate the intact epithelium. A riboflavin solution (0.1%, dextran- and NaCl-free, with potential enhancers such as benzalkonium chloride, NaCl, or EDTA) is supplied via a corneal ring electrode in about 5 minutes, followed by conventional accelerated UV-A irradiation. This approach promotes riboflavin stromal absorption and strives for more efficient crosslinking, although its overall efficacy remains debatable due to variability between studies [29]. Bilgihan K et al., presented transepithelial DAI-CXL in 2017, which combines iontophoresis with 10% ethanol pretreatment, signifying a step forward in transepithelial crosslinking protocol development [30].

Transepithelial Iontophoresis-Assisted Crosslinking (I-CXL)

Transepithelial iontophoresis is a non-invasive approach of treating KC that uses electromigration to enhance the passage of an ionised material into tissue across tight junctions of an undamaged corneal epithelium [31,32]. It is a contemporary procedure that is performed under topical anaesthesia [33]. The I-CXL approach creates repulsive electromotive forces through passing a low electrical current through an iontophoretic chamber, increasing riboflavin absorption into the corneal stroma. I-CXL treatment is based on the use of riboflavin, a small molecule that plays a vital role in the process. This molecule contains a molecular weight of 376.4 g/mol and a negative charge, making it ideal for therapy. The exact riboflavin formula used in the therapy surpasses treatments that employ topical riboflavin delivery because of its ability to keep the epithelium intact and minimise the riboflavin saturation period. Preclinical studies have demonstrated that I-CXL increases the mechanical durability of the cornea [34]. The I-CXL approach uses a 0.1% riboflavin solution with no additional dextran or sodium chloride. Furthermore, different enhancers that involve benzalkonium chloride, sodium chloride, sodium ethylene diamine tetra acetic acid, or trometamol could be used to improve epidermal penetration [33]. The I-CXL approach requires an electrical circuit that consists of a current generator and two electrodes. The first electrode, which is negatively charged and has a diameter of 8 mm, is connected to a device which suctions onto the patient's cornea using a suction ring. The second electrode, usually is positively charged, is connected to a patch placed on the cervical vertebrae or the forehead. The corneal ring electrode is introduced and filled with 0.5 millilitres of riboflavin solution. The continuous current generator is then set to 1 mA, and the molecules circulate across the epithelium in five minutes, resulting in a total dose of 5 mA/5 min. A slit lamp is used to verify stromal riboflavin soakage, which is then followed by UV-A radiation. Following the surgery, the cornea is cleansed with a balanced saline solution, and a therapeutic contact lens is inserted to protect the epithelium from potential UV damage for the first few days [34]. According to recent

study, there are two I-CXL procedures, each with a different process length of 5 minutes and 10 minutes. After a 12-month follow-up period, the lengthier approach proved to be more successful than the 5-minute procedure in reducing the progression of KC [35].

Compared to CCXL operations, I-CXL surgery reduces postoperative problems such as corneal edema/haze. Furthermore, the I-CXL therapy leads to quicker functional gains. This involves lowering average keratometry readings, stabilising uncorrected astigmatism, and increasing Endothelial Cell Density (ECD) during 12-24 months [31]. Bikbova G and Bikbov M found that I-CXL could slow the course of KC for up to a year [36]. In another study, Deshmukh R et al., found that postoperative discomfort is reduced and there are fewer incidences of infective keratitis [32]. Previous research has indicated that the I-CXL treatment is more successful than TE-CXL in slowing KC development, but not as effective as the CCXL approach [37,38]. Overall, I-CXL is regarded as a suitable replacement for CCXL, despite evidence that it leads in very minimal flattening [39].

Diluted Alcohol and Iontophoresis-Assisted Corneal Cross-Linking (DAI-CXL)

Bilgihan K et al., (2017) developed transepithelial DAI-CXL, a modified form of I-CXL [40]. This unique CXL procedure included two enhancers: a diluted alcohol solution comprising 10% ethanol and iontophoresis. The purpose of this approach was to improve riboflavin diffusion into the corneal stroma by using an intact epithelium. Additionally, the total UV-A exposure might be raised to 7.2 J/cm² to achieve successful cross-linking inside the stroma. A total of 93 eyes from 80 individuals with KC were treated with either CCXL or DAI-CXL. CDVA, keratometry, KC indices, pachymetry, and aberrations were measured prior to treatment as well as 1, 3, 6, and 12 months after the operation. A combined total of 46 eyes from 40 patients received DAI-CXL, whereas 47 eyes from 40 patients got CCXL. Following DAI-CXL therapy, the epithelium remained intact, and therapeutic contact lenses were readily removed from all eyes on the first day. On the other hand, in the CCXL group, epithelial repair took 2-3 days. Throughout the 12-month follow-up period, no patients had infections, substantial vision blur, or any other problems. Visual, topographical, and aberrometric metrics improved significantly in both the DAI-CXL and CCXL groups throughout a 12-month post-treatment period. The authors noticed a quicker improvement in UCDVA and CDVA with DAI-CXL than with CCXL. Furthermore, both the DAI-CXL and CCXL groups showed a significant improvement in corneal symmetry index after 6-month follow-up. Furthermore, only the DAI-CXL group showed a substantial improvement in CDVA after 12 months of follow-up. The results also showed that the demarcation line was apparent in all participants in both the DAI-CXL and CCXL groups one month after the operation. However, it had entirely vanished in all of these individuals after 12 months of therapy. Long-term clinical results have revealed improvements in CDVA along with modifications in corneal topography similar to those related with the epithelium-off CXL technique throughout a four-year follow-up period [30,40].

Another research compared the long-term effects of DAI-CXL and epithelium-off CXL on KC patients with thin corneas (<400 µm). The study included 13 DAI-CXL patients and 12 ACXL individuals. It was revealed that no patient had a postoperative epithelial defect. In cases of ACXL therapy, the epithelial defect healed within 3-4 days, and the contact lens was removed. Throughout the follow-up period, neither group of treated patients exhibited haze nor scarring that might jeopardise vision or infection. Furthermore, the median UDVA in the ACXL group improved significantly after 12 and 24 months as compared to the original tests. In contrast, in the DAI-CXL group, UDVA improved only after 24 months. Analysis of HOAs demonstrated substantial improvement only in the DAI-CXL group at the 24-month period [27].

CXL Combined Method

The CXL combination approach (or CXL plus method) was created to target visual results while also halting the growth of KC. Photorefractive Keratectomy (PRK), Phototherapeutic Keratectomy (PTK), intrastromal rings (such as MyoRing), and corneal transplantation with contemporaneous or later CXL are examples of combined techniques [41]. Combined therapies have the potential to improve visual results, but they need costly equipment.

Myring implantation is a surgical treatment with established clinical results. The microkeratome or femtosecond laser is used to create a pocket inside the corneal stroma during the surgical operation. The pocket is completely closed, with the exception of a minor incision tunnel. The ring implant is then put into the pocket. The implant is constructed of poly (methyl methacrylate) and has specified size according to the required refractive correction. The implantation is conducted with a particular applicator that is visible to the surgeon due to its transparency. The treatment works by modifying the curvature and shape of the cornea [42]. In a research by Daxer A et al., following the surgery, there was a considerable improvement in UDVA by over 10 lines, in CDVA by almost three lines, the keratometry readings fell by an average of 5.76 D, evident spherical and cylindrical refractive errors, SE [43]. Bikbova G et al., examined two procedures where 41 eyes after MyoRing implantation and 39 eyes following a combination of MyoRing and CXL implantation. Both treatments have demonstrated efficacy in treating KC. After 36 months, the group that got MyoRing paired with CXL showed slightly superior results in SE and keratometry readings [44].

Krueger R and Kanellopoulos A introduced the Athens protocol, which involves manual epithelial debridement and partial refractive correction. This approach corrects approximately 70% of cylinder and sphere measurements, with a maximum ablation depth of 50 µm using topography-guided PRK. Following the PRK treatment, 0.02% mitomycin C is used to limit cell growth and lessen the likelihood of corneal haze development. Then, CCXL is conducted [45,46]. In a study by Kanellopoulos A et al., 144 eyes were evaluated over a 10-year period. The study found substantial improvements in UDVA, CDVA, corneal thickness, steep keratometry, and Kmax. Ectasia stabilised in 94.4% of cases, with a few having overcorrection or hyperopic shift [46].

Kymionis G et al., devised the Cretan protocol, which is an alternate combination procedure that uses the CXL method and transepithelial PTK. The depth of ablation is 50 µm inside the 7.0 mm zone. Mechanical debridement is then utilised to widen the de-epithelialised region to 8.0 mm in diameter. T-PKT is followed by CCXL [47]. Grentzelos M et al., conducted a research in which 15 eyes comprising 13 patients were treated using the Cretan regimen. The control group included 15 eyes from 13 patients who had undergone CCXL. The Cretan protocol group had substantial improvements in CDVA and corneal astigmatism, but the Dresden protocol group did not. In a four-year follow-up, epithelial removal by applying t-PTK during CXL produced superior long-term results than mechanical epithelial debridement [48]. Cretan protocol plus is an expansion of the Cretan protocol in which the corneal epithelium is treated with t-PTK following topical anaesthesia. This procedure involves ablating a 6.5 mm optical zone to a depth of 50 µm, followed by mechanical enlargement of the treatment area to 8.0-9.0 mm. Subsequently, conventional PRK is performed, with a maximum ablation depth of 50 µm within a 5.5 mm zone. Corneal thickness is measured, and riboflavin is administered appropriately. UV-A irradiation was applied for 30 minutes with an anticipated intensity of 3.0 mW/cm² [49]. Grentzelos M et al., studied 31 eyes of 22 patients who had simultaneous t-PTK and conventional PRK, followed by CXL utilising the cretan protocol plus. There were no problems during the surgery, and CDVA, refractive error, and corneal astigmatism improved significantly over a three-year follow-up. ECD remained steady over the study period [50].

Tel Aviv protocol (ePRK-CXL) is a modified version of the Cretan protocol in which the epithelium is destroyed with an excimer laser. It corrects 50% of refractive astigmatism and allows for a maximum ablation depth of 50 µm, followed by further CXL [51]. Rabina G et al., studied 131 eyes, dividing them into two groups: the Tel Aviv Protocol (50 patients) and Alcohol-assisted Epithelial Removal (AICCX). The Tel Aviv protocol group improved significantly in UDVA, CDVA, Kmax, and cylinder compared to the AICCX group, which did not alter much [51]. In a study of 20 eyes by Kaiserman I et al., the Tel Aviv protocol resulted in a considerable improvement in UCVA and a 2.21 D decrease in Kmax. Importantly, this was done with less tissue ablation than the Athens procedure (46 vs. 70 µm) [52].

Further research is needed to determine whether I-SCXL can enhance the long-term outcomes of the gold standard CXL surgery. To summarise, I-SCXL has the potential to enhance the regular CXL in order to arrest the course of ectatic illness by shortening treatment duration and enhancing soaking time.

DISCUSSION

The CXL is now recognised as a key component in the treatment of KCN, slowing disease development through biomechanical reinforcement of the corneal stroma. While the typical epithelium-off (epi-off) Dresden technique remains the gold standard due to its demonstrated success, it has significant downsides, including postoperative pain, delayed epithelial healing, infection risk, stromal haze, and patient discomfort [53]. These constraints have prompted the development of alternate approaches aimed at increasing patient safety and acceptability while preserving treatment results [29].

The I-CXL is a notable achievement in this field. I-CXL tackles one of the key problems of transepithelial methods by increasing riboflavin penetration across an intact epithelium using a low-intensity electric current [54]. Several investigations have shown that I-CXL provides more homogenous and deeper riboflavin diffusion than traditional transepithelial CXL, resulting in improved biomechanical reinforcement while maintaining epithelial integrity [55,56]. This corresponds to less postoperative discomfort, faster visual recovery, and a lower risk of epithelial-related problems, making it especially desirable for paediatric patients, those with thin corneas, and individuals who are sensitive to epi-off treatments [16].

Despite these benefits, data shows that the biomechanical stiffening effect obtained by I-CXL may be less apparent than that of the traditional epi-off approach, especially in patients with advanced KCN. This might be attributable to lower stromal riboflavin concentrations and decreased oxygen bioavailability during transepithelial operations [57]. As a result, careful patient selection is critical, and I-CXL may be best suited for early diseases, paediatric patients, or patients who have thin corneas, where epithelium loss offers an added danger. In addition to KCN, iontophoresis-assisted and expedited CXL treatments have prospective uses in other corneal diseases, such as infectious keratitis and bullous keratopathy, whereby antimicrobial effects as well as corneal stabilisation may be advantageous [58]. However, long-term comparative data on progression of disease, corneal biomechanics, as well as visual outcomes are limited. Future randomised controlled studies with long-term follow-up are required to define standardised methods, optimise energy settings, and determine the precise function of iontophoresis-assisted CXL in the developing field of corneal cross-linking treatments.

CONCLUSION(S)

The I-CXL is a significant improvement in KCN care because it addresses important drawbacks of traditional epithelium-off CXL, such as patient pain, epithelial problems, and lengthy recovery time. By increasing transepithelial riboflavin penetration via a non-invasive electrical gradient, I-CXL provides a safer and more patient-friendly option while maintaining corneal biomechanical stability. Current data

shows that I-CXL is helpful in arresting disease development in mild to moderate KCN, with satisfactory visual, topographic, and safety results, however it may be somewhat less effective than regular CXL in advanced patients. Future research should concentrate on optimising iontophoresis settings, irradiation techniques, and patient selection criteria in order to clarify the precise function of I-CXL in the treatment spectrum of KCN and perhaps broaden its applicability to other corneal disorders.

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